Efficacy of Antidepressant Treatment for Inpatients with

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Efficacy of Antidepressant Treatment for Inpatients with Severe Depression

Effectiviteit van antidepressiva bij de behandeling van opgenomen patiënten met een ernstige depressieve stoornis

P R O E F S C H R I F T

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
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Prof.dr. H.A.P. Pols
en volgens besluit van het College voor Promoties.

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CHAPTER 1

General introduction

EPIDEMIOLOGY AND DIAGNOSIS OF MAJOR DEPRESSION

Mood disorders are highly prevalent and constitute a large burden on individuals and for the society. According to the WHO World Mental Health (WMH) surveys, the lifetime prevalence of any mood disorder was found to be approximately 12% in the general population.[1] In the Dutch general population aged 18–64 years, the estimated lifetime prevalence of major depressive disorder (MDD) is 18.7% with a 12-month prevalence of 5.2%, as reported in NEMESIS-2.[2]

Distinguishing "major depressive disorder" as a classified mental disorder from "depression" as a non-pathological mood state can be quite challenging. Diagnosis of major depressive disorder (MDD) is based on clinical interview including the clinical history and psychiatric examination. The American Psychiatric Association developed The Diagnostic and Statistical Manual of Mental Disorders, fourth Edition (DSM-IV), which was updated in 2000.[3] Mental disorders, e.g. major depressive disorder, can be diagnosed according to the standardized DSM-IV classification system. The Structural Clinical Interview for DSM-IV Axis I disorders (SCID-I) is a semi-structured interview which can be used to confirm the diagnosis major depressive disorder.[4]

In this thesis we used the DSM-IV criteria to diagnose major depressive disorder, as described below.[3] Recently, after the recruitment of eligible patients for this thesis, the American Psychiatric Association updated the DSM-IV criteria in the new Diagnostic and Statistical Manual of Mental Disorders, fifth Edition (DSM-5).[5] In the new DSM-5 classification system neither the list of symptoms (criteria A) for the diagnosis major depressive episode nor the required duration of at least two weeks has been changed. A subtle change to the subjective descriptors of (1) depressed mood is made, adding the word "hopeless" to "sad or empty" in the new DSM-5 criteria. Further, the bereavement exclusion (criteria E) has been removed in the DSM-5 criteria. Nowadays in clinical practice, the new DSM-5 criteria are used to diagnose major depressive disorder.

Depressive disorder can be sub-diagnosed for the following: severity (mild, moderate and severe); single and recurrent episodes; with and without psychotic symptoms; with an without melancholic symptoms (described below); and partial and full remission. To determine the severity of depressive symptoms, the 17-item Hamilton Rating Scale for Depression (HAM-D) is used.[6] The total HAM-D score is the sum from the first 17 items: score 0-7 = No Depression, score 8-13 = Mild Depression, score 14-18 = Moderate Depression, score 19-22 = Severe Depression, and score ≥ 23 = Very Severe Depression.

Major depressive disorder DSM-IV criteria:[3]

A. At least five of the following symptoms have been present almost every day for at least two weeks; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure in daily activities
    1. Depressed mood or irritable most of the day, nearly every day
    2. Decreased interest or pleasure in most activities, most of each day
    3. Significant weight change or change in appetite
    4. Insomnia or hypersomnia
    5. Psychomotor agitation or retardation
    6. Fatigue or loss of energy
    7. Feelings of worthlessness or excessive or inappropriate guilt
    8. Diminished ability to think or concentrate, or indecisiveness
    9. Recurrent thoughts of death or suicide, or has suicide plan
B. The symptoms do not meet criteria for a mixed episode
C. The symptoms cause clinically significant impairment in social, occupational, or other important areas of functioning almost every day
D. The episode is not due to the effects of a substance or to another medical condition
E. The symptoms are not better accounted for by bereavement

Melancholic features, as a subtype of major depressive disorder:

- Either anhedonia (lack of pleasure in positive things) or a lack of mood reactivity, or both, and
- At least three of the following symptoms:
    1. Depression that is subjectively different from grief or loss
    2. Diurnal mood variation (feeling worse in the morning)
    3. Early morning awakening (at least two hours earlier than usual)
    4. Significant weight loss or loss of appetite
    5. Psychomotor agitation or retardation
    6. Guilt feelings that are excessive

TREATMENT OF MAJOR DEPRESSION

In clinical practice, effective treatment of mood disorders has been recognized as quite challenging. Approximately 30-40% of patients with major depressive disorder are non-responder to initial antidepressant monotherapy and many of these patients develop chronic depressive symptoms.[7]

The "Trimbos Instituut Multidisciplinaire Richtlijn Depressie, 3e revisie"[8] provides a stepped-care model for the treatment of patients with MDD. The Trimbos Instituut Practice Guideline recommends pharmacotherapy (with supportive counseling), whether or not in combination with psychotherapy. The recommended pharmacological therapy consists of antidepressant monotherapy and, in case of non-response, lithium addition. Electroconvulsive therapy (ECT) is recommended in case of non-response to pharmacological therapy. To optimize and enhance treatment outcome for the treatment of MDD, it is advised to use treatment guidelines, i.e. treatment algorithms.

The efficacy of different antidepressants in MDD have been evaluated in a large number of studies. Inpatients with MDD responded more favorably to imipramine compared to mirtazapine[9] and the efficacy of imipramine is superior compared to fluvoxamine.[10] In depressed inpatients, tricyclic antidepressants (TCAs) are found to have significantly higher efficacy and unfortunately also slightly higher treatment discontinuation due to adverse effects compared to selective serotonin reuptake inhibitors (SSRIs), as concluded in a meta-analysis.[11] On the other hand, a meta-analysis of in- and outpatients with MDD found similar efficacy between TCAs and SSRIs, but TCAs were more effective for the inpatient subgroup.[12] In yet two other studies of in- and outpatients with MDD, the efficacy of venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), was found to be significantly higher compared with SSRIs.[13,14] In summary, for the treatment of inpatients with severe depression, both tricyclic antidepressants (TCAs), such as imipramine, and venlafaxine appear to be superiorly effective compared with selective serotonin reuptake inhibitors (SSRIs).

However as previously mentioned, due to the relatively common adverse effects, TCAs appear to be slightly less tolerable compared to SSRIs.[11] Similarly, in a meta-analysis of in- and outpatients with MDD, treatment discontinuation due to adverse effects of SSRIs was significantly lower compared to TCAs.[12] In contrast, venlafaxine and SSRIs appear to have similar tolerability,[13,14] therefore it has been suggested that the tolerability of venlafaxine is superior compared with TCAs. Unfortunately, despite these insights, the

literature lacks explicitness whether commonly prescribed TCAs, such as imipramine, and venlafaxine are comparable both in efficacy and in tolerability for the treatment of severely depressed inpatients.

For patients with MDD not responding to first-line antidepressant monotherapy, clinical practice guidelines recommend lithium addition as second-line augmentation treatment. A meta-analysis found lithium addition to various antidepressants (mostly TCAs) to be significantly more effective compared with placebo addition for the treatment of both unipolar and bipolar depression.[15] In inpatients with MDD, lithium addition to imipramine was found to have significantly higher efficacy compared to similar strategies with lithium addition to mirtazapine[16] or lithium addition to fluvoxamine.[17] Unlike lithium addition to TCAs, lithium addition to venlafaxine has only rarely been studied. Two small open-label uncontrolled studies investigating treatment-resistant depression did find lithium addition to venlafaxine to be effective.[18,19] However, it remains uncertain whether, in case on non-response to antidepressant monotherapy in patients with MDD, lithium addition to venlafaxine is an effective treatment strategy.

To further optimize treatment outcome for the treatment of MDD, clinicians and researchers are continuously searching for predictors of antidepressant treatment response. Up to date, definite predictors of antidepressant treatment response remain unknown, but several predictors have been suggested. The likelihood of eventual non-response to antidepressant treatment is greater the longer a patient fails to respond to an antidepressant.[20] Early drug response, that is, improvement occurring within the first two weeks of antidepressant treatment, is mentioned as a possible predictor of eventual treatment response. In addition, gender differences (male versus female) and menopausal status (premenopausal versus postmenopausal status) are suggested to influence antidepressant treatment response.

AIMS OF THIS THESIS

As mentioned, the literature remains ambiguous whether commonly prescribed TCAs, such as imipramine, and venlafaxine are comparable both in efficacy and in tolerability for the treatment of severely depressed inpatients. Furthermore, lithium addition to venlafaxine as second-line augmentation treatment has only scarcely been studied and it remains uncertain whether it is an effective treatment strategy. For that reason, the present thesis intends to further investigate these queries. The main aim of this thesis was to evaluate the efficacy of three phases of a treatment algorithm of inpatients with severe depression: *phase I* optimal antidepressant monotherapy (plasma level-

targeted dose imipramine or high-dose (375 mg/day) venlafaxine); *phase II* subsequent lithium addition in case of insufficient improvement of antidepressant monotherapy; *phase III* subsequent ECT in case of insufficient improvement of antidepressant-lithium treatment. Additionally, this thesis aims to further investigate predictors of antidepressant treatment response, i.e. early drug response, gender and menopausal status.

Chapter 1 (general introduction) provides a general overview of this thesis. **Chapter 2** describes a randomized double-blind clinical trial comparing the efficacy of 7-weeks treatment with plasma level-targeted dose imipramine versus high-dose venlafaxine in severely depressed inpatients; this was phase I of the study. **Chapter 3** describes the efficacy of two 11-week antidepressant treatment strategies in severely depressed inpatients, that is, imipramine versus venlafaxine, both with subsequent lithium addition in case of insufficient response; the treatment strategies consist of phase I and II of the study combined. **Chapter 4** evaluates the treatment algorithm under study in this thesis, i.e. the overall feasibility and efficacy of the 3-phase treatment algorithm of severely depressed inpatients, as described above; the algorithm comprises phase I, II and III of the study combined. **Chapter 5** describes the predictive value of early improvement, i.e. early drug response occurring within the first two weeks of antidepressant treatment, in the course of treatment with imipramine or venlafaxine in severely depressed inpatients. **Chapter 6** describes the influence of gender and menopausal status on antidepressant treatment response in severely depressed inpatients, treated with either imipramine or fluvoxamine. Finally, **chapter 7** (summary and general discussion) provides the main findings of this thesis and recommendations for future research are made.

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CHAPTER 2

A double-blind randomized study comparing plasma level-targeted dose imipramine and high-dose venlafaxine in depressed inpatients

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ABSTRACT

Objective: To compare the efficacy of plasma level-targeted dose imipramine and high-dose venlafaxine in depressed inpatients in a randomized double-blind study.

Methods: The study included 85 patients with a diagnosis of major depressive episode according to the DSM-IV criteria and a 17-item Hamilton Rating Scale for Depression (HAM-D) score ≥ 17. Patients were randomized to imipramine or venlafaxine. The dose of imipramine was adjusted for each patient to a predefined blood level of 200-300 ng/ml. The dose of venlafaxine was increased gradually to 300-375 mg/day. Efficacy was evaluated after 7 weeks of treatment.

Results: The mean age of the study group was 54.5 (range 29-82) years. There was no significant difference according to the primary outcome criterion of a ≥ 50% reduction on the HAM-D score: 17 of 43 (39.5%) patients on imipramine were responders compared to 21 of 42 (50%) patients on venlafaxine. When considering remission as outcome criterion (HAM-D score ≤ 7), 10 of 43 (23.3%) patients on imipramine were remitters compared to 15 of 42 (35.7%) patients on venlafaxine; again, no significant difference. When analysing a subpopulation of patients without psychotic features, with remission as outcome criterion, a significant difference was found: 5 of 34 (14.7%) patients on imipramine were remitters compared to 12 of 31 (38.7%) patients on venlafaxine.

Conclusions: The present study used optimal doses in depressed inpatients and showed that venlafaxine is at least equal in efficacy to imipramine. The results in the subgroup without psychotic features indicate a possible superiority of venlafaxine.

INTRODUCTION

Comparisons have been made of the efficacy of various antidepressants in major depressive disorder. For example, in depressed inpatients, imipramine is considerably more effective than mirtazapine[1] and imipramine is more efficacious than fluvoxamine.[2] A meta-analysis concluded that tricyclic antidepressants (TCAs) were significantly more effective than selective reuptake inhibitors (SSRIs) in depressed inpatients; however, significantly more TCA-treated patients stopped treatment due to adverse effects compared to patients using SSRIs.[3] A meta-analysis of 102 randomized controlled trials (RCTs) of inpatients/outpatients with unipolar major depression showed no overall difference in efficacy between TCA-treated patients versus SSRI-treated patients; however, for the inpatient subgroup TCAs were more effective.[4] When comparing venlafaxine with SSRIs (fluoxetine, paroxetine and fluvoxamine) in eight comparable randomized double-blind studies of inpatients/outpatients with major depressive disorder, remission rates were significantly higher with venlafaxine than with an SSRI.[5] Similarly, a pooled analysis of eight double-blind RCTs of inpatients/outpatients with major depression revealed that venlafaxine was significantly more effective than SSRIs (fluoxetine, paroxetine and fluvoxamine) in improving depression.[6] In summary, it can be concluded that both TCAs (especially in inpatient populations) and venlafaxine appear to be more effective than SSRIs for the treatment of depression.

TCAs, such as imipramine, are characterized by the inhibition of serotonin and noradrenaline reuptake.[7] Unfortunately, the anticholinergic mechanisms of TCAs are accountable for the relatively common side-effects such as a dry mouth, constipation, blurry vision, urinary retention, glaucoma, and adverse cardiovascular effects, mainly orthostatic hypotension and cardiac conduction abnormalities.[8] As mentioned, significantly more patients stop treatment due to adverse effects on TCAs compared to SSRIs.[3] A meta-analysis of 95 RCTs of inpatients/outpatients with unipolar major depression showed significantly lower rates of treatment discontinuations due to side-effects in the SSRI-treated population when compared to TCAs.[4] However, when comparing the tolerability of venlafaxine versus SSRIs, no significant difference could be found due to adverse reactions.[5-6] Therefore, it has been suggested that venlafaxine is better tolerated when compared to TCAs. Venlafaxine is an antidepressant with dual mechanisms of action: venlafaxine selectively inhibits serotonin at low doses (75 mg/day) whereas at high doses (375 mg/day) it inhibits both serotonin and noradrenaline reuptake,[9] and to a small degree dopamine.[10] An interesting effect of mixed uptake

inhibitors, such as venlafaxine and imipramine, is the regulation of the permeability of the blood-brain barrier, found in animal studies, which could partially explain their antidepressant effect.[11]

As mentioned, both TCAs (especially in inpatient populations) and venlafaxine appear to be more effective than SSRIs for the treatment of depression. However, it is uncertain whether TCAs and venlafaxine have comparable efficacy[7] and it is unclear whether venlafaxine is better tolerated in comparison to TCAs. When treating unipolar psychotic depression, there was no significant difference in response rates and remission rates between imipramine and venlafaxine.[12] A systematic review was performed to investigate the relative efficacy and tolerability of (low dose) venlafaxine compared with (low dose) TCAs; no overall significant difference in treatment effect or withdrawals could be found[7]; however, the authors stated that, because of the heterogeneity of the odds ratios, one cannot conclude that TCAs and venlafaxine are of equal efficacy.

This study compares the antidepressant efficacy of venlafaxine and imipramine among inpatients with a major depressive episode. Although others have compared the efficacy of venlafaxine with imipramine,[13-15] two of these studies were performed in an outpatient setting and none used dose adjustment based on targeted plasma levels of imipramine. Furthermore, all three studies used a relatively low mean daily dose of venlafaxine (75-182 mg/day) and did not restrict the use of benzodiazepines, which could mask the diagnosis and/or effects of the antidepressants.

Aim of the study

The present study is designed to compare the antidepressant efficacy of high-dose (375 mg/day) venlafaxine with plasma level-targeted dose imipramine in severely depressed inpatients (both with and without psychotic features).

METHODS

Study design and patient selection

The study was performed in a single centre: the inpatient depression unit of the Department of Psychiatry of the Erasmus Medical Centre in Rotterdam. The unit has a regional function for treatment of uncomplicated depressed patients and a super-regional function for treatment of refractory depressed patients. Recruitment took place between March 2005 and March 2010. Routinely psychotropic drugs are discontinued after admission. After a drug-free wash-out period of seven days, during

which period diagnosis was confirmed with the Structural Clinical Interview for DSM-IV Axis I disorders,[16] depressed patients were screened for inclusion and exclusion criteria. Both depression with psychotic features and depression with melancholic features are defined according to DSM-IV criteria. Included were patients aged 18-65 years, diagnosed with a major depressive disorder according to the DSM-IV criteria, single or recurrent episode and a score ≥ 17 on the 17-item Hamilton Rating Scale for Depression (HAM-D). Excluded were patients with bipolar disorder, schizophrenia or other primary psychotic disorder, refractoriness to adequate treatment with imipramine or venlafaxine during the index episode, drug or alcohol dependence during the last 3 months, mental retardation (IQ < 80), pregnancy or possibility of pregnancy, breastfeeding, serious medical illness affecting the central nervous system (e.g. Parkinson, SLE, brain tumour, CVA), relevant medical illness as contra-indications for the use of study medication such as recent myocardial infarction and severe liver or kidney failure, medication affecting the central nervous system [e.g. antidepressants and/or antipsychotics other than study medication, steroids, mood stabilisers, benzodiazepines (if not being tapered) > 3 mg lorazepam or equivalent], and a direct indication for electroconvulsive therapy.

About two years after the start of the study, we wrote an addendum to the protocol in order to include patients aged ≥ 65 years, provided that their first episode of depression had occurred before age 65 years. This addendum was approved by the Ethics Committee.

Eligible patients provided written informed consent after study procedures were fully explained. Patients were randomly allocated to a double-blind treatment with either imipramine or venlafaxine. Randomization was performed by the department of Pharmacy from the Erasmus MC using a random number table which is generated by the computer. The dose of imipramine was adjusted for each patient to a predefined blood level of 200-300 ng/ml (imipramine + desipramine).[17] The dose of venlafaxine was increased gradually to 300-375 mg/day. Two weeks after the start of study medication the dose was held constant. The study medication was supplied by the department of Pharmacy from the Erasmus MC using a double-dummy technique. All study medication was taken in the presence of the nursing staff. Dose adjustment based on plasma levels of imipramine and adverse effects were performed by an independent psychiatrist, keeping the study blind for the treating physician and the investigators. The HAM-D and the Clinical Global Impression scale (CGI) were scored at baseline and weekly thereafter. Outcome was assessed after seven weeks of acute treatment. All assessments were done by the two research psychiatrists (WWvdB, TKB). To ensure comparable ratings, interrater reliability sessions took place 10 times per year during the study. Excellent interrater reliability was achieved (κ=0.95) between the participating psychiatrist

regarding the total score on the HAM-D. Of the 85 patients included in the analyses, 20 patients, suffering from psychotic depression, participated in a similar double-blind comparison between imipramine and venlafaxine, which was reported by Wijkstra et al.[12]

Measures

For imipramine the dose administered was adjusted for each patient to obtain a predefined blood level of 200-300 ng/ml (sum of imipramine + desipramine). Plasma levels of imipramine were monitored weekly by an independent psychiatrist. Adverse effects for both imipramine and venlafaxine were monitored weekly by an independent psychiatrist. The vital signs (pulse, blood pressure and weight) were determined weekly. The patients were evaluated on a weekly basis using the HAM-D and the CGI.

Evaluation of blindness

After completing seven weeks of medication, the assessors were asked to guess which treatment each patient had received.

Concomitant treatment

No concomitant pharmacological drugs are allowed, with the exception of lorazepam (and equivalents) up to maximally 3 mg/day in case of severe anxiety. Analgetics, oral contraceptives and other medication not affecting the central nervous system were allowed.

Statistical analyses

Based on previous studies, the assumption for a power analysis was that 50% of patients would respond to imipramine.[1-2] A difference of 25% in response would be clinically relevant. With an α of 0.05 and a β of 0.20 (power 80%), it was planned to include two groups of 58 patients.

For this analysis, a SPSS software package was used. The statistical significance was defined as $p<0.05$. The primary effect measure in this trial was the difference in the proportion of responders and the difference in proportion of remitters after seven weeks between treatment with imipramine and venlafaxine. The difference in the proportion of responders and the difference in the proportion of remitters was analysed using Fisher's exact test and the last observation carried forward. The response criterion was defined a priori as a reduction of 50% or more on the HAM-D score after seven weeks of acute antidepressant treatment compared to the baseline HAM-D score. A difference of 25% in response was considered clinically relevant. The remission criterion was defined

a priori as a HAM-D score ≤ 7 after seven weeks of acute antidepressant treatment. In addition, the odds ratio (OR) of the chance of meeting the response and remission criterion was estimated using logistic regression analysis, adjusted for the pre-specified co-variable: psychotic features.

For the secondary effect measure, Kaplan-Meier curves were constructed for the graphical comparison of time-related response and time-related remission between the two treatment groups. Differences in time to response and time to remission were analysed using Cox proportional hazards regression model, adjusted for the following pre-defined co-variables: psychotic features, duration of the current episode and previous antidepressant treatment during the current episode: the degree of previous antidepressant treatment during the current episode was evaluated using the Antidepressant Treatment History Form (ATHF). Dropouts were censored at the time of drop-out. In addition, the mean reduction in HAM-D scores was analysed using mixed model analysis, adjusted for psychotic features, duration of the current episode, and previous antidepressant treatment during the current episode. Clinically relevant is a difference between the two treatment groups of at least 4 points reduction of the mean HAM-D scores.

Ethical considerations

The protocol was approved by the Medical Ethics Committee of the Erasmus MC Rotterdam. The protocol was carried out in accordance with the ethical standards laid down in the Declaration of Helsinki (1964), as amended in Edinburgh (2000).

RESULTS

Patient population and drop-outs

A total of 85 patients were analysed (Fig. 1): 43 patients received treatment with imipramine and 42 patients received treatment with venlafaxine (Table 1). The mean baseline HAM-D score for the imipramine treatment group was 27.4 (SD ± 5.2) and for the venlafaxine treatment group it was 26.1 (SD ± 4.9) (Table 2). Six patients dropped-out during the study (Fig. 1).

Previously prescribed pharmacotherapy was rated using the ATHF, which assigns a score of 1-5 to a trial based on drug choice, dose, and duration of administration; adequate treatment is defined as at least one medication trial rating ≥ 3. Based on this definition,11

of the 43 patients allocated to imipramine (26%) and 14 of the 42 patients allocated to venlafaxine (33%) received a previous adequate treatment with antidepressants during the index episode.

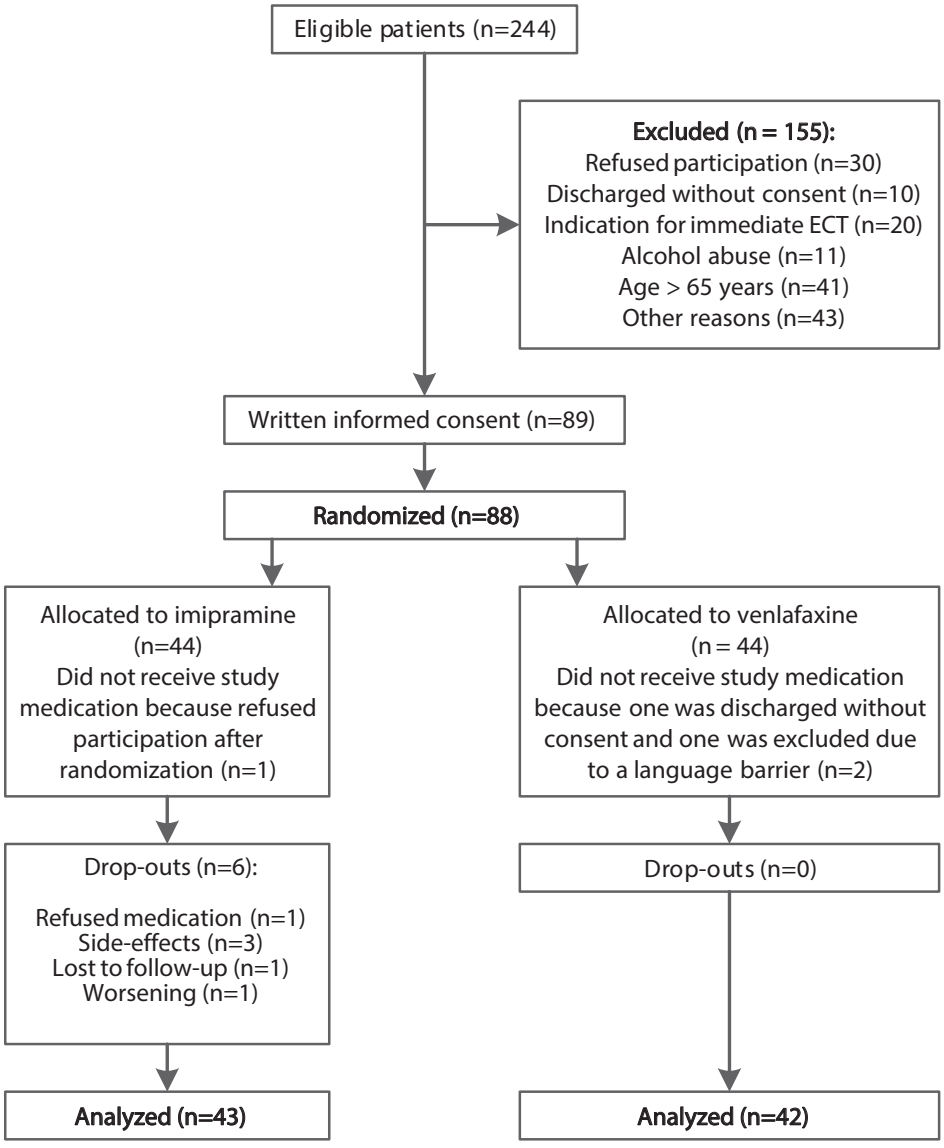

Figure 1. Flow diagram of participation in the study.

Table 1. Demographic and clinical characteristics of the patients included in the analysis.

Baseline variable	Imipramine (n=43)	Venlafaxine (n=42)	P-value
Age: mean ± SD (range) in years	56 ± 9.6 (32-82)	53 ± 9.2 (29-67)	0.28
Sex: male/female	18/25	21/21	0.52
Duration index episode ≤ 1 year > 1 year	 37 (86%) 6 (14%)	 34 (81%) 8 (19%)	0.53
First episode	17 (40%)	17 (40%)	0.93
Psychotic type	9 (21%)	11 (26%)	0.57
Melancholic features	42 (98%)	40 (95%)	0.54
Adequate pre-treatment with antidepressants	11 (26%)	14 (33%)	0.43
Baseline HAM-D score, mean ± SD (range)	27.4 ± 5.2 (18-37)	26.1 ± 4.9 (18-35)	0.24
History of suicide attempt(s)	9 (21%)	15 (36%)	0.13
Education level: lower than high school	6/43 (14%)	3/42 (7%)	

Table 2. Mean Hamilton rating scale of depression (HAM-D) scores at baseline and after 7 weeks of antidepressant treatment.

	Imipramine (n=43)	Venlafaxine (n=42)	P-value
Baseline HAM-D ± SD	27.4 ± 5.2	26.1 ± 4.9	0.24
Endpoint HAM-D ± SD	16.6 ± 9.4	13.8 ± 10.0	0.15

Blood levels and doses

The mean daily dose after seven weeks treatment for imipramine was 206.1 (SD ± 89.4, range 50-450) mg/day with a mean blood level of imipramine + desmethylimipramine of 281.7 (SD ± 68.2, range 134.0-432.0) ng/ml. The mean daily dose after seven weeks treatment for venlafaxine was 371.4 (SD ± 16.2, range 300-375) mg/day.

Concomitant medication

Five patients on imipramine treatment (12%) and seven patients on venlafaxine treatment (17%) were prescribed benzodiazepine during the trial, all of which stayed under the predefined maximum dosage of lorazepam 3 mg/day (or equivalent). The total number of patients using benzodiazepine was 12/85 (14%) which was ignored in the analyses because of the small number of patients. Of the 85 patients, two were

treated with haloperidol 2 mg/day, one was a responder (imipramine) and one was a non-responder (venlafaxine); similarly, this was ignored in the analyses because of the small number of patients.

Treatment effects

According to the a priori defined criterion of a 50% reduction or more on the HAM-D score, 17 of 43 (39.5%) patients on imipramine were responders compared to 21 of 42 (50%) patients on venlafaxine. There was no significant difference (p=0.39) in the proportion of responders according to Fisher's exact test. Using logistic regression analysis adjusted for psychotic features, there is no significant association between the type of antidepressant used and the chance of meeting the response criterion (OR=1.51, p=0.35, 95% CI 0.64-3.58).

According to the a priori defined criterion of a HAM-D score ≤ 7, 10 of 43 (23.3%) patients on imipramine were remitters compared to 15 of 42 (35.7%) patients on venlafaxine. There was no significant difference (p=0.24) in the proportion of remitters according to Fisher's exact test. Using logistic regression analysis adjusted for psychotic features, there was no significant association between the type of antidepressant used and the chance of meeting the remission criterion (OR=1.79, p=0.23, 95% CI 0.69-4.65).

There was no significant difference (p=0.18) in time to response between the two treatment groups using Kaplan-Meier curves. There was no significant difference in time to response using the Cox proportional hazards regression model, adjusted for psychotic features, duration of the current episode and previous antidepressant treatment during the current episode. The response rate ratio for venlafaxine relative to imipramine for a 50% reduction on the HAM-D was 1.51 (p=0.18, 95% CI 0.82-2.78).

There was no significant difference (p=0.33) in time to remission between the two treatment groups using Kaplan-Meier curves. There was no significant difference in time to remission using the Cox proportional hazards regression model, adjusted for psychotic features, duration of the current episode and previous antidepressant treatment during the current episode. The response rate ratio for venlafaxine relative to imipramine for a HAM-D score ≤ 7 was 1.72 (p=0.22, 95% CI 0.73-4.09).

The mean reduction of the HAM-D score in the venlafaxine treatment group was 2.02 points per week (p<0.0005, 95% CI 1.66-2.37) using mixed model analysis adjusted for psychotic features, duration of the current episode and previous antidepressant treatment during the current episode. The mean reduction of the HAM-D score in the imipramine treatment group was 1.65 points per week (p<0.0005, 95% CI 1.28-2.02) using

mixed model analysis adjusted for psychotic features, duration of the current episode and previous antidepressant treatment during the current episode. No difference in weekly mean reduction of the HAM-D score between both treatment groups was found (p=0.15, 95% CI -0.13-0.87).

Treatment effects in patients without psychotic features

Additionally, we analysed a subpopulation filtering out those patients with psychotic features. In total 65 patients were included in this analysis, 34 patients received treatment with imipramine and 31 patients received treatment with venlafaxine. According to the a priori defined criterion of a 50% reduction or more on the HAM-D score, 11 of 34 (32.4%) patients on imipramine were responders compared to 17 of 31 (54.8%) patients on venlafaxine. There was no significant difference (p=0.083) in the proportion of responders according to Fisher's exact test. According to the a priori defined criterion of a HAM-D score ≤ 7, 5 of 34 (14.7%) patients on imipramine were remitters compared to 12 of 31 (38.7%) patients on venlafaxine. There was a significant difference (p=0.046) in the proportion of remitters according to Fisher's exact test.

Adverse events

Three patients taking imipramine dropped-out due to adverse events (urine retention, orthostatic hypotension, agitation). Other non-serious common adverse events are presented in Table 3. Both constipation and agitation occurred significantly more often in the imipramine-treated sample.

Table 3. Most common adverse events (AEs) with imipramine and venlafaxine.

Event	Imipramine (n=43)		Venlafaxine (n=42)	
	No. of AEs	%	No. of AEs	%
Dizziness	2	5	3	7
Agitation[a]	10	23	3	7
Headache	3	7	1	2
Dry mouth	12	28	7	17
Tremor	1	2	3	7
Transpiration	7	16	5	12
Constipation[a]	8	19	1	2

[a] significant difference (p=0.03) between treatment groups according to Fisher's exact test.

DISCUSSION

This study demonstrates that treatment with high-dose venlafaxine is at least equal in efficacy to imipramine dosed according to a predefined plasma level in a sample of severely depressed inpatients. Both the proportion of responders (50.0% vs. 39.5%), and the proportion of remitters (35.7% vs. 23.3%) is larger in the venlafaxine-treated group, but not at a significant level. Also, the mean reduction in HAM-D score (12.3 vs. 10.8 points) is larger in the venlafaxine-treated group, again not at a significant level. When analyzing the subgroup of patients without psychotic features (n=65), there is a trend towards a higher response rate in the venlafaxine-treated sample (54.8% vs. 32.4%). Venlafaxine treatment leads to a significantly higher remission rate in the nonpsychotic subgroup (38.7% vs. 14.7%).

In the present sample, the accuracy of diagnosis was greatly enhanced by both our routine drug-free observation period and confirmation of the diagnosis by a semi-structured interview conducted by clinicians. We consider this to be a major strength of the present study.

Both the response and remission rate to imipramine treatment were lower compared to previous imipramine-controlled studies with similar methodology performed at our depression unit.[1-2] In these two (imipramine-controlled) latter studies, the proportion of imipramine-treated patients achieving response and remission was 50% and nearly 30%, respectively. Comparing the present study with the two previous studies reveals that the patient sample of the present study is slightly older and the proportion of patients with a previous depressive episode is slightly larger (60% vs. 45%). In all three studies, the proportion of patients with psychotic depression and the baseline HAM-D scores are comparable. We found no obvious explanation for the mediocre efficacy of imipramine in the present study.

High-dose venlafaxine appears to be a relatively effective treatment for severe melancholic depression. We used relatively high doses of venlafaxine range 300-375 mg/day. Harrison et al.[10] reported that venlafaxine is tolerated fairly well at even higher doses up to 600 mg daily. The response and remission rate to venlafaxine in the present study is almost the same as the results for imipramine in earlier studies at our depression unit.[1-2]

Comparison with previous reports

Three studies that compared the efficacy of imipramine and venlafaxine in a double-blind RCT found no difference in efficacy between the two antidepressants.[13-15] All three studies used relatively low mean doses of both imipramine (176 mg, max. 200 mg, and 116 mg, respectively) and venlafaxine (182 mg, 150 mg, and 125 mg, respectively). Remarkably, these relatively low doses seem to have had no negative effect on the response rate of both antidepressants: the response rate to imipramine was 79%, 61%, and 66%, respectively. Venlafaxine treatment had a response rate of 90%, 52%, and 83%, respectively. These favourable results are surprising, since the efficacy of venlafaxine is higher at dosages ≥ 225 mg compared with dosages ≤150 mg.[18] The same applies to the average doses of imipramine, which are also relatively low. Using plasma level-targeted dosing can greatly enhance efficacy and compliance. Therapeutic drug monitoring is state-of the-art for imipramine and is necessary for imipramine not to fall short of its full efficacy potential.[19-20] In a study on 113 patients who received imipramine with plasma level-targeted dosing, the dose range to attain a therapeutic plasma level was 50-450 mg/day.[21] The mean daily dose necessary to attain the target plasma level was 248 mg. In that study, when receiving 150 mg daily (a fairly usual dose in clinical trials) only 23% of the patients attained a therapeutic plasma level.

In all three previous studies[13-15] the drop-out rate was fairly high, i.e. about 30% compared to 7% in the present study. A low drop-out rate appears to contribute to the discriminative power in RCTs comparing antidepressants.[22]

In the present study only 14% of patients were treated with benzodiazepines, which is exceptional for comparative trials of antidepressants. Unfortunately, the three previous studies comparing imipramine and venlafaxine only mention that concurrent use of benzodiazepines is allowed, but they do not report the proportion of patients receiving benzodiazepines. Angst[23] has argued that co-medication with benzodiazepines increases response to placebo treatment and considerably decreases the power of a comparative study. It may be of significance, therefore, that the two previous studies that were placebo-controlled[13,15] reported response rates to placebo of ≥ 50%.

Study limitations

The main limitation of the present study is that it is underpowered. Because we were unsuccessful in getting the study started in the second centre, only 85 patients were included instead of the planned 116. Nevertheless, we can conclude that venlafaxine is at least equal in efficacy to imipramine for severely depressed inpatients. Another limitation of the present study could be that venlafaxine was increased gradually to

maximum dosage instead of measuring blood levels of venlafaxine. However, dose-blood level relationships have not been established for venlafaxine.[24] To minimize non-compliance, all study medication (imipramine and venlafaxine) was taken in the presence of the nursing staff.

In conclusion, previous studies, using suboptimal doses in less severely depressed patients suggested a similar antidepressant efficacy of imipramine, compared with venlafaxine. HAM-D score ≤ 7, 10 of 43 (23.3%) patients on imipramine were remitters compared to 15 of 42 (35.7%) patients on venlafaxine. The present study, characterized by a very low drop-out rate and very limited use of concurrent psychotropic drugs, used optimal doses in severely depressed inpatients, and showed that venlafaxine is at least equal in efficacy to imipramine. The subgroup of patients without psychotic features showed a trend towards a higher response rate and a significantly higher remission rate to venlafaxine. However, whether the efficacy of venlafaxine is in fact superior to that of imipramine cannot be concluded from the present data.

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CHAPTER 3

A randomized clinical trial comparing two two-phase treatment strategies for in-patients with severe depression

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ABSTRACT

Objective: To compare the efficacy of two antidepressant treatment strategies in severely depressed in-patients, that is, imipramine vs. venlafaxine, both with subsequent lithium addition in non-responders.

Method: In-patients (n=88) with major depressive disorder were randomized to 7-week treatment with imipramine or venlafaxine (phase I). All non-responders (n=44) received 4-week plasma level-targeted dose lithium addition (phase II). Efficacy was evaluated after 11 weeks of treatment.

Results: Analyzing phases I and II combined, non-inferiority was established and the difference in the proportion of responders (HAM-D score reduction ≥ 50%) by the end of phase II demonstrated the venlafaxine-lithium treatment strategy to be significantly superior to the imipramine-lithium treatment strategy (77% vs. 52%) ($\chi^2(1)=6.03$; P=0.01). Regarding remission (HAM-D score ≤ 7), 15 of 44 (34%) patients in the imipramine-lithium treatment group were remitters compared to 22 of 44 (50%) patients in the venlafaxine-lithium treatment group, a non-significant difference. Patients in the venlafaxine-lithium treatment group had a non-significant larger mean HAM-D score reduction compared with patients in the imipramine-lithium treatment group (16.1 vs. 13.5 points, respectively; Cohen's $d = 0.30$).

Conclusion: The venlafaxine-lithium treatment strategy can be considered a valuable alternative for the imipramine-lithium treatment strategy in the treatment of severely depressed in-patients.

Significant outcomes

- Based on the predefined non-inferiority margin, non-inferiority was established, and subsequently, the difference in the proportion of responders when analyzing phases I and II combined demonstrated the venlafaxine-lithium treatment strategy to be significantly superior to the imipramine-lithium treatment strategy (77% vs. 52%) ($\chi^2(1)=6.03$; P=0.01).
- By taking into account the efficacy of optimal first-line treatment in phase I, the present two-phase study design allows for an accurate quantification of the efficacy of subsequent lithium addition in non-responders in phase II.
- This study is the first to compare the two antidepressant treatment strategies and provides new and clinically valuable insights, that is, the results in favor of the venlafaxine-lithium treatment strategy add to the current knowledge on antidepressant treatment strategies for treatment-resistant major depressive disorder.

Limitations

- The study was underpowered. Nevertheless, a significant superiority was shown in favor of the venlafaxine-lithium treatment strategy.
- The study did not include a placebo control group; therefore, it is uncertain whether placebo response biased the results.
- The generalizability of the results is limited due to a homogenous group of severely depressed in-patients, which may also be considered a major strength of the study.

INTRODUCTION

Despite that both tricyclic antidepressants (TCAs) and venlafaxine have a well-demonstrated clinical efficacy as first-line antidepressant for the treatment of major depressive disorder (MDD),[1-4] treatment-resistant depression remains a major clinical challenge. Around 30–50% of patients with MDD are non-responders to first-line antidepressant treatment, irrespective of the type of antidepressant used.[5] Clinical practice guidelines recommend lithium addition for patients suffering from treatment-resistant depression; lithium addition is the best-investigated second-line augmentation treatment, in accordance with several meta-analyses.[5-8] A meta-analysis of 10 randomized controlled trials concluded that addition of lithium to various antidepressants (mostly TCAs) was significantly more effective than the addition of placebo in the depressive phase of unipolar or bipolar disorder.[7]

Lithium addition to imipramine is significantly more effective than similar strategies with lithium addition to mirtazapine[9] or fluvoxamine.[10] Lithium addition to venlafaxine has only rarely been studied: two small open-label uncontrolled studies reported that it was effective in treatment-resistant depression.[11-12] No previous study has investigated whether, in severely depressed inpatients, the treatment strategy of venlafaxine and subsequent lithium addition in non-responders is comparable in efficacy to the treatment strategy of imipramine and subsequent lithium addition in non-responders.

A two-phase study design is important because only when taking into account the efficacy of optimal first-line treatment can the efficacy of subsequent lithium addition in non-responders be accurately quantified. This study is a two-phase, double-blind, randomized, non-inferiority trial comparing the efficacy and tolerability of two antidepressant treatment strategies in severely depressed in-patients: *strategy A* plasma level-targeted dose imipramine (phase I) and subsequent lithium addition in non-responders to imipramine (phase II); *strategy B* high-dose (375 mg/day) venlafaxine (phase I) and subsequent lithium addition in non-responders to venlafaxine (phase II). It was hypothesized that the two treatment strategies will have a comparable efficacy in in-patients with MDD, that is, that the venlafaxine-lithium treatment strategy is no less effective than the imipramine-lithium treatment strategy.

Aims of the study

The aim of the study was to compare the efficacy of two antidepressant treatment strategies (phases I and II combined) in severely depressed in-patients, that is, plasma level-targeted dose imipramine and subsequent lithium addition in non-responders vs. high-dose (375 mg/day) venlafaxine and subsequent lithium addition in non-responders.

METHOD

Patients

The study was conducted at the in-patient depression unit of the Department of Psychiatry of the Erasmus Medical Center Rotterdam (EMCR), between March 2005 and March 2010.

Included were in-patients aged 18–65 years, diagnosed with major depressive disorder (MDD), single or recurrent episode, and a baseline score ≥ 17 on the 17-item Hamilton Rating Scale for Depression (HAM-D).[13] An addendum to the protocol allowed for the inclusion of eligible patients aged ≥ 65 years. The diagnosis MDD was confirmed with the Structural Clinical Interview for DSM-IV Axis I disorders[14] during a drug-free washout period of 1 week. Depressed patients both with and without psychotic features were included.

Excluded were patients with bipolar I/II disorder (characterized by a history of at least one (hypo)manic episode), primary psychotic disorder, refractoriness to adequate treatment with imipramine or venlafaxine during the index episode, drug or alcohol dependence during the last 3 months, mental retardation (IQ < 80), (possibility of) pregnancy, breastfeeding, serious medical illness affecting the central nervous system, relevant medical illness as contraindications for the use of study medication or lithium, and a direct indication for electroconvulsive therapy (ECT). Also excluded were patients using psychotropic medication other than study medication; benzodiazepines at a dose of ≤ 3 mg lorazepam or equivalent were allowed as well as analgetics, oral contraceptives and other medication not affecting the central nervous system. After study procedures were fully explained, all eligible patients provided written informed consent.

Procedures

Phase I: eligible patients were randomized (using a random number table generated by the computer with an allocation ratio of 1 : 1) for 7-week double-blind treatment with either imipramine or venlafaxine. Using a double-dummy technique, the study medication was supplied by the Department of Pharmacy from the EMCR. Imipramine was administered once a day starting with 75 mg and doubled after 2 days; for each patient, the dose was adjusted to a predefined plasma level of 200–300 ng/ml (sum of imipramine + desipramine).[15] Patients in the imipramine treatment group were at an adequate plasma level at day 21 (dose-adjusted at day 15), and the intention was to treat at least 4 weeks (28 days) at adequate plasma levels; therefore, patients received 7-week double-blind antidepressant treatment. Venlafaxine was administered once a day starting with 75 mg; the dose was increased gradually to 300 mg/day at day 11, and in case of non-response at day 14, the venlafaxine dose was increased to 375 mg/day at day 15. Similarly, the intention was to treat at least 4 weeks (28 days) between 300 mg and 375 mg; therefore, patients received 7-week double-blind antidepressant treatment. The results of phase I are presented elsewhere.[4]

Phase II: an open trial of 4-week lithium addition for patients achieving insufficient improvement on antidepressant monotherapy during phase I. Patients with a HAM-D score > 13 after 7 weeks of treatment were included in phase II. The antidepressant from phase I (imipramine or venlafaxine) was continued at the same dose while maintaining double-blind conditions. After screening for contraindications, lithium addition was administered under open conditions once a day starting with 600 mg/day; for each patient, the lithium dose was adjusted to a predefined plasma level of 0.6–1.0 mmol/L.[16] Phases I and II combined form an 11-week treatment strategy which was conducted entirely while the patients were hospitalized.

Measures

Plasma levels (drawn 12 h after the last dose) and adverse effects during phases I and II were monitored weekly by an independent psychiatrist. Vital signs were determined weekly. Blind to the treatment option, the HAM-D was scored weekly by two research psychiatrists (WWvdB, TKB), with proven excellent inter-rater reliability (κ=0.95) regarding the total score on HAM-D.

Statistical analysis

This study is a two-phase non-inferiority trial.[17] The non-inferiority margin was based on clinical significance. Based on previous studies,[9-10] the proportion of response was estimated at 65% for the imipramine-lithium treatment group and a difference of 25% was considered clinically relevant. Power analysis showed that 58 patients per treatment group were required to exclude a difference in favor of the imipramine-lithium treatment group of > 25% (power of 80%; alpha of 5%). Therefore, it was aimed to include 116 patients in phase I, resulting in 58 patients in phase II by assuming a 50% non-responder rate by the end of phase I. Assuming 5% of the patients did not give informed consent and 10% of the patients dropped out before randomization, it was planned to select a total of 138 patients in phase I of the study.

Data were analyzed according to the Consort Guidelines 2010,[18] on an intention-to-treat basis, using SPSS 21 software. Efficacy was evaluated by analyzing phase I and phase II combined. The last observation carried-forward (LOCF) method, and the mean of surrounding values were used to account for missing values (i.e., drop-outs). The data were tested for normality, and no outliers were found. Differences in demographic and clinical characteristics and adverse events between the two treatment groups were tested using Student's *t*-test (in case of continuous variables) and a chi-square test or Fisher's exact test (FET) (in case of categorical variables).

The primary outcome criterion evaluated non-inferiority using the 95% bilateral CI for the difference in the proportion of responders. As previously mentioned, the non-inferiority margin for the primary outcome was estimated as a difference of 25%. Response was defined a priori as a reduction of ≥ 50% on the HAM-D score, relative to the baseline HAM-D score in phase I. The number of patients achieving response was determined by the end of phase I (after 7 weeks) and phase II (after 11 weeks). The 95% CI for the difference in the proportion of responders between the two treatment groups by the end of phase II was calculated using the Wilson procedure without a correction for continuity.[19] Subsequently, to test for superiority, differences in the proportion of responders between the two treatment groups were determined using a chi-square test.

As secondary outcome criterion, remission was used, defined a priori as a final HAM-D score ≤ 7. Remission was analyzed in a similar manner as the response analysis. As an additional outcome criterion, the difference in the mean HAM-D score reduction by the end of phase I and by the end of phase II (both relative to baseline phase I) between the two treatment groups was tested using Student's *t*-test. Effect sizes were calculated

using Cohen's *d*, taking the mean HAM-D score reduction and the standard deviation (SD) for the mean HAM-D score reduction by the end of phase II of each treatment group.[20]

Additionally, time to response and time to remission were analyzed using the Kaplan–Meier method.[21-22] Log-rank tests were used as an a priori planned analysis to test whether the survival curves between the two treatment groups were equivalent.

To assess the stability of the findings, analyses were repeated in the completers' subsample. In a similar manner, analyses were performed on an intention-to-treat basis in a subpopulation, analyzing phase II separately. Additional analysis was performed on a subset of the combined phase I and phase II data in which patients with psychotic features were removed from the analysis (modified intention to treat).

Ethical considerations

Both the protocol and the addendum were approved by the Medical Ethics Committee of the EMCR. The protocol is carried out in accordance with the Declaration of Helsinki (1964), as amended in Edinburgh (2000).

RESULTS

Patient population and drop-outs

In total, 88 patients were randomized for phase I (Fig. 1): 44 patients received imipramine and 44 patients received venlafaxine. During phase I, eight (9%) patients dropped out (six patients in the imipramine treatment group and two patients in the venlafaxine treatment group). Of these, three patients dropped out after randomization, but before study medication was started: one refused participation after randomization, one was discharged without consent and one was excluded due to a language barrier. Thus, a total of 80 (91%) patients completed phase I. The demographic and clinical characteristics, including the mean baseline HAM-D score in phase I, are summarized in Table 1. Further, the proportion of responders and remitters by the end of phase I are summarized in Table 2.

In total, 44 (50%) patients met the inclusion criteria for phase II (Fig. 1): 24 patients received imipramine and lithium addition, whereas 20 patients received venlafaxine and lithium addition. During phase II, 10 (23%) patients dropped out (five patients in the imipramine-lithium treatment group and five patients in the venlafaxine-lithium

treatment group), and 34 (77%) patients completed phase II. The mean baseline HAM-D score in phase II for the imipramine-lithium treatment group was 22.2 (SD ± 5.3) (n=24) and for the venlafaxine-lithium treatment group was also 22.2 (SD ± 7.0) (n=20).

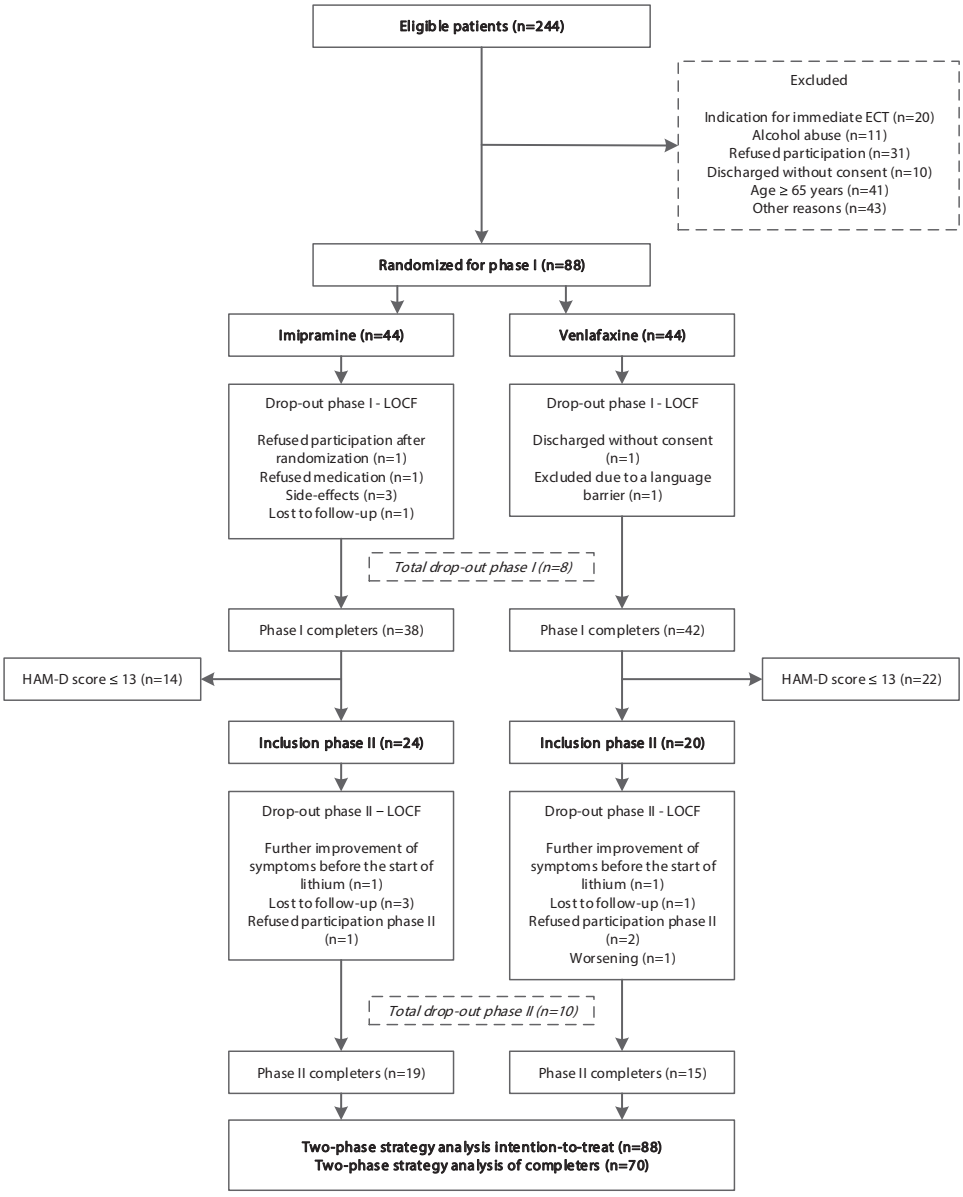

Figure 1. Patient flow through phase I and phase II of the study. ECT, electroconvulsive therapy; LOCF, last observation carried-forward.

Table 1. Demographic and clinical characteristics of the patients randomized for phase I and phase II combined.

Baseline variable	Imipramine (n=44)				Venlafaxine (n=44)				Test	*P* value
	Mean	SD	N	%	Mean	SD	N	%		
Age (years)	56	9.4			53	9.1			$t(1)=1.29$	0.20
Female sex			26	59			22	50	$X^2(1)=0.73$	0.39
Education: less than high school [b]			6	14			4	9		0.52 [a]
Duration of index episode [c] ≤ 1 year > 1 year			 37 6	 86 14			 34 8	 81 19	 $X^2(1)=0.40$	 0.53
First episode [b]			17	40			18	41	$X^2(1)=0.02$	0.90
Psychotic type			9	20			11	25	$X^2(1)=0.26$	0.61
Melancholic features [b]			42	98			42	95		0.99 [a]
Adequate pre-treatment with antidepressants [d]			11	27			15	34	$X^2(1)=0.53$	0.47
Baseline HAM-D score phase I	27.2	5.3			26.1	4.8			$t(1)=1.01$	0.31

[a] Fisher's exact test.
[b] Data missing n=1, refused participation after randomization.
[c] Data missing n=3, one refused participation after randomization, two are unknown.
[d] Data missing n=3, one refused participation after randomization, two are unknown. Adequate pre-treatment is defined as at least one medication trial rating ≥ 3 using the Antidepressant Treatment History Form (ATHF), which assigns a score of 1-5 to a trial based on drug choice, dose, and duration of administration.

Plasma levels and doses

Imipramine doses and imipramine plasma levels were available for 43 of 44 patients randomized for phase I; after 7-week treatment, the mean daily imipramine dose was 206.1 (SD ± 89.4, range 50–450) mg/day with a mean plasma level of 281.7 (SD ± 68.2, range 134.0–432.0) ng/ml. Venlafaxine doses were available for 42 of 44 patients randomized for phase I; after 7-week treatment, the mean daily venlafaxine dose was 371.4 (SD ± 16.2, range 300–375) mg/day.

Lithium doses and lithium plasma levels were available for 40 of 44 patients included in phase II. After 4-week treatment, the mean daily lithium dose for the imipramine treatment group was 785.7 (SD ± 190.5, range 500–1200) mg/day with a mean lithium plasma level of 0.77 (SD ± 0.20, range 0.27–1.30) mmol/L (n=21), and the mean daily lithium dose for the venlafaxine treatment group was 968.4 (SD ± 260.5, range 600–1400) mg/day with a mean lithium plasma level of 0.77 (SD ± 0.12, range 0.59–0.98) mmol/L (n=19). The missing dosing information in both phases I (n=3) and II (n=4) was due to drop-outs.

Table 2. Number of responders, remitters, and the mean HAM-D score reduction by the end of phase I (after 7 weeks of antidepressant monotherapy) and by the end of phase II (after 11 weeks of antidepressant-lithium treatment strategy).

Intention-to-treat analysis (n=88)										
Clinical measure	**Imipramine (n=44)**				**Venlafaxine (n=44)**				**Test**	***P* value**
	Mean	**SD**	**N**	**%**	**Mean**	**SD**	**N**	**%**		
Number of responders										
Phase I			17	39			21	48	$X^2(1)=0.74$	0.39
Phase II			23	52			34	77	$X^2(1)=6.03$	0.01
Number of remitters										
Phase I			10	23			15	34	$X^2(1)=1.40$	0.24
Phase II			15	34			22	50	$X^2(1)=2.29$	0.13
HAM-D score reduction										
Phase I	10.57	10.87			11.73	8.74			$t(1)=0.55$	0.58
Phase II	13.45	9.95			16.14	8.17			$t(1)=1.38$	0.17
Analysis of completers (n=70)										
Clinical measure	**Imipramine (n=33)**				**Venlafaxine (n=37)**				**Test**	***P* value**
	Mean	**SD**	**N**	**%**	**Mean**	**SD**	**N**	**%**		
Number of responders										
Phase I			14	42			21	57	$X^2(1)=1.43$	0.23
Phase II			20	61			33	89	$X^2(1)=7.75$	0.01
Number of remitters										
Phase I			10	30			15	41	$X^2(1)=0.80$	0.37
Phase II			15	46			22	60	$X^2(1)=1.37$	0.24
HAM-D score reduction										
Phase I	11.52	11.60			12.97	8.71			$t(1)=0.60$	0.55
Phase II	15.52	9.60			18.05	7.05			$t(1)=1.27$	0.21

Concomitant treatment

Benzodiazepines were prescribed in 12 of 88 (14%) patients during phases I and II [all stayed under the predefined maximum dosage of lorazepam 3 mg/day (or equivalent)]: 5 patients on imipramine-lithium treatment group (11%) and seven patients on venlafaxine-lithium treatment group (16%). Haloperidol 2 mg/day was prescribed in case of agitation in two of 88 (2%) patients during phases I and II, one in each treatment group. Officially, the latter was a protocol violation however, as they were evenly distributed and the small number justified these two patients to be included in the analysis.

Efficacy of two-phase treatment strategies (intention-to-treat analysis, n=88)

According to the a priori defined criterion of a ≥ 50% reduction on the HAM-D score by the end of phase II (after an 11-week treatment strategy of phases I and II combined), 23 of 44 (52%) patients in the imipramine-lithium treatment group were responders compared to 34 of 44 (77%) patients in the venlafaxine-lithium treatment group (Table 2). The difference in the proportion of responders between the two groups was +25% (95% CI 5–42) in favor of the venlafaxine-lithium treatment group, which established non-inferiority based on the predefined non-inferiority margin. Subsequently, superiority was tested as the lower bound of the 95% CI was >0. Significant superiority of the venlafaxine-lithium treatment group was shown; the difference in the proportion of responders by the end of phase II was significant, in favor of the venlafaxine-lithium treatment strategy ($\chi^2(1)=6.03$; P=0.01).

According to the a priori-defined criterion of a HAM-D score ≤ 7 by the end of phase II, 15 of 44 (34%) patients in the imipramine-lithium treatment group were remitters compared to 22 of 44 (50%) patients in the venlafaxine-lithium treatment group: this was a non-significant difference ($\chi^2(1)=2.29$; P=0.13) (Table 2). The mean HAM-D score reduction by the end of phase II (after an 11-week treatment strategy of phases I and II combined) was 13.45 (SD ± 9.95) points for the patients in the imipramine-lithium treatment group and 16.14 (SD ± 8.17) points for the patients in the venlafaxine-lithium treatment group (Table 2). Patients in the latter had a non-significant larger mean HAM-D score reduction from baseline phase I until endpoint phase II compared to patients in the imipramine-lithium treatment group (a small to moderate effect size, Cohen's d = 0.30, 95% CI -0.12–0.72).

The difference in time to response between the two treatment strategies was showing a trend in favor of the venlafaxine-lithium treatment strategy ($\chi^2(1)=3.50$; P=0.06, log rank). Kaplan–Meier curves were constructed to compare time-related response between the two treatment strategies (Fig. 2). There was no significant difference ($\chi^2(1)=2.34$; P=0.13, log rank) in time to remission between the two treatment strategies.

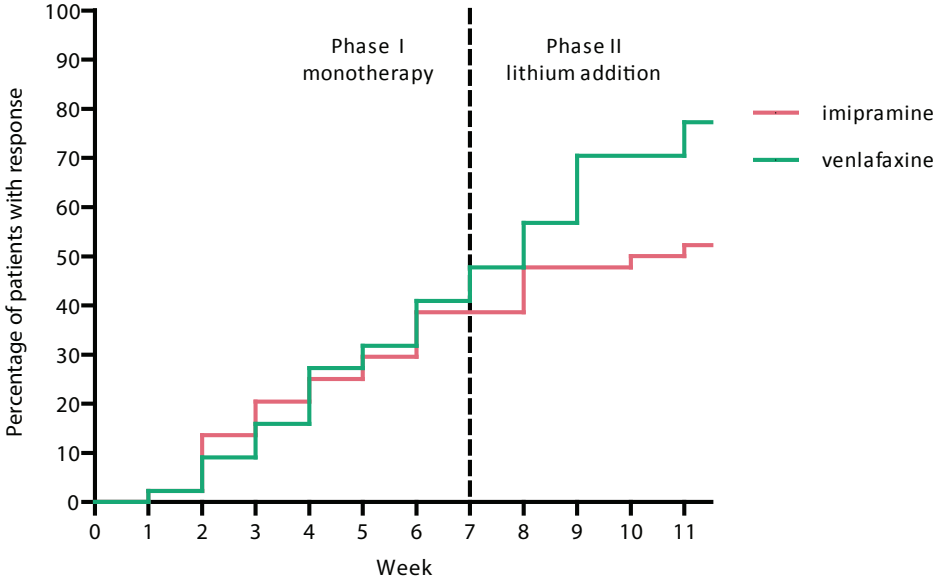

Figure 2. Time course of response: survival distributions divided into imipramine (n=44) and venlafaxine (n=44) ($\chi^2(1)=3.50$; P=0.06, log rank). Response is defined as ≥ 50% reduction on the HAM-D score.

Efficacy of two-phase treatment strategies (analysis of completers, n=70)

Analyses were repeated per protocol with all drop-outs from phase I (n=8) and phase II (n=10) removed. By the end of phase II (after an 11-week treatment strategy of phases I and II combined), 20 of 33 (61%) patients in the imipramine-lithium treatment group were responders compared to 33 of 37 (89%) patients in the venlafaxine-lithium treatment group (Table 2). The difference in the proportion of responders between the two groups was +28% (95% CI 8–47) in favor of the venlafaxine-lithium treatment group; thus, non-inferiority was established based on the predefined non-inferiority margin. Subsequently, superiority was tested in the analysis of completers. There was a

significant difference in the proportion of responders by the end of phase II ($\chi^2(1)=7.75$; P=0.01), and significant superiority of the venlafaxine-lithium treatment strategy was shown.

The number of remitters and the mean HAM-D score reduction of the completers' analysis by the end of phase II are summarized in Table 2; no significant differences were found. Patients in the venlafaxine-lithium treatment group had a nonsignificant larger mean HAM-D score reduction from baseline phase I until endpoint phase II compared to patients in the imipramine-lithium treatment group (a small to moderate effect size, Cohen's *d* = 0.30, 95% CI -0.17–0.78).

There was a significant difference ($\chi^2(1)=4.56$; P=0.03, log rank) in time to response in favor of the venlafaxine-lithium treatment strategy, but no significant difference ($\chi^2(1)=1.43$; P=0.23, log rank) in time to remission between the imipramine-lithium (n=33) and the venlafaxine-lithium (n=37) treatment groups.

Efficacy of phase II separately (n=44)

When analyzing phase II separately on an intention-to-treat basis (n=44), six of 24 (25%) patients in the imipramine-lithium treatment group were responders compared to 13 of 20 (65%) patients in the venlafaxine-lithium treatment group. The difference in the proportion of responders between the two groups was +40% (95% CI 11–61) in favor of the venlafaxine-lithium treatment group; thus again, non-inferiority was established. Subsequently, significant superiority was shown; there was a significant difference in the proportion of responders in favor of the venlafaxine-lithium treatment strategy ($\chi^2(1)=7.11$; P=0.01) when analyzing phase II separately.

There was no significant difference in the proportion of remitters ($\chi^2(1)=1.10$; P=0.29) when analyzing phase II separately: five of 24 (21%) patients in the imipramine-lithium treatment group were remitters compared to seven of 20 (35%) patients in the venlafaxine-lithium treatment group. When analyzing phase II separately, the mean HAM-D score reduction during phase II was 5.29 (SD ± 9.01) points for the patients in the imipramine-lithium treatment group (n=24) and 9.30 (SD ± 9.41) points for the patients in the venlafaxine-lithium treatment group (n=20). Patients in the venlafaxine-lithium treatment group had a non-significant higher mean HAM-D score reduction from baseline phase II until endpoint phase II compared with patients in the imipramine-lithium treatment group (a moderate effect size, Cohen's *d* = 0.44, 95% CI -0.16–1.04).

There was a significant difference ($\chi^2(1)=6.27$; P=0.01, log rank) in time to response in favor of the venlafaxine-lithium treatment strategy, but no significant difference ($\chi^2(1)=1.25$; P=0.26, log rank) in time to remission between the imipramine-lithium treatment group (n=24) and the venlafaxine-lithium treatment group (n=20) when analyzing phase II separately.

Efficacy in patients without psychotic features (n=68)

Analyses were repeated on a subset of the data in which patients with psychotic features were removed from the analysis (n=68). The data are not presented, but were of similar range and support the results of all previous analyses.

Adverse events

Analyzing phase II separately (n=44), no patients dropped out due to (non-)serious adverse events. There were no significant differences (FET) in the following non-serious common adverse events (reported as moderate and severe) between the imipramine-lithium and the venlafaxine-lithium treatment groups: tremor (n=7 vs. n=2, respectively), transpiration (n=8 vs. n=7, respectively), dry mouth (n=9 vs. n=4, respectively), diarrhea (n=0 for both treatment groups), myoclonus (n=1 for both treatment groups), nausea (n=6 vs. n=4, respectively), agitation (n=0 vs. n=1, respectively), anxiety (n=0 vs. n=1, respectively) and insomnia (n=1 vs. n=2, respectively) (Table 3).

Table 3. Most common adverse events with imipramine-lithium and venlafaxine-lithium (phase II separately).

Event	Imipramine-lithium (n=24)		Venlafaxine-lithium (n=20)		*P* value
	N	%	N	%	
Tremor	7	29	2	10	0.15 [a]
Transpiration	8	33	7	35	1.00 [a]
Dry mouth	9	38	4	20	0.32 [a]
Diarrhea	0	-	0	-	-
Myoclonus	1	4	1	5	1.00 [a]
Nausea	6	25	4	20	0.73 [a]
Agitation	0	-	1	5	0.46 [a]
Anxiety	0	-	1	5	0.46 [a]
Insomnia	1	4	2	10	0.58 [a]

[a] Fisher's exact test.

DISCUSSION

Although the present study was slightly underpowered, the difference in the proportion of responders between the two antidepressant treatment strategies met the predefined non-inferiority margin in favor of the antidepressant treatment strategy of high-dose venlafaxine and subsequent lithium addition in non-responders to venlafaxine, when compared to a similar strategy with imipramine. Subsequently testing for superiority, the difference in the proportion of responders by the end of phase II (52% vs. 77%), which is not accounted for by the difference at the end of phase I, demonstrated that the venlafaxine-lithium treatment strategy was significantly superior to the imipramine-lithium treatment strategy in a population of severely depressed in-patients. The stability of this finding is shown by the consistent superiority of the venlafaxine-lithium treatment strategy, that is, analysis of completers and subsample analysis in which patients with psychotic features were removed from the analysis. Further, the proportion of remitters by the end of phase II (34% vs. 50%) was larger for the venlafaxine-lithium treatment strategy, but not at the level of statistical significance. Using the mean HAM-D score reduction to analyze the two antidepressant treatment strategies, the effect size was small to moderate (Cohen's $d = 0.30$) in both the intention-to-treat and the completers' analysis; there was no significant difference between them.

Overall, the venlafaxine-lithium treatment strategy had a better response and there is no straightforward explanation. A suggested explanation might be that lithium addition in treatment-resistant depression may alter serotonin transmission to achieve treatment response[23] and the hypothesis that lithium addition works preferentially with serotonergic antidepressants, that is, venlafaxine.[24] Yet, contradicting this hypothesis is a previous lithium addition study which did not show a serotonergic agent to have superior efficacy, when compared to a tricyclic antidepressant.[10]

Severely depressed in-patients both with and without psychotic features were included in the present study. Including patients with psychotic features could be arguable as, for example, the American Psychiatric Association Practice Guideline for the treatment of patients with MDD recommends the combination of an antidepressant and an antipsychotic for the treatment of major depressive disorder with psychotic features, although it is also noted that the results of previous treatment studies were inconclusive.[25] A systematic review in the Cochrane Library also suggests the combination of an antidepressant plus an antipsychotic to be more effective than either treatment alone for treating psychotic depression.[26] However, it is noted by the authors that the evidence is limited and the conclusions cannot be generalized as they are based on

very few and small trials with different designs.[26] In two previous studies by our research group, imipramine was shown to be more effective in severely depressed patients with psychotic features when compared with severely depressed patients without psychotic features.[27-28] Based on these results, we chose similar inclusion criteria for the present study, deciding not to exclude severely depressed patients with psychotic features.

Major strengths of the present study include the two-phase study design and the optimal dosing of the antidepressant treatment in phase I. This strategy is in accordance with the American Psychiatric Association Practice Guideline for the treatment of patients with MDD.[25] A two-phase study design is not commonly used in previous studies investigating lithium addition;[6-8,11-12] it allowed us to perform optimal antidepressant monotherapy in phase I and subsequently to accurately quantify the effect of lithium addition in non-responders in phase II. To ensure optimal efficacy and compliance, high-dose venlafaxine[29] and plasma level-targeted dosing of imipramine[15] were used, both for sufficient duration (7 weeks of treatment) before subsequent lithium addition, and all study medications were taken in the presence of the nursing staff. The use of a semistructured interview conducted by clinicians and a routine drug-free observation period allowed for accurate diagnosis prior to inclusion. Other strengths of the present study are broad inclusion criteria and the relatively low drop-out rate (20%). Finally, the low proportion of patients using concomitant medication (14%) is interpreted as a strength, particularly given the severely depressed study population and the high-dose venlafaxine treatment that was used in the present study.[30] The low proportion of patients using concomitant medication was obtained by maintaining a strong local tradition at the in-patient depression unit of restricting, for example, benzodiazepine use meanwhile patients received strong support from the nursing staff to deal with adverse events such as anxiety and insomnia.

Comparison with previous reports

In contrast to the beneficial results of the present study, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study observed modest response rates (16.2%) with lithium augmentation for out-patients who had not had a satisfactory response to one or two trials of antidepressant medications.[31] The contradicting results can be explained by the difference in study population, the present study consisting of older patients (55 vs. 41 years), a higher mean baseline HAM-D score (26 vs. 19 points), a larger proportion of melancholic features (96% vs. 16%), and a less chronic course of the symptoms.

To our knowledge, venlafaxine-lithium as a two-phase antidepressant treatment strategy has only rarely been studied. The efficacy of lithium addition to venlafaxine in patients with treatment-resistant depression was larger in the present study compared with previous studies,[11-12] both regarding the proportion of responders (65% vs. 36%, respectively) and the proportion of remitters (35% vs. 14%, respectively). However, these two small open-label studies did not focus exclusively on severely depressed in-patients and did not investigate lithium addition as a two-phase treatment strategy, which may have contributed to the discrepancies in results.

Limitations

The study was underpowered, a major limitation. It was originally planned to include 58 patients in phase II but, due to lack of success in starting the study in a second center, only 44 patients were included in phase II. Nevertheless, the venlafaxine-lithium treatment strategy was shown to be significantly superior to the imipramine-lithium treatment strategy, based on the primary outcome criterion. Another limitation is that the study was conducted over a 5-year period which is considered a long study duration. Also considered a limitation is that, due to the absence of a placebo control group, the possibility that placebo response biased the results cannot be excluded. However, placebo response in melancholic depression is presumably low.[32] Finally, although a major strength is that the study population consisted of a homogenous group of severely depressed in-patients, this limits the generalizability of the results. Nevertheless, these results provide clinicians with important information to guide treatment selection, and likewise, we believe the antidepressant treatment strategy to be useful for the treatment of major depressive disorder (with melancholic features) in out-patient settings.

In conclusion, we believe that the results in favor of the venlafaxine-lithium treatment strategy provide new and clinically valuable insights and add to the current knowledge on antidepressant treatment strategies for treatment-resistant major depressive disorder.

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CHAPTER 4

Outcome of a three-phase treatment algorithm for inpatients with melancholic depression

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ABSTRACT

Background: In patients suffering from major depressive disorder, non-response to initial antidepressant monotherapy is relatively common. The use of treatment algorithms may optimize and enhance treatment outcome.

Methods: A single-center 3-phase treatment algorithm was evaluated for inpatients with major depressive disorder, i.e. phase I (n=85): 7 weeks optimal antidepressant monotherapy (imipramine or venlafaxine); phase II (n=39): 4 weeks subsequent plasma level-targeted dose lithium addition in case of insufficient improvement of antidepressant monotherapy; and phase III (n=8): subsequent electroconvulsive therapy in case of insufficient improvement of antidepressant-lithium treatment. Overall feasibility of the 3-phase algorithm was determined by the number of dropouts, and overall efficacy was evaluated using weekly scores on the 17-item Hamilton Rating Scale for Depression (HAM-D) during the treatment phases of the algorithm. This paper is based on an RCT comparing the two antidepressants in phase I and adding lithium in phase II.

Results: Of the 85 patients analyzed, overall dropout during the 3-phase treatment algorithm was 24 (28%) patients. When analyzing the 3-phase treatment algorithm on a modified intention-to-treat basis, 39 (46%) patients achieved complete remission (HAM-D score ≤ 7) by the end of the algorithm. Regarding response (HAM-D score reduction ≥ 50%): of the 85 patients, 60 (71%) were responders by the end of the algorithm.

Conclusion: The favorable outcome of the 3-phase treatment algorithm emphasizes the importance of pursuing stepwise antidepressant treatment in patients who are nonresponsive to the first antidepressant.

INTRODUCTION

According to the WHO World Mental Health (WMH) surveys, mental disorders are common in the general population, with mood disorders being the second most prevalent class (anxiety disorders being the most prevalent class).[1] Mood disorders place a considerable burden on individuals and the society. In the WMH surveys, the lifetime prevalence of any mood disorder in the general population was found to be approximately 12%.[1] Moreover, the adequacy of treatment of mood disorders, with regard to dose and duration, remains a challenge in clinical practice. About 30–40% of patients with major depressive disorder (MDD) are non-responders to initial antidepressant monotherapy and a substantial proportion of these patients develop chronic depressive symptoms.[2] The use of treatment guidelines (also known as treatment algorithms) for the treatment of MDD optimizes and enhances treatment outcome by stepwise ordering of the different treatments and providing guidance on how best to implement the different treatments.[2-7]

Aim of the study

The present study aimed to evaluate the overall feasibility and efficacy of a 3-phase treatment algorithm for inpatients with major depression: phase I optimal antidepressant monotherapy (imipramine or venlafaxine); phase II subsequent lithium addition in case of insufficient improvement of antidepressant monotherapy; phase III subsequent electroconvulsive therapy (ECT) in case of insufficient improvement of antidepressant-lithium treatment. All three phases were carried out while the patients were hospitalized. Phase I, II and III combined form the entire treatment algorithm under evaluation. This paper is based on an RCT comparing the two antidepressants in phase I and adding lithium in phase II.[8-9]

METHODS

Sample

Recruitment took place at the inpatient depression unit of the Department of Psychiatry of the Erasmus Medical Center Rotterdam (EMCR), between March 2005 and March 2010. Patients suffering from uncomplicated MDD and patients suffering from treatment-resistant depression are treated at the depression unit. Included were all patients admitted to the depression unit, aged 18 years and older, diagnosed with single or recurrent MDD, both with and without psychotic features, and a baseline score

≥ 17 on the 17-item Hamilton Rating Scale for Depression (HAM-D).[10] After admission, all patients were observed during a routine drug-free washout period of 1 week, and the Structural Clinical Interview for DSM-IV (SCID) Axis I disorders[11] was used to confirm the diagnosis. Both melancholic and psychotic features were assessed with the SCID.

Excluded were patients with bipolar disorder, primary psychotic disorder, refractoriness to adequate treatment with imipramine or venlafaxine (i.e. ≤ 50% reduction in HAM-D score during treatment with imipramine with plasma level ≥ 200 ng/ml during 4 weeks, or treatment with venlafaxine ≥ 300 mg/day during 4 weeks) during the index episode, drug or alcohol dependence during the last 3 months, mental retardation (IQ < 80), (possibility of) pregnancy, breastfeeding, serious medical illness affecting the central nervous system, relevant medical illness as contraindications for use of the study medication or lithium, and a direct indication for ECT. Also excluded were patients using psychotropic medication other than the study medication, with the exception of benzodiazepines at a dose of ≤ 3 mg lorazepam or equivalent, as well as analgetics, oral contraceptives and other medication not affecting the central nervous system.

Study procedures: phase I antidepressant monotherapy

Eligible patients were randomized for 7 weeks double-blind treatment with either imipramine or venlafaxine. Randomization was performed by the Department of Pharmacy from the EMCR using a random number table generated by the computer with an allocation ratio of 1:1. The Department of Pharmacy also supplied the study medication using a double-dummy technique, allowing the study medication to remain blind for the patient, the treating physician, and the investigators. During the first 3 weeks, for each patient, the antidepressant was adjusted to an optimal dose: imipramine was adjusted to a predefined plasma level of 200–300 ng/ml (sum of imipramine + desipramine) and venlafaxine was gradually increased to 300–375 mg/day. The limit of ≥ 200 ng/ml is based on previous studies,[12-13] the upper limit was chosen to avoid serious adverse events. Altogether, to guarantee at least 4 weeks treatment with either imipramine at adequate plasma levels or venlafaxine at high dose, all patients received 7 weeks double-blind antidepressant treatment. The results of phase I of the study are published elsewhere.[8] Since tricyclic antidepressants (TCAs) have been shown to be superior in efficacy to SSRIs in depressed inpatients,[14-15] a TCA would be appropriate as reference antidepressant. We chose imipramine because of its reliable target plasma levels.

Study procedures: phase II lithium addition

All patients achieving insufficient improvement on antidepressant monotherapy at the end of phase I (defined a priori as a HAM-D score > 13 after 7 weeks of antidepressant treatment) were included in phase II of the study. Patients included in phase II continued the antidepressant from phase I at the same dose (maintaining the double-blind conditions for the antidepressant) and all received 4 weeks lithium addition irrespective of the antidepressant. Patients were screened for contraindications after which lithium was administered and adjusted, under open conditions, to a predefined plasma level of 0.6–1.0 mmol/l.[16] The results of phase I and phase II combined, i.e. two antidepressant treatment strategies in severely depressed inpatients, are published elsewhere.[9] Lithium addition was chosen as second treatment step, because it is the best-investigated second-line augmentation treatment.[17-18]

Study procedures: phase III electroconvulsive therapy

All patients achieving insufficient improvement on combined antidepressant-lithium treatment at the end of phase II (defined a priori as a HAM-D score > 13 and a < 50% reduction on the HAM-D score) were included in phase III of the study. The antidepressant and lithium were discontinued for a 10-day washout period, because of insufficient efficacy, after which a course of ECT was started. ECT was chosen as third treatment step, because it is effective even in resistant major depression.[19] A constant-current ECT device was used, delivering brief-pulse stimulus. During the first ECT session, stimulus dose titration was used as a method to accurately determine the seizure threshold for each patient. For right unilateral ECT the dosage was set at 5 times the initial seizure threshold, and for bilateral ECT the dosage was set at 1.5 times the initial seizure threshold. Patients started treatment with right unilateral ECT and were switched to bilateral ECT if response was insufficient (i.e. reduction on the HAM-D ≤ 50%) after 6 sessions. Patients in a critical condition (e.g. mutistic, refusing food) received exclusively bilateral ECT. All patients received ECT twice weekly, which is standard of care in the Netherlands. During the course of ECT, stimulus dose settings were adjusted upward to maintain a seizure duration of at least 25 s. The cuff technique was used to monitor motor seizure activity.

Measures

During all three treatment phases, the HAM-D was scored weekly by two research psychiatrists (WWvdB, TKB), with proven excellent interrater reliability (κ=0.95) regarding the total score on the HAM-D. During all three phases, adverse effects were monitored weekly by an independent psychiatrist. Vital signs were determined weekly. Maintaining a 12-h sampling time, plasma levels were monitored weekly by

an independent psychiatrist. The research psychiatrists were blinded, whereas the independent psychiatrist was not. Adverse effects were monitored with a list, which was tailored to the interventions, based on consensus between three of the authors (MV, WWvdB and TKB). Prior to treatment with ECT, previous prescribed pharmacotherapy resistance was rated with the Antidepressant Treatment History Form (ATHF).[20-21] The ATHF assigns a score of 1–5 to a trial, based on drug choice, dose, and duration of administration; adequate treatment is defined as at least one medication trial rating ≥ 3.

Statistical analysis

Data were analyzed using SPSS 21 software. The proportion of patients actually included in the algorithm was calculated to determine the suitability of the 3-phase algorithm. Overall feasibility of the 3-phase algorithm was determined by the number of dropouts during the treatment phases and the number of dropouts between the treatment phases. Efficacy of the 3-phase algorithm was evaluated using weekly HAM-D scores during the treatment phases of the algorithm. The last observation carried-forward (LOCF) method and the mean of surrounding values were used to account for missing values (i.e. dropouts). Data were tested for normality and no outliers were found. Both the proportion of patients achieving remission (defined a priori as a final HAM-D score ≤ 7) and the proportion of patients achieving response (defined a priori as a reduction of ≥ 50% on the HAM-D score relative to the baseline HAM-D score in phase I) were determined at the end of all three phases of the algorithm on a modified intention-to-treat basis (i.e. an intention-to-treat analysis, with the removal of three patients, who were randomized, but dropped out before the start of study medication) and were repeated in the completers subsample.

Additionally, binary logistic regression analyses were performed to determine the effects of the different baseline demographic and clinical characteristics on the likelihood that patients with severe depression would achieve remission during the course of the 3-phase treatment algorithm: odds ratios (OR) and 95% confidence intervals (95% CI) were determined. The binary logistic regression analyses were performed on a modified intention-to-treat basis (n=85). All analyses were performed after completion of the full algorithm.

Ethical considerations

All eligible patients received a thorough explanation of the study procedures and all provided written informed consent before randomization. The inclusion of patients aged 18–65 years was approved in the original protocol. During the study period, the Medical Ethics Committee of the EMCR approved an addendum to the protocol regarding the

inclusion of inpatients aged ≥ 65 years, provided that their first episode of depression had occurred before age 65 years. The inclusion of patients over 65 years was done to increase the generalizability of our study. We refrained from including patients with late-onset depression (first episode > 65 years). Both the protocol and the addendum were approved by the Medical Ethics Committee of the EMCR. The protocol is carried out in accordance with the Declaration of Helsinki (1964), as amended in Edinburgh (2000).

RESULTS

Patient population

Between March 2005 and March 2010, 244 patients with MDD were admitted to the inpatient depression unit of the Department of Psychiatry of the EMCR; of these, 125 (51%) were excluded (Table 1). Of the remaining 119 eligible patients, 31 (26%) refused participation in an RCT or receiving double-blind medication.

Of the 244 patients, 88 (36%) were included in the 3-phase treatment algorithm; of these, 3 (1%) patients dropped out after randomization but before study medication was started, i.e. 1 refused participation after randomization, 1 was discharged without consent, and 1 was excluded due to a language barrier. Thus, of the 244 patients, 85 (35%) were finally analyzed on a modified intention-to-treat basis in the 3-phase treatment algorithm.

Of the 85 patients who received antidepressant monotherapy, 43 (51%) received treatment with imipramine and 42 (49%) received treatment with venlafaxine. The demographic and clinical characteristics of the study population at the start of phase I (n=85) are presented in Table 2. The flow of patients through the phases of the algorithm is shown in Fig. 1.

Table 1. Reasons for exclusion of eligible patients (n=244) in the study before the start of phase I.

Exclusion criteria	**N**	**%**
Indication for immediate electroconvulsive therapy	20	8
Alcohol abuse	11	4
Age ≥ 65 years	41	17
Discharged without consent	10	4
Other reasons	43	18
Refused participation before randomization	31	13
Dropout after randomization, but before study medication was started	3	1
Total exclusion	**159**	**65**

Table 2. Demographic and clinical characteristics of the study population at the start of phase I (n=85).

Baseline variable	**Mean**	**SD**	**N**	**%**
Age (years) (range)	54.6 (29-82)	9.4		
Male sex			39	46
Education: less than high school			9	11
Duration of index episode [a] ≤ 1 year > 1 year			 71 12	 86 14
First episode			34	40
Psychotic type			20	24
Melancholic features			82	96
Without adequate pre-treatment with antidepressants [b]			58	68
Baseline HAM-D score (range)	26.7 (19-37)	5.1		

[a] Data missing n=2.

[b] Data missing n=2. Adequate pre-treatment is defined as at least one medication trial rating ≥ 3 using the Antidepressant Treatment History Form (ATHF), which assigns a score of 1-5 to a trial based on drug choice, dose, and duration of administration.[20] The ATHF score refers to the index episode.

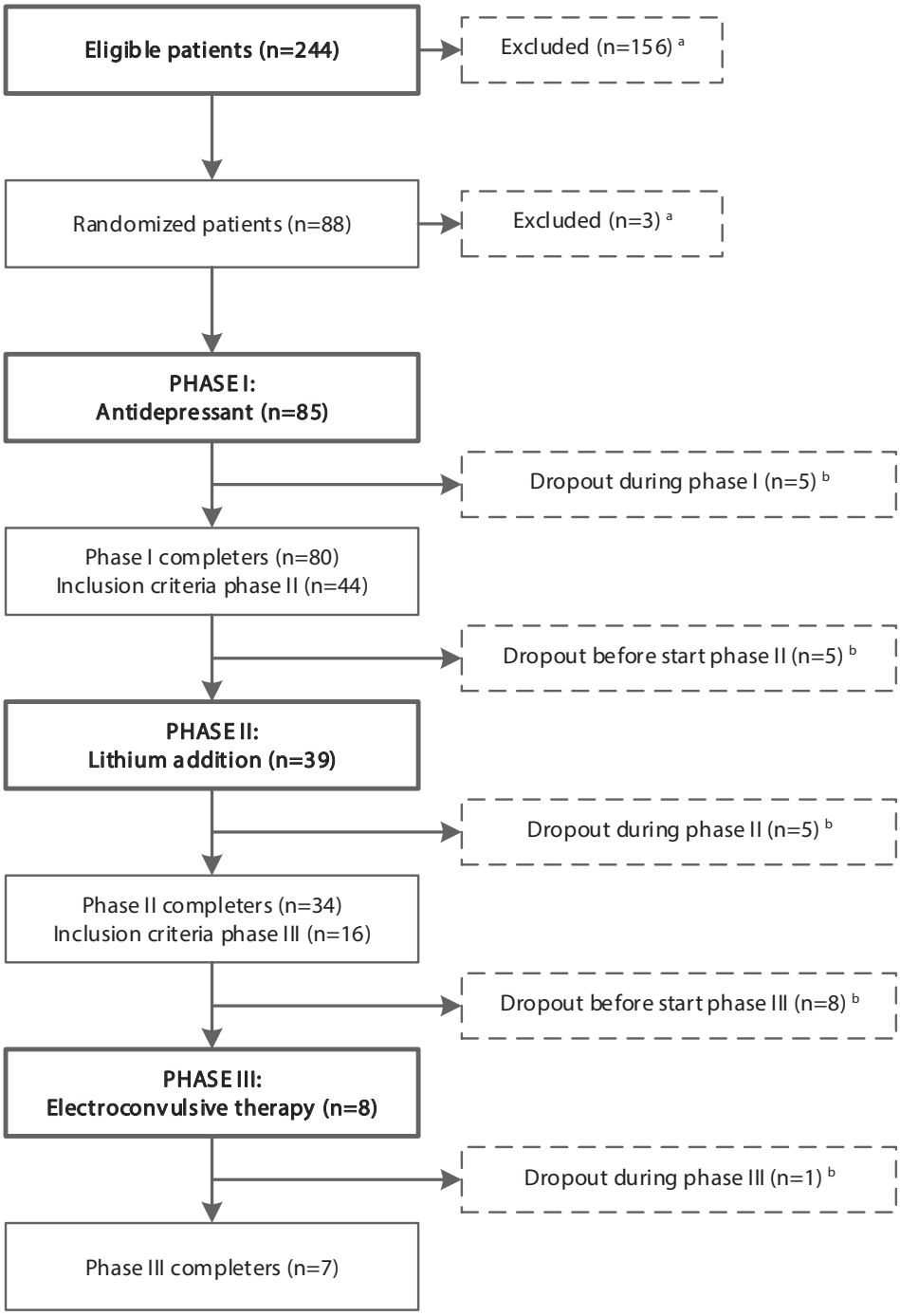

Figure 1. Patient flow through the different phases of the algorithm. [a] See Table 1; [b] See Table 3.

Algorithm: phase I antidepressant monotherapy

Of the 85 patients who received antidepressant monotherapy with either imipramine or venlafaxine in phase I, 25 (29%) achieved complete remission and 38 (45%) were responders. After 7 weeks treatment the mean daily imipramine dose was 206.1 (SD ± 89.4, range 50–450) mg/day (n=41, missing n=2) with a mean imipramine + desmethylimipramine plasma level of 281.7 (SD ± 68.2, range 134.0–432.0) ng/ml (n=43), and the mean daily venlafaxine dose was 371.4 (SD ± 16.2, range 300–375) mg/day (n=42). Of the 85 patients, 12 (14%) received benzodiazepines as concomitant medication, all of which stayed under the predefined maximum dosage of lorazepam 3 mg/day (or equivalent) and 2 (2%) were concomitantly treated with haloperidol 2 mg/day. Six of the 43 patients on imipramine had plasma levels < 200 ng/ml, which was ignored in the analyses because of the small number of patients.

Of the 85 patients, 5 (6%) dropped out during phase I: 1 refused further medication after 5 weeks treatment with imipramine, 3 dropped out due to side-effects (1 developed orthostatic hypotension from using imipramine; 1 developed an allergic reaction to imipramine; and 1 developed an intoxication delirium from using imipramine and was transferred to the Department of Neurology), and 1 patient was lost to follow-up after being transferred to a different hospital for kidney stone surgery (Table 3). Analysis of treatment guesses at treatment week 5, in a subset of patients with psychotic features, showed that agreement between guessed and actual medication was only slightly higher than expected on the basis of chance, with a Kappa statistic of 0.14.

Algorithm: phase II lithium addition

Of the remaining 80 patients who completed phase I, 44 (55%) met the criteria for inclusion in phase II (lithium addition), of which 1 (1%) patient worsened (attempted strangulation) after 5 weeks antidepressant monotherapy with imipramine in phase I and immediately started phase II. Of the 44 patients, 5 (11%) dropped out before the start of phase II (Table 3): 3 refused participation in phase II, and 2 had further improvement of symptoms before the start of lithium. Thus, 39 patients received lithium addition in phase II.

Of the 39 patients who received lithium addition to either imipramine or venlafaxine in phase II, 12 (31%) were remitters and 18 (46%) were responders. After 4 weeks treatment, the mean lithium plasma level was 0.78 (SD ± 0.16, range 0.27–1.30) mmol/l (n=36, missing n=3). Only two patients had subtherapeutic lithium levels, which was ignored in the analyses because of the small number of patients.

Of the 39 patients, 5 (13%) dropped out during phase II: 1 due to worsening of symptoms while receiving venlafaxine and lithium addition (this patient eventually received treatment with a monoamine oxidase inhibitor) and 4 were lost to follow-up (1 stopped taking all medication, 1 had further improvement of symptoms but was lost to follow-up, and 2 were lost to follow-up after they developed hypomanic symptoms and immediately stopped treatment with imipramine and venlafaxine, respectively) (Table 3). Hypomania during lithium addition may be caused by lithium with low levels, which may have an antidepressant, but no antimanic effect.

Algorithm: phase III electroconvulsive therapy

Of the 34 remaining patients who completed phase II, 16 (47%) met the criteria for inclusion in phase III (treatment with ECT). Of these 16 patients, 8 (50%) dropped out before the start of phase III (Table 3): 1 refused ECT, 3 had further improvement of symptoms before the start of ECT, 3 received treatment with a monoamine oxidase inhibitor (MAOI) which is considered a protocol violation (failing to stick to the algorithm protocol), and 1 was lost to follow-up before receiving treatment with ECT (discharged without consent). Thus, 8 patients received treatment with ECT in phase III.

Table 3. Reasons for dropout during the different phases of the algorithm.

Reason for dropout	**During phase I (n=85): Antidepressant**	**Before the start of phase II (n=44)**	**During phase II (n=39): Lithium addition**	**Before the start of phase III (n=16)**	**During phase III (n=8): ECT**
Total, N (%)	**5 (6%)**	**5 (11%)**	**5 (13%)**	**8 (50%)**	**1 (13%)**
Refused participation, N	1	3		1	
Discharged without consent, N					
Language barrier, N					
Side-effects, N	3				1
Worsening of symptoms, N			1		
Lost to follow-up, N	1		4	1	
Further improvement of symptoms before the start, N		2		3	
Protocol violation: indication for treatment with a MAOI, N				3	

Abbreviations: ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor.

Of the 8 patients who received ECT in phase III, 2 (25%) achieved complete remission and 4 (50%) were responders. Two patients started treatment with right unilateral ECT and later switched to bilateral ECT, and 6 patients received bilateral ECT exclusively. The mean number of ECT treatments was 14.8 (SD ± 4.5, range 7–20) (n=8). Of the 8 patients, 1 (13%) dropped out during the ECT course due to side-effects: a severely prolonged wakeup from the anesthesia (Table 3). Finally, of the 8 patients, 7 (87%) completed phase III.

Overall result of the algorithm

The proportion of remitters and the proportion of responders (all relative to baseline phase I) during the different phases of the algorithm are summarized in Table 4. When analyzing the 3-phase treatment algorithm on a modified intention-to-treat basis, of the 85 patients, 39 (46%) achieved complete remission based on the a priori defined criterion of a HAM-D score ≤ 7 by the end of the algorithm (Table 4). According to the a priori defined criterion of a ≥ 50% reduction on the HAM-D score by the end of the 3-phase treatment algorithm, of the 85 patients, 60 (71%) were responders. Binary logistic regression analyses identified three baseline variables as predictors of remission: an education less than high school, a duration of the index episode ≤ 1 year, and not having an adequate pre-treatment with antidepressants (Table 5). Binary logistic regression analyses were not performed for the baseline clinical characteristic melancholic features, since almost all patients had melancholic features (n=82/85, 96%); therefore, in the present study population, this was a non-distinctive variable.

Of the 85 patients, overall dropout of the 3-phase treatment algorithm was 24 (28%) patients. In the completers subsample, analyses were repeated after removal of all dropouts in phase I (n=5), phase II (n=10) and phase III (n=9) (Table 4). Based on this analysis of completers, of the 61 patients, 39 (64%) achieved complete remission and 57 (93%) were responders at the end of the 3-phase treatment algorithm.

Table 4. Number of remitters and responders (all relative to baseline phase I) during the different phases of the algorithm.

Modified intention-to-treat analysis (n=85)					
Phase	**Total, N**	**Remission**		**Response**	
		N	**%**	**N**	**%**
I: Antidepressant monotherapy	85	25	29	38	45
II: Lithium addition	39	12	31	18	46
III: Electroconvulsive therapy	8	2	25	4	50
Overall algorithm	**85**	**39**	**46**	**60**	**71**
Analysis of completers (n=61)					
Phase	**Total, N**	**Remission**		**Response**	
		N	**%**	**N**	**%**
I: Antidepressant monotherapy	80 [a]	25	31	35	44
II: Lithium addition	34 [b]	12	35	18	53
III: Electroconvulsive therapy	7 [c]	2	29	4	57
Overall algorithm	**61 [d]**	**39**	**64**	**57**	**93**

[a] At the start of phase I n=85 with dropout during phase I n=5.
[b] At the start of phase II n=39 with dropout during phase II n=5.
[c] At the start of phase III n=8 with dropout during phase III n=1.
[d] At the start of phase I n=85 with overall dropout during phase I through phase III n=24 (see also Table 3).

Table 5. Binary logistic regression. Odds ratios (OR) and 95% confidence intervals (95% CI) of achieving remission in the 3-phase treatment algorithm for the different demographic and clinical characteristics (n=85).

Baseline variable	**OR**	**95% CI**	**P-value**
Age (years)	1.04	0.99, 1.09	0.11
Male sex	1.82	0.77, 4.31	0.18
Education: less than high school	4.81	0.94, 24.71	0.06
Duration of index episode ≤ 1 year [a]	5.44	1.11, 26.63	0.04
First episode	1.32	0.55, 3.15	0.53
Psychotic type	2.11	0.76, 5.86	0.15
Without adequate pre-treatment with antidepressants [b]	2.76	1.00, 7.59	0.05

[a] Data missing n=2, two are unknown.
[b] Data missing n=2, two are unknown. Adequate pre-treatment is defined as at least one medication trial rating ≥ 3 using the Antidepressant Treatment History Form (ATHF), which assigns a score of 1-5 to a trial based on drug choice, dose, and duration of administration.[20]

DISCUSSION

Discussion and comparison with previous reports

During the 5-year study period, 244 patients with MDD were admitted to the depression unit and 36% of them participated in the 3-phase algorithm. Twenty-six percent of the eligible patients refused to provide informed consent, despite receiving thorough information about the study procedures from the nursing staff. Most patients refused receiving double-blind medication. All patients who participated suffered from severe major depression, as evidenced by both the mean baseline 17-item HAM-D score (26.7), the proportion of patients with melancholic depression (96%), and the proportion of patients with psychotic depression (24%). For the participating patients, the 3-phase algorithm was relatively effective, as shown by a 46% remission rate and a 71% response rate. Analyses were performed on a modified intention-to-treat basis, which often underestimates the true treatment effect. Including patients both with and without psychotic features could be arguable, as several guidelines recommend the combination of an antidepressant and an antipsychotic for the treatment of major depression with psychotic features, although it is noted that the results of previous studies were inconclusive.[22-23] Mulsant et al.[24] found similar efficacy of TCA monotherapy compared with a TCA-antipsychotic combination in patients with psychotic depression.

In two previous studies by our group, imipramine was shown to be more effective in depressed patients with psychotic features when compared with depressed patients without psychotic features.[25-26] Based on these results, we chose not to exclude depressed patients with psychotic features.

In the present study, the outcome of the 3-phase algorithm is less favorable compared with a previously tested 4-step algorithm[5] at the same depression unit; however, no obvious explanation can be found for the reduced efficacy of the 3-phase algorithm compared with the 4-step algorithm. The 6 weeks longer duration of the latter may be an explanation for the difference in efficacy. Both samples consisted of middle-aged patients with severe major depression. When compared with the previous study, the present sample had less patients with an episode longer than 1 year, less patients with psychotic depression, and about the same proportion of patients with a first depressive episode. The number of patients receiving adequate pretreatment with antidepressants was also about the same.

When looking at the analysis of completers, the results of the 3-phase algorithm are more favorable, with a 64% remission rate and a 93% response rate. Especially the results of the completer analysis show the importance of persisting with further antidepressant treatment when patients show nonresponse to the first antidepressant. The relatively high remission rate in the completer analysis may be due to the specialized character of the depression unit. Patients participate in a rather intensive treatment program, including psychoeducation and group cognitive therapy. Furthermore, avoiding the use of benzodiazepines as concomitant medication may have reduced the feasibility of the algorithm. It is difficult to estimate whether refraining from benzodiazepines as concomitant medication has influence the efficacy of our algorithm. In routine practice, many depressed patients receive concurrent medication (e.g. benzodiazepines) this might decrease the efficacy of antidepressant treatment,[27] although there is no consensus about the influence of benzodiazepines on antidepressant response.

In phase I, the response and remission rates during antidepressant monotherapy were acceptable, i.e. 45% and 29%, respectively. The efficacy of antidepressant monotherapy might be decreased by the inclusion of many patients (68%) who had received previous treatment with antidepressants. Phase II (lithium addition to ongoing treatment with an antidepressant) was relatively successful, as shown by a 46% response and a 31% remission rate. In phase III, the efficacy of treatment with ECT was relatively modest, as evidenced by a 50% response rate and a 25% remission rate. We have no obvious explanation for the modest efficacy of ECT, since all patients eventually received bilateral ECT and did not receive benzodiazepines or other drugs that might interfere with ECT. However, in phase III, the number of patients receiving treatment with ECT was small (n=8).

Although the efficacy of our 3-phase algorithm is lower than that of a previously examined 4-step algorithm, consisting of antidepressant monotherapy during 6 weeks, lithium addition during 5 weeks, monotherapy with an MAOI during 5 weeks, and an ECT course,[5] our results are in accordance with the results of Bauer et al.,[3] who tested a treatment algorithm in depressed inpatients and found a 54% remission rate. Furthermore, the efficacy of our algorithm is in line with a recent large German study.[28] Our algorithm has much in common with that of Bauer et al.,[3] since both studies include subsequent treatment with antidepressant monotherapy, lithium addition, and ECT. However, the algorithm of Bauer et al.[3] is much more extensive (comprising 10 different treatment steps) and its feasibility is lower.

The relatively good outcome with algorithm-guided treatment is consistent with previous reports. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D)[29] project is a multisite randomized trial for depressed outpatients consisting of 4 treatment steps for citalopram nonresponders; however, because of the variation within the treatment steps, no meaningful comparison can be made with our algorithm.

Strengths and limitations

An important strength of the present study is the strictly protocolized treatment, and embeddedness of the protocol within a double-blind randomized clinical trial design comparing two effective medications in phase I. We used standardized instruments; all participating staff was trained in the treatment and assessment protocol. As a result, the risk of bias is low and the results show a high level of measurement precision. However, validity was potentially compromised by the assessors who were not blind for treatment in phase II and III. Furthermore, the relative effectiveness could not be estimated since we did not use a comparison condition receiving "treatment as usual" in phase II and III. We used a limited set of potential predictors, in future studies it may be useful to analyze a larger set of predictors, such as marital and work status.

The study faced substantial dropout (28%) and refusals (26%) of (eligible) participants, which may have biased our treatment effect. However, dropout was strictly monitored. Concerning the overall dropout rate, because the dropout was higher between the different phases and lower during the treatment phases, the substantial dropout (28%) does not seem to be a tolerability issue. In the effect analyses we chose to perform a modified intention-to-treat analysis, which resulted in a conservative estimation of the treatment effect. The subsequent analysis of completers represented the optimal treatment effect. Both the modified intention-to-treat analysis and the analysis of completers showed positive results of the treatment algorithm. Due to the strict set of inclusion and exclusion criteria, and our single-center study setting (including only inpatients from a university hospital) the results are not easily generalizable to all patients with MDD. However, the reliability and validity of the results benefited from our use of a homogenous patient group. Obviously, during inpatient treatment aspecific factors are substantially different from outpatient treatment. Nevertheless, our results may also apply to outpatients with melancholic depression.

In conclusion, the present results emphasize the importance of pursuing stepwise antidepressant treatment in patients not responding to the first antidepressant. In the completers, the favorable outcome of the algorithm is shown by a 93% response rate and a 64% remission rate. Adherence to the algorithm was reasonable, with an overall

dropout rate of 28%. Both an index episode less than one year and not having received previous adequate treatment predicted a greater chance of achieving remission with the treatment algorithm.

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CHAPTER 5

Early improvement as a predictor of eventual antidepressant treatment response in severely depressed inpatients

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ABSTRACT

Rationale: Traditionally, the therapeutic effect of antidepressants is thought to take several weeks. However, several studies found evidence of early drug response occurring within the first 2 weeks of antidepressant treatment and that this early onset response may predict eventual treatment outcome.

Objective: This study aims to investigate the predictive value of early improvement in the course of treatment with imipramine or venlafaxine in an inpatient population with severe major depression.

Method: A post hoc analysis was conducted after pooling data from two almost identical trials. The study included 149 patients with DSM-IV diagnosis major depression and a baseline score ≥ 17 on the 17-item Hamilton Rating Scale for Depression (HAM-D). Patients were randomized for double-blind treatment with either antidepressant. Early improvement (≥ 25% reduction on HAM-D score) was evaluated after 2 weeks and response (≥ 50% reduction on HAM-D score) after 6 weeks of acute treatment.

Results: Of 64 patients achieving early improvement, 38 (59%) became responders, whereas of 85 patients not achieving early improvement, only 23 (27%) became responders. There was a significant difference in time to response between patients achieving early improvement and patients not achieving early improvement. Early improvement is a modest sensitive predictor for eventual response.

Conclusion: In the present study, although the sensitivity of early improvement was modest, based on the severity of clinical symptoms, a clinician treating a patient with severe major depression may seriously consider changing the treatment at an earlier stage than is presently customary.

INTRODUCTION

Clinicians continue to search for predictors of antidepressant response. As mentioned by Nierenberg,[1] the longer a patient fails to respond to an antidepressant, the greater the likelihood of eventual nonresponse. Traditionally, the therapeutic effect of antidepressants is thought to take several weeks. Quitkin et al.[2-7] pleaded for the delayed antidepressant response theory and concluded that early improvement shortly after initiating treatment may be a placebo effect.[4] Three previous studies[8-10] reported similar results.

In contrast, several studies found evidence of early drug response occurring within the first 2 weeks of antidepressant treatment and that this early onset response may predict eventual treatment outcome.[11-25] Three meta-analyses[26-28] concluded that antidepressant response can take place early in the course of treatment. The presence or absence of early improvement as a predictive variable is of clinical value because it can help clinicians decide at an earlier stage to continue or change treatment, thereby preventing delay, increasing patient wellbeing, increasing treatment compliance, and decreasing morbidity.

Despite considerable studies exploring the topic "time course of response to antidepressants", the literature remains inconclusive. Both tricyclic antidepressants and venlafaxine appear to be more effective (especially in inpatient populations) than selective reuptake inhibitors for the treatment of severe depression;[29-31] however, the time course of response to treatment with imipramine and venlafaxine has not been specifically studied in an inpatient population with severe major depression with melancholia. Moreover, the predictive value of early improvement in the course of treatment with imipramine or venlafaxine has been scarcely investigated.

Since a substantial number of previous studies found evidence for early improvement being predictive of eventual response, we considered it relevant to assess this topic in a population of severely depressed inpatients. Our hypothesis: during treatment with imipramine or venlafaxine, treatment response at 6 weeks occurs significantly more often in patients who attain early improvement at 2 weeks.

Aim of the study

The data were analyzed to test whether, in a population consisting of severely depressed inpatients, early improvement occurs and to test the predictive value of early improvement in the course of treatment with imipramine or venlafaxine. A secondary aim of the study was to test the predictive value of different definitions of early improvement.

MATERIAL AND METHODS

Study design

The present study pools data from two almost identical (but independent) randomized controlled trials of severely depressed inpatients: study 1[32] comparing the efficacy of imipramine with fluvoxamine and study 2[33] comparing the efficacy of venlafaxine with imipramine. Because imipramine appeared to be superior to fluvoxamine,[32] we excluded fluvoxamine-treated patients from the present analysis, using only the data of patients treated with imipramine or venlafaxine.

Study 1 recruited inpatients aged 18–65 years from two centers: the depression units of the Department of Psychiatry of the Erasmus Medical Center in Rotterdam (EMCR) and Parnassia Psychomedical Centre in The Hague, both from April 1997 to July 2001. Study 2 recruited inpatients aged ≥ 18 years from the depression unit of the Department of Psychiatry of EMCR from March 2005 to March 2010. Both units are reserved almost exclusively for patients with severe major depression. The units have a relatively large staff, including a psychiatrist, two residents, nurses, a psychomotor therapist, and a creative therapist. This has resulted in a rather intensive treatment program, including group psycho-education.

Patients included in both studies were diagnosed with a major depressive disorder according to the DSM-IV criteria and a baseline score ≥ 17 on the 17-item Hamilton Rating Scale for Depression (HAM-D).[34] HAM-D is a 17-item questionnaire used to rate the severity of their depression by probing mood, feelings of guilt, suicide ideation, insomnia, agitation or retardation, anxiety, weight loss, and somatic symptoms. Its internal, interrater, and retest reliability are mostly good.[35] Diagnosis was confirmed with the Structural Clinical Interview for DSM-IV Axis I disorders.[36] Patients with bipolar disorder were excluded from both studies. All eligible patients provided written informed consent after the study procedures have been fully explained.

Further information on the study design and patient selection of both studies is presented elsewhere.[32-33] In summary, both studies included a drug-free wash-out period of 1 week during which the diagnosis was confirmed, after which patients were randomized for double-blind treatment with either antidepressant. For imipramine, the dose was administered once a day starting with 75 mg and doubled after 2 days. Blood levels were monitored once a week; the dose of imipramine was adjusted for each patient to a predefined blood level of 200–300 ng/ml (sum of imipramine + desipramine). Venlafaxine was administered once a day starting with 75 mg, and the dose was increased gradually to 300–375 mg/day within 2 weeks. For the majority of patients, the dose of imipramine and venlafaxine was held constant for 2 weeks after the start of study medication until the end of the study period. The same research psychiatrists performed all the assessments in both studies, with proven excellent interrater reliability (κ=0.95) regarding the total score on HAM-D.

Measures

Plasma levels (of imipramine) and adverse effects (for both imipramine and venlafaxine) were monitored weekly by an independent psychiatrist. The patients were evaluated on a weekly basis using HAM-D by raters blind to the treatment option.

Concomitant treatment

The only concomitant treatment that was allowed during both studies was one to six tablets a day of an extract of valerian 45 mg in case of severe anxiety or insomnia, lorazepam equivalents maximally 3 mg/day in case of severe anxiety, and haloperidol 1–10 mg a day in case of severe psychotic symptoms. In study 1, the total number of patients using concurrent medication was 12/138 (8.6%),[32] and in study 2 this was 14/85 (16%).[33] In the present analysis, these latter data were ignored due to the small numbers of patients involved.

Statistical analysis

For this analysis, SPSS Statistics 21 software package was used. Statistical significance was defined as $p<0.05$, two-tailed. The last observation carried forward method was used to account for missing values (dropouts), and the mean of surrounding values for the individual person was used to account for single missing values. We tested the data for normality and verified the data for outliers; no outliers were found. Differences in demographic and clinical characteristics between the two studies were tested using Student's *t*-test (in case of continuous variables) and chi-square test (in case of categorical variables).

The primary outcome measure is HAM-D, with the endpoint HAM-D score defined as the HAM-D score after 6 weeks of acute treatment. Differences in baseline and endpoint HAM-D scores, differences in HAM-D scores after 2 weeks of antidepressant treatment, and differences in HAM-D score reduction after 6 weeks between the three treatment subgroups (i.e., imipramine, study 1; imipramine as well as venlafaxine, study 2) were tested using ANOVA tests.

Response is defined as a reduction of ≥ 50% from the baseline HAM-D score at 6 weeks of antidepressant treatment. We tested three different definitions of early improvement, i.e., 20, 25, and 30% reduction of the HAM-D score at 1 and 2 weeks of antidepressant treatment, respectively. These definitions were chosen based on the results from previous studies.[12-13] To investigate the predictive value of early improvement for eventual response, we calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), false-positive rate, false-negative rate, and receiver operating characteristics (ROC) curves of the various definitions of early improvement according to the procedure of Szegedi et al.[13] ROC curves were used to explore the overall accuracy of the instrument, characterized by an area under the curve value (AUC). AUC values range from 0 to 1.0, in which a value of 1.0 indicates a perfect prediction, and a value of 0.5 indicates a prediction equal to chance. Sensitivity is the probability of a positive result given the condition is present. Specificity is probability of a negative result given the condition is absent. Subsequently, positive predictive value (PPV) is the probability of a positive diagnosis after a positive screening, and negative predictive value (NPV) is the probability of a negative diagnosis after a negative screening. Finally, false-positive and false-negative rate refer to the probabilities of incorrect prediction of cases where the condition was absent or present, respectively (i.e., 1-specificity and 1-sensitivity, respectively). Predictive values range from 0 to 1, in which a value closer to 1 reflects a better predictive value.

The number of patients achieving response at 6 weeks and the number achieving early improvement at 2 weeks was determined relative to baseline. Also, differences in the rate of response and in the rate of early improvement between the three treatment subgroups, and between the total imipramine treatment group (from study 1 and study 2) and the venlafaxine treatment group, were determined using the chi-square test.

Considering each treatment subgroup separately (imipramine study 1, imipramine as well as venlafaxine study 2), and the total imipramine treatment group (from study 1 and study 2) and the venlafaxine treatment group (study 2) separately, we analyzed time to response using the Kaplan–Meier method.[37-38] Logrank tests were used to test whether the survival curves were equivalent. Subsequently, all three treatment subgroups

were combined for the Kaplan–Meier analysis, comparing time to response in patients achieving early improvement with patients not achieving early improvement. Again, log-rank tests were used to test whether the survival curves were equivalent.

As a final step, sensitivity analyses were performed to assess the robustness of the findings. Analyses were repeated on subsets of the data, that is, data from which dropouts and patients with concomitant medication were removed. Subsequently, analyses were repeated with remission (defined as a Hamilton score ≤ 7) as outcome at 6 weeks of antidepressant treatment.

Ethical considerations

The protocols of study 1 and study 2 were approved by the Medical Ethics Committee of the EMCR. Both protocols were carried out in accordance with the Declaration of Helsinki (1964), as amended in Edinburgh (2000).

RESULTS

Patient population and dropouts

A total of 155 patients was included in the present analysis (Fig. 1): study 1 included 70 patients receiving treatment with imipramine, and study 2 included 43 patients receiving treatment with imipramine plus 42 patients receiving treatment with venlafaxine. As shown in Fig. 1, patients who were randomized but did not receive study medication were excluded from the analysis. To "balance" the two datasets, from study 2 we excluded all patients aged > 65 years (n=6), leaving a total of 149 patients to be analyzed. Ten patients dropped out during the study but were included in the analysis. All patients who discontinued the study were using imipramine; they dropped out in the first 3 weeks of the study, five due to side effects and three due to worsening condition.

The demographic and clinical characteristics of patients in both studies are presented in Table 1. The mean daily dose of imipramine and venlafaxine and the mean blood levels of imipramine are shown in Table 2. The mean baseline HAM-D score for the imipramine treatment group of study 1 was 24.5 (SD ± 5.3); for the imipramine treatment group of study 2, it was 27.9 (SD ± 5.3); and for the venlafaxine treatment group of study 2, it was 26.1 (SD ± 4.9). The mean reduction in HAM-D scores after 6 weeks of treatment with imipramine in study 1 was 9.40 (SD ± 7.94). The mean reduction in HAM-D scores after 6 weeks of treatment with imipramine in study 2 was 10.84 (SD ± 10.83), and the mean reduction in HAM-D scores after 6 weeks of treatment with venlafaxine in study 2 was 11.95 (SD ± 7.77) (Table 2).

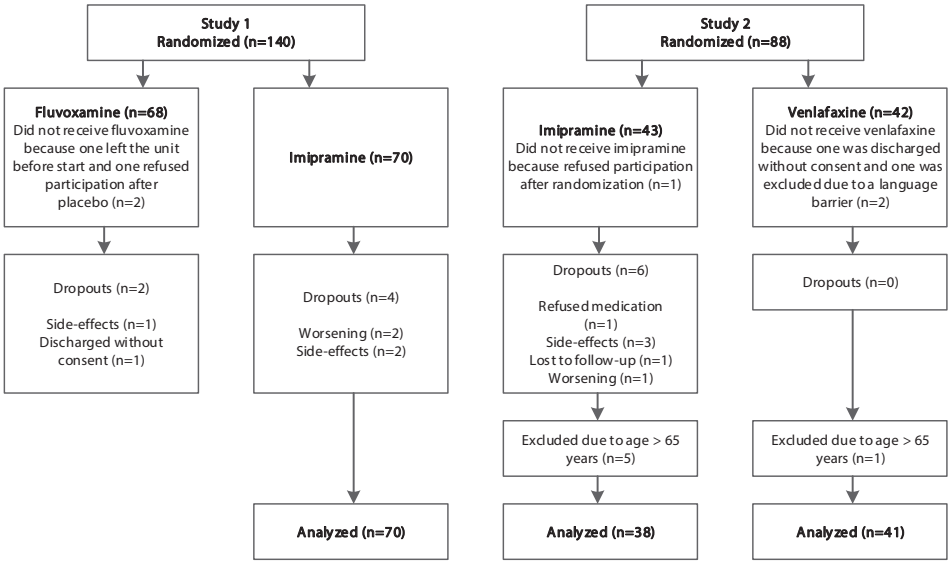

Figure 1. Flow diagram of participation in the present study.

Table 1. Demographic and clinical characteristics of the study population.

Baseline variable	Study 1[32] Imipramine (n=70)	Study 2[33] Imipramine (n=38) and Venlafaxine (n=41)	Test	*P* value
Age: mean ± SD (range) in years	51 ± 9.1 (19-65)	53 ± 8.4 (29-65)	$t(1)=2.10$	0.15
Sex: male/female	27/43	36/43	$X^2(1)=0.75$	0.39
Education level: lower than high school	10 (14%)	8 (10%)	$X^2(1)=0.60$	0.44
Baseline HAM-D score, mean ± SD (range)	24.5 ± 5.3 (14-37)	27.0 ± 5.1 (19-40)	$t(1)=8.35$	0.01
Duration of index episode < 1 year ≥ 1 year	 46 (66%) 24 (34%)	 66 (85%) 12 (15%)	 $X^2(1)=7.16$	 0.01
First depression episode: yes/no	42 (60%)	33 (42%)	$X^2(1)=4.23$	0.04
Melancholic features	54 (79%)	70 (89%)	$X^2(1)=2.34$	0.13
Psychotic type	25 (36%)	20 (25%)	$X^2(1)=2.07$	0.15
Medication: imipramine/ venlafaxine	70/0	38/41	$X^2(1)=50.12$	0.01

Table 2. Mean daily dose of imipramine and venlafaxine, mean blood level of imipramine, mean Hamilton rating scale of depression (HAM-D) scores at baseline, after 2 weeks of antidepressant treatment, after 6 weeks (endpoint) of antidepressant treatment, and the reduction in HAM-D score after 6 weeks compared with the baseline HAM-D score.

	Study 1 Imipramine (n=70)	**Study 2 Imipramine (n=38)**	**Study 2 Venlafaxine (n=41)**	***P* value**
Mean daily dose ± SD (range)	253.3 ± 76.9 (150-450) mg/day	209.7 ± 94.0 (50-450) mg/day	371.3 ± 16.4 (300-375) mg/day	
Mean blood level ± SD (range)	290.8 ± 68.5 (191.9-520.6) ng/ml	287.3 ± 70.4 (134.0-432.0) ng/ml	-	
Baseline HAM-D score, mean ± SD (range)	24.5 ± 5.3 (14-37)	27.9 ± 5.3 (19-40)	26.1 ± 4.9 (19-37)	$F(2)=5.36$; p=0.01
HAM-D score at week 2, mean ± SD (range)	18.7 ± 6.9 (2-34)	20.6 ± 5.8 (3-31)	20.5 ± 6.6 (6-39)	$F(2)=1.37$; p=0.26
Endpoint HAM-D score, mean ± SD (range)	15.1 ± 8.2 (2-30)	17.1 ± 8.9 (1-34)	14.2 ± 8.8 (1-36)	$F(2)=1.16$; p=0.32
Reduction HAM-D score after 6 weeks, mean ± SD	-9.40 ± 7.94	-10.84 ± 10.83	-11.95 ± 7.77	$F(2)=1.15$; p=0.32

Overall response

According to the criterion of a ≥ 50% reduction on the HAM-D score, 61 of the 149 (41%) patients were responders after 6 weeks of antidepressant treatment: 26 of 70 (37%) patients treated with imipramine in study 1 were responders, 16 of 38 (42%) patients treated with imipramine in study 2 were responders, and 19 of 41 (46%) patients treated with venlafaxine in study 2 were responders. There was no difference regarding the rate of response between the three treatment subgroups ($\chi^2(2)=0.93$, p=0.63) and between the combined imipramine treatment subgroup (from study 1 and study 2) and the venlafaxine treatment subgroup ($\chi^2(1)=0.68$, p=0.41).

Predictive value of early improvement

We analyzed the predictive value of early improvement as a predictor of eventual response. As mentioned earlier, response was defined as a ≥ 50% reduction on HAM-D score relative to the baseline HAM-D score. We calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), false-positive rate, false-negative rate, and area under the curve (AUC) to investigate the predictability of early improvement to predict eventual response. For early improvement, we used several definitions, i.e., a ≥ 15, 20, 25, or 30% reduction on HAM-D score at weeks 1 and 2, respectively (Table 3). Our results show that early improvement is a moderately sensitive predictor for eventual response. Also, a higher cutoff level tends to decrease

the sensitivity; e.g., the cutoff level of 30% early improvement shows a lower sensitivity compared with the cutoff level of 25% early improvement. To identify a predictor with both acceptable specificity and sensitivity, we constructed ROC curves comparing a ≥ 15, 20, 25, and 30% reduction on the HAM-D score at week 2: the cutoff point of at least 25% improvement on the HAM-D score at week 2 showed both acceptable specificity and sensitivity. The area under the ROC curve for the predictor 25% improvement at week 2 to predict eventual response was 0.66, indicating poor predictability. Sensitivity analyses supported the choice of the 25% cutoff point. After removal of the dropouts, area under the curve was 0.65 (sensitivity 0.61; specificity 0.69), and after removal of the patients using concomitant medication, area under the curve was 0.67 (sensitivity 0.63; specificity 0.72). Figure 2 presents the sensitivity of the predictor: of the 85 patients not achieving early improvement after 2 weeks of antidepressant treatment, only 23 (27%) were responders after 6 weeks of antidepressant treatment. The limited specificity of the predictor is also shown: of the 64 patients achieving early improvement after 2 weeks of antidepressant treatment, 26 (41%) were non-responders after 6 weeks of antidepressant treatment.

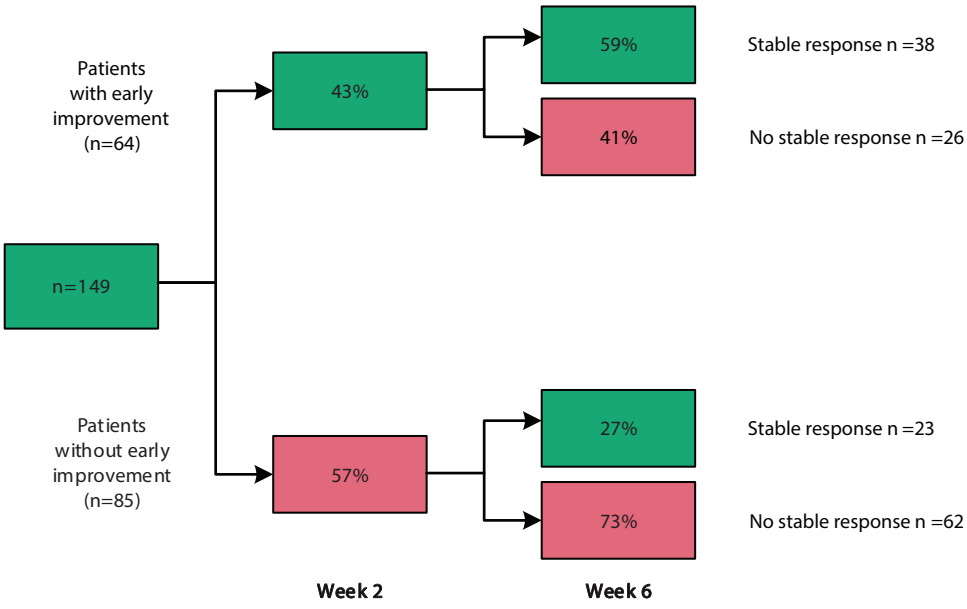

Figure 2. Flow diagram of predictive value of early improvement (≥ 25% reduction on HAM-D score at week 2) for eventual response (≥ 50% reduction on HAM-D score at week 6).

Table 3. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC) of improvement on Hamilton rating scale of depression (HAM-D) score to predict response at week 6 (n=149).

Week	Sensitivity	Specificity	PPV	NPV	False-positive rate	False-negative rate	AUC
Improvement (predictor) "at least 15% reduction on HAM-D score"; response "at least 50% reduction at week 6".							
1	0.62 (38/61)	0.67 (59/88)	0.57 (38/67)	0.72 (59/82)	0.33 (29/88)	0.38 (23/61)	0.65
2	0.74 (45/61)	0.45 (40/88)	0.48 (45/93)	0.71 (40/56)	0.55 (48/88)	0.26 (16/61)	0.60
3	0.87 (53/61)	0.43 (38/88)	0.51 (53/103)	0.83 (38/46)	0.57 (50/88)	0.13 (8/61)	0.65
Improvement (predictor) "at least 20% reduction on HAM-D score"; response "at least 50% reduction at week 6".							
1	0.48 (29/61)	0.74 (65/88)	0.56 (29/52)	0.67 (65/97)	0.26 (23/88)	0.52 (32/61)	0.61
2	0.66 (40/61)	0.59 (52/88)	0.53 (40/76)	0.71 (52/73)	0.41 (36/88)	0.34 (21/61)	0.62
3	0.84 (51/61)	0.48 (42/88)	0.53 (51/97)	0.81 (42/52)	0.52 (46/88)	0.16 (10/61)	0.66
Improvement (predictor) "at least 25% reduction on HAM-D score"; response "at least 50% reduction at week 6".							
1	0.36 (22/61)	0.85 (75/88)	0.63 (22/35)	0.66 (75/114)	0.15 (13/88)	0.64 (39/61)	0.61
2	0.62 (38/61)	0.70 (62/88)	0.59 (38/64)	0.73 (62/85)	0.30 (26/88)	0.38 (23/61)	0.66
3	0.80 (49/61)	0.61 (54/88)	0.59 (49/83)	0.82 (54/66)	0.39 (34/88)	0.20 (12/61)	0.71
Improvement (predictor) "at least 30% reduction on HAM-D score"; response "at least 50% reduction at week 6".							
1	0.26 (16/61)	0.92 (81/88)	0.70 (16/23)	0.64 (81/126)	0.08 (7/88)	0.74 (45/61)	0.59
2	0.51 (31/61)	0.81 (71/88)	0.65 (31/48)	0.70 (71/101)	0.19 (17/88)	0.49 (30/61)	0.66
3	0.79 (48/61)	0.73 (64/88)	0.67 (48/72)	0.83 (64/77)	0.27 (24/88)	0.21 (13/61)	0.76

According to the defined criterion of a ≥ 25% reduction on the HAM-D score, 64 of 149 (43%) patients achieved early improvement after 2 weeks of antidepressant treatment: 31 of 70 (44%) patients in study 1 achieved early improvement after weeks of treatment with imipramine, 20 of 38 (53%) patients in study 2 achieved early improvement after 2 weeks of treatment with imipramine, and 13 of 41 (32%) patients in study 2 achieved early improvement after 2 weeks of treatment with venlafaxine. There was no difference between the three treatment subgroups regarding the rate of early improvement after 2 weeks of antidepressant treatment ($\chi^2(2)=3.62$, $p=0.16$). Also, there was no difference between the combined imipramine treatment subgroup (from study 1 and study 2) and the venlafaxine treatment subgroup ($\chi^2(1)=2.92$, $p=0.09$).

Survival analysis

Although there was a significant difference in several demographic and clinical characteristics between study 1 and study 2 (Table 1), this had no effect on time-related response. There was no difference ($\chi^2(1)=0.07$, $p=0.80$, log rank) in time to response between the imipramine treatment patients in study 1 and those in study 2. Similarly, there was no difference ($\chi^2(1)=0.76$, $p=0.38$, log rank) in time to response between the total imipramine treatment group (from study 1 and study 2) and the venlafaxine treatment group (from study 2). Therefore, we felt justified in combining the three treatment subgroups in order to compare time-related response. When combining the three treatment subgroups, there was a significant difference ($\chi^2(1)=30.58$, $p<0.001$, log rank) in time to response between patients achieving early improvement (≥ 25% reduction on HAM-D score at week 2) and patients not achieving early improvement (< 25% reduction on HAM-D score at week 2). The results from the sensitivity analyses support this finding. Kaplan-Meier curves were constructed to compare time-related response between patients achieving early improvement and those not achieving early improvement (Fig. 3). Difference between patients with and without early improvement was found after removal of the dropouts ($\chi^2(1)=26.14$, $p<0.001$, log rank) and after removal of the patients using concomitant medication ($\chi^2(1)=30.20$, $p<0.001$, log rank).

Early improvement and remission

We analyzed the predictive value of early improvement as a predictor of eventual remission. As mentioned earlier, remission was defined as a final HAM-D score ≤ 7. A significant difference ($\chi^2(1)=22.18$, $p<0.001$, log rank) was found in time to remission between patients achieving early improvement (≥ 25% reduction on HAM-D score at week 2) and patients not achieving early improvement (< 25% reduction on HAM-D score at week 2).

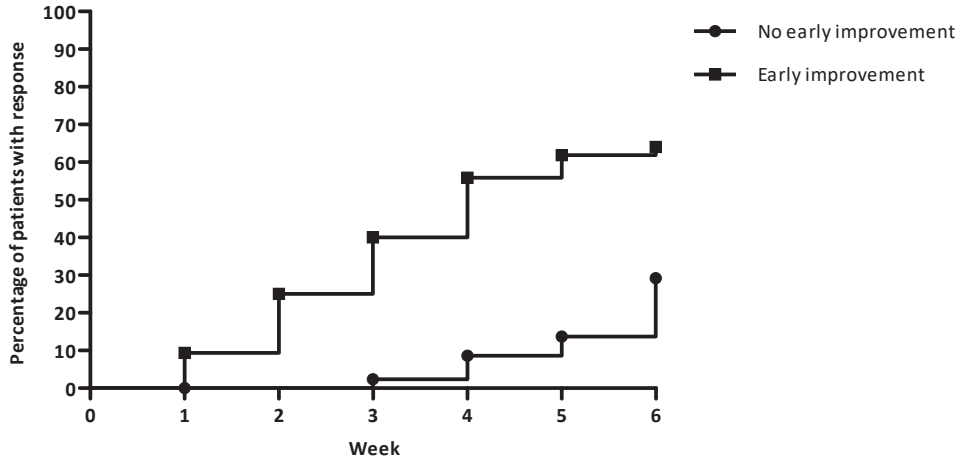

Figure 3. Time course of response (n=149): survival distributions divided into early improvement and no early improvement. Early improvement is defined as ≥ 25% reduction on HAM-D score at week 2. No early improvement is defined as < 25% reduction on HAM-D score at week 2. Response is defined as ≥ 50% reduction on HAM-D score at week 6.

DISCUSSION

This study shows that early improvement within 2 weeks of treatment with imipramine or venlafaxine is a moderately sensitive predictor for eventual response in an inpatient population with melancholic depression. However, 59% of the patients achieving early improvement became responders, whereas only 27% of the patients not achieving early improvement attained eventual response (Fig. 2). Although the sensitivity was modest, based on the severity of clinical symptoms, if early improvement is not seen after 2 weeks of treatment with imipramine or venlafaxine, a clinician treating a patient with severe major depression may seriously consider either switching antidepressant drug or the addition of lithium or switching to electroconvulsive therapy at an earlier stage than is presently customary. Since remission is often considered an outcome of higher clinical significance[39] than response, we also analyzed the predictive value of early improvement for eventual remission; early improvement was found to predict remission as well.

Comparison with previous reports

The present results lead us to conclude that early improvement within 2 weeks of treatment with imipramine or venlafaxine predicts eventual response. These results are in accordance with Entsuah et al.[15] and Khan et al.[18] who investigated the early onset of antidepressant response of venlafaxine treatment and also in accordance with Khan et al.[17] and Volz et al.[20] who examined the early onset of antidepressant response of imipramine treatment. The response rate of 27% in patients without early improvement is larger than the response rate in similar patients found in a large meta-analysis.[40]

In contrast, our results are not in agreement with the results of Quitkin et al.[2-7] A possible explanation for this discrepancy could be that Quitkin et al. mainly investigated outpatients with mild to moderate depression, whereas we investigated severely depressed inpatients with melancholic subtypes of depression. Another explanation could be that Quitkin et al. used the Clinical Global Impression Scale as primary outcome measure, whereas we used HAM-D. Moreover, different active drugs were investigated: in their analysis, Quitkin et al.[2-7] mostly combined patients treated with desipramine, mianserin, phenelzine, or imipramine.

Our statistical approach is similar to that of previous studies.[12-13,25] Overall, we found a 41% response rate and a 43% early improvement rate, defined as a reduction of ≥ 25% from the baseline HAM-D score after 2 weeks of antidepressant treatment. Compared with the previously mentioned studies, our response and early improvement rates were lower, which might be attributed to a more severely depressed patient population. Low placebo response rates are seen in severely depressed patients.[41] Based on the severity of our sample, we assume that placebo response in our study would have been low, lowering the overall response rate. Furthermore, the differences in results might be explained by differences in patient population, in the type of antidepressants used, and in study design. Szegedi et al.[13] investigated an outpatient population with a mean baseline HAM-D-17 score of 22.4; the patients were randomly assigned to treatment with either mirtazapine or paroxetine. Van Calker et al.[25] investigated an inpatient population with a mean baseline HAM-D-17 score of 23.2; 65% of their patients had melancholic features, and they were assigned to treatment with either sertraline or amitriptyline plus additional psychotherapy. Henkel et al.[12] investigated an inpatient population with a mean baseline HAM-D-21 score of 25.1; their patients were treated with various antidepressants and co-medication.

The present study investigated a sample of severely depressed inpatients treated with either imipramine or venlafaxine: these had a baseline HAM-D score ≥ 24, 80–90% had melancholic features, and 25–36% of the patients had psychotic features.

The homogeneity and severity of the depressive symptoms and the accuracy of the diagnosis (enhanced by a routine drug-free observation period and confirmation of the diagnosis by a structured interview) are considered major strengths of the study. Also considered as strength is the small percentage of our patients receiving concomitant treatment because benzodiazepines may affect HAM-D scores through their influence on symptoms (e.g., anxiety, insomnia); this may have affected the response rates to antidepressants in previous studies.

The definition of "early improvement" needs further discussion: different cutoff points of early improvement have been used by others (e.g., a reduction of ≥ 20, ≥ 25, or ≥ 30% at 2 weeks of antidepressant treatment). We have no explanation for this difference in cutoff points defining early improvement. In our analysis, we found that the cutoff point of ≥ 25% improvement from the baseline HAM-D score at 2 weeks of antidepressant treatment showed the most acceptable combination of sensitivity and specificity.

Study limitations

Due to the absence of a placebo control group, we are unable to draw definite conclusions about the rate of a spontaneous improvement during a specific time period. Furthermore, the provided treatment program was in fact multimodal rather than strictly pharmacological. Other ingredients of the treatment program may have affected both early improvement and treatment response. However, since the included patients suffered from melancholic depression, we assume that the placebo response in the present study would have been low.

The homogeneity and severity of depressive symptoms in our patients (a major strength of the study) is also a limitation due to its limited generalizability to "real-world" outpatient settings. We deliberately choose to include patients with a major depressive disorder both with melancholic features and/or psychotic features (patients with bipolar disorder were excluded from both studies); the broader patient selection may have caused an underestimation of the overall treatment response. Likewise, overall response may have been underestimated due to the study design: some patients may require a treatment period over 6 weeks to respond. Another limitation is that the time of onset of response was not the primary objective of the two studies used for the present analysis, which was conducted in a post hoc manner. Also, although the pooling of data from two independent studies can be questioned, both studies were almost identical in study design;[32-33] moreover, we performed a sensitivity analysis to justify pooling the data.

We conclude that the present study is a relevant analysis since it shows the time course of response to treatment with either imipramine or venlafaxine in an inpatient population with melancholic depression. The most relevant finding is that 59% of the patients achieving early improvement became responders, whereas only 27% of the patients not achieving early improvement attained eventual response. These results lead us to conclude that, based on the severity of clinical symptoms, if early improvement is not seen after 2 weeks of treatment with imipramine or venlafaxine, a clinician treating a patient with severe major depression may seriously consider changing the treatment at an earlier stage than is presently customary. For a definite answer, whether antidepressants should be changed in case of early nonresponse, there is a need for controlled prospective studies. These studies should compare a switch strategy with a continuation strategy in early nonresponders to antidepressants.

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CHAPTER 6

Influence of gender and menopausal status on antidepressant treatment response in depressed inpatients

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ABSTRACT

Objective: The present study investigated the influence of gender and menopausal status on treatment response in depressed inpatients, treated with either imipramine or fluvoxamine.

Method: The patients were divided into three groups: men, premenopausal women and postmenopausal women. A multivariate analysis was performed using the difference in Hamilton score (pretreatment – post-treatment) for imipramine and fluvoxamine as dependent variable. The following independent variables were used: the baseline Hamilton score, the antidepressant used, the gender-group and the interaction between the type of antidepressant and gender.

Results: In total, 138 patients with a DSM-IV diagnosis of depressive disorder were analysed. Men responded more favorably to imipramine (B=7.12, P=0.005). Premenopausal women had a better response rate to fluvoxamine than men (B=−8.66, P=0.027).

Conclusion: In depressed inpatients, men respond more favorably to imipramine than to fluvoxamine. Premenopausal women respond more frequently to fluvoxamine than men.

INTRODUCTION

The prevalence of depression is different among men and women, with women twice as likely to suffer from depression.[1] Especially the changing hormonal milieu during the perimenopausal transition is thought to contribute to the increased susceptibility of depression in that period.[2] Available data show that depression in older postmenopausal women is associated with estradiol levels below a certain threshold.[3] Estradiol levels may also influence the therapeutic potential of antidepressants. Estrogen may enhance serotonergic responsivity and enable receptor down-regulation or normalize blunted serotonergic responsivity.[4-5] The effects of estrogen on the serotonergic system could contribute to differences in antidepressant response.

Several articles have explored the topic of gender differences in terms of response to antidepressants. In a 12-week multicentre, double-blind, randomised, parallel-group comparative trial, premenopausal women showed better response rates when taking sertraline, a selective serotonin reuptake inhibitor (SSRI), whereas men showed better response rates when taking imipramine, a tricyclic antidepressant (TCA), and postmenopausal women showed similar response rates for both antidepressants.[6] It was concluded that women might respond better to SSRIs than to TCAs and that there is indeed a difference in response rate by menopausal status.[6] The results of most previous studies are comparable to this trial.[7-13] In a recent study with a large sample of real world patients from primary and psychiatric specialty care centres, women were more likely to reach remission and response with citalopram than men.[14]

However, complementary studies have failed to find different response rates to antidepressants between men and women. Quitkin et al.[15] performed a retrospective analysis on depressed outpatients (the majority with atypical depression) and concluded that the statistical significant difference in response rates to TCAs and monoamine oxidase inhibitors (MAOIs) based on gender and menopausal status was not clinically relevant. Similarly, other studies concluded that there is no difference in antidepressant treatment response based on gender[16-19] or on menopausal status.[20]

Overall the conclusions on the influence of gender and menopausal status on antidepressant treatment response in depressed patients are inconsistent; therefore, this study explores these groups in a relatively homogenous population of depressed inpatients. Moreover, the failure to detect gender differences in response to antidepressants may be due to methodological shortcomings. The present study differs from other studies with regard to optimization of dose with blood level targeting for both

drugs, the paucity of concurrent medication to prevent obscuring severity assessment of the depression, high compliance and a low dropout rate.[21] The close monitoring of plasma levels rules out pharmakinetic explanations for response differences.

The present study is a post hoc analysis of a randomised trial in which imipramine and fluvoxamine were compared with depressed inpatients.[21] The results showed a significant difference in response between the two antidepressants: the efficacy of imipramine being superior to that of fluvoxamine. The focus of the present study is on three gender-groups: men, premenopausal women, and postmenopausal women. First, the three groups are investigated separately, and then they are compared with each other, to see if there is a difference in response in terms of efficacy of imipramine and fluvoxamine.

Objective of this study

We hypothesized that men will show a better response rate to imipramine than to fluvoxamine and that postmenopausal women will also better respond to imipramine than to fluvoxamine, and that premenopausal women will better respond to fluvoxamine than to imipramine. When comparing men with premenopausal women, we expect that men will respond to imipramine with greater efficacy than premenopausal women, but that there will be no difference in response to either drug when comparing men with postmenopausal women. Finally, it is hypothesized that premenopausal women will respond to fluvoxamine with greater efficacy than postmenopausal women.

MATERIALS AND METHODS

Methods and patient selection

Data were collected at the Department of Psychiatry of the Erasmus Medical Centre in Rotterdam and at the Parnassia Psychomedical Centre in The Hague between April 1997 and July 2001. After admission, all psychotropic drugs were discontinued and following written informed consent, the patients participating in the study received single blind placebo over a period of 4 days. After this four-day period, the patients were reassessed with the 17-item version of the Hamilton Rating Scale for Depression (HRSD). Patients with schizophrenia, bipolar or schizo-affective disorder, organic brain syndrome, chronic alcohol or drug abuse, relevant somatic illness and presence of absolute contraindication for either imipramine or fluvoxamine, refractoriness to clinical treatment with a TCA or fluvoxamine with adequate plasma level for at least 4 weeks during present episode, pregnancy or the risk to become pregnant, and an improvement of ≥ 50% on the HRSD

during the four-day placebo run-in period were excluded from the study. Those patients still meeting the inclusion criteria after the four-day placebo period were randomly assigned to a double-blind treatment with either imipramine or fluvoxamine. For both imipramine and fluvoxamine, the dose administered was adjusted for each patient to obtain a predefined blood level. The predefined blood level was 200–300 ng/mL for imipramine and 150–200 ng/mL for fluvoxamine. In total, 138 patients aged 18–65 years with a DSM-IV diagnosis of depressive disorder and a HRSD score ≥ 17 were included. Of these, 70 patients were assigned to receive imipramine and 68 patients were assigned to receive fluvoxamine (Table 1).

Table 1. Characteristics of the patients included in the analysis.

	Imipramine (n=70)	**Fluvoxamine (n=68)**
Gender groups		
Male	27	18
Female < 50 years	16	15
Female ≥ 50 years	27	35
Change in HRSD score from baseline adjusted for baseline score		
Male (SE)	-16.3 (1.6)	-11.3 (2.0)
Female < 50 years (SE)	-9.0 (2.1)	-12.1 (2.2)
Female ≥ 50 years (SE)	-13.9 (1.6)	-13.1 (1.4)
Age		
Mean ± SD (range) in years	51.7 ± 9.1 (19-65)	53.2 ±10.0 (27-65)
Male mean ± SD in years	52.6 ± 7.1	53.5 ± 9.1
Female < 50 years ± SD	40.4 ± 7.1	40.2 ± 7.3
Female ≥ 50 years ± SD	57.6 ± 4.9	58.8 ± 4.5
Baseline HRSD		
Mean total score ± SD (range)	24.5 ± 5.3 (14-37)	24.4 ± 4.9 (14-37)
Male mean total score ± SD (range)	24.9 ± 5.4 (17-37)	27.2 ± 3.6 (21-34)
Female < 50 mean total score ± SD (range)	26.3 ± 4.9 (17-35)	22.3 ± 4.6 (16-33)
Female ≥ 50 mean total score ± SD (range)	23.1 ± 5.2 (17-35)	23.7 ± 5.2 (14-37)
Difference in HRSD		
Mean difference between HRSD at baseline and the last HRSD score ± SD (range)	-9.4 ± 8.3 (-27-12)	-6.3 ± 8.5 (-29-15)

Abbreviations: HRSD, Hamilton Rating Scale of Depression; SE, standard error.

For the analysis, the patients receiving each antidepressant are subdivided into three groups based on gender and menopausal status (Figure 1). The first group consists of men; the second consists of women under the age of 50 years (premenopausal women), and the third group includes women aged 50 years and older (postmenopausal women). We used the age of 50 as a parameter for menopausal status. This is only a

proxy for menopausal status in women. The three groups are analysed individually to establish whether there are any intragroup different responses in terms of efficacy of imipramine and fluvoxamine. Furthermore, the three groups are compared with each other (inter group) to reveal any differences in-group responses in terms of efficacy of the two antidepressants.

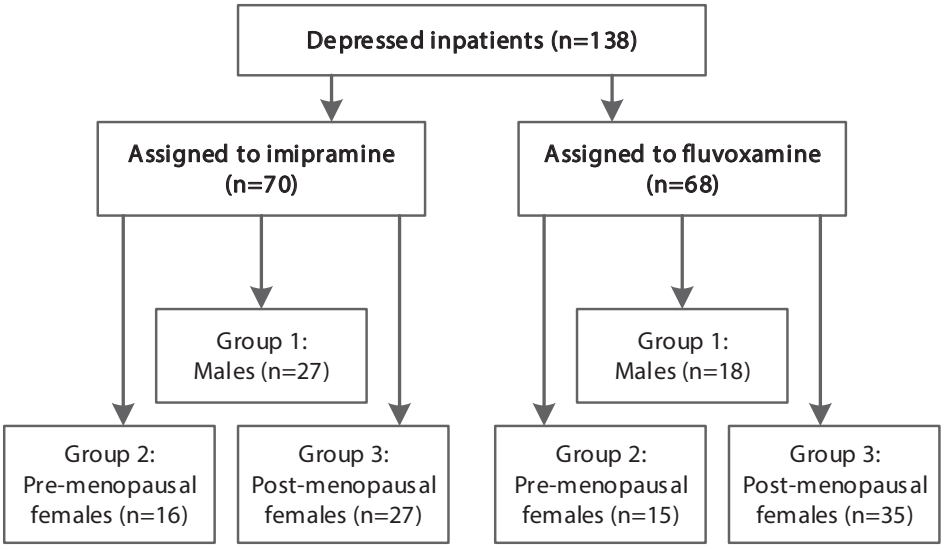

Figure 1. Subdivision of three groups based on gender and menopausal status.

Measures

The patients were evaluated on a weekly basis using the HRSD and the Clinical Global Improvement (CGI) scale, which was continued until 4 weeks after attaining predefined blood levels.[21]

Statistical analysis

The response to antidepressants is measured using the difference between the HRSD score at baseline and the last HRSD score or the HRSD score 4 weeks after attainment of the predefined blood level. Multivariate analysis is used as statistical method. The dependent variable is the difference in Hamilton score (pretreatment – post-treatment) for imipramine and fluvoxamine. In the multivariate analysis, the following independent variables are used: the baseline Hamilton score, the antidepressant used (imipramine or fluvoxamine, random); the gender group (men, women < 50 and women ≥ 50

years); and the interaction between the type of antidepressant and gender. Differences between gender groups are analysed with multiple linear regression analysis with the difference in Hamilton scores for fluvoxamine and imipramine as dependent variable, and baseline HRSD, the type of antidepressant and the other gender-groups introduced as independent variables. For this analysis, a SPSS version 13 for windows (SPSS Inc., Chicago, Ill.) package is used. The statistical significance is defined as $P<0.05$.

RESULTS

In total, 140 subjects were randomised. Of these 140 subjects 138 were analysed. The two remaining subjects had missing values on all HRSD scores throughout; one male of 56 years and one female of 42 years old, both randomised to the fluvoxamine group.

The mean changes from baseline in HRSD scores, adjusted for baseline HRSD score per group are also presented in Table 1. The difference of change from baseline between fluvoxamine minus imipramine adjusted for baseline HRSD in men was 4.9; in the group of women < 50 and ≥ 50 years it was −3.1 and 0.8, respectively.

Multiple linear regression analyses showed that for men there was a significant difference in response to imipramine and fluvoxamine (B=7.12, P=0.005); men respond more favourably to imipramine. For premenopausal and postmenopausal women, there was no significant difference in response to both antidepressants (B=−1.55, P=0.600 and B=2.33, P=0.260) (Table 2).

Multiple linear regression analysis was used to compare the three gender groups for significant differences between groups in response to antidepressant treatment. Comparison of men with premenopausal women showed that men had a significantly better response rate to imipramine than premenopausal women (B=8.66, P=0.027), and that premenopausal women had a significantly better response rate to fluvoxamine than men (B=−8.66, P=0.027). When comparing men with postmenopausal women, no significant difference was found in response to imipramine or fluvoxamine (B=4.78, P=0.138; B=−4.78, P=0.138). Similarly, when comparing postmenopausal and premenopausal women there was no significant difference in response to both antidepressants (B=3.88, P=0.284; B=−3.88, P=0.284) (Tables 3 and 4).

Table 2. Regression coefficients, with the difference in Hamilton scores for fluvoxamine and imipramine as dependent variable, adjusted for baseline Hamilton score.

Gender group	Unstandardized coefficients		95% CI	*P* value
	B	SE		
Males	7.12	2.47	2.28–11.95	0.005
Females				
< 50 years	–1.55	2.94	–7.31–4.21	0.600
≥ 50 years	2.33	2.06	–1.70–6.37	0.260

Abbreviations: *B*, beta; SE, standard error; CI, confidence interval.

Table 3. Regression coefficients, when comparing the gender-groups to one another for the antidepressant treatment response analysis.

Gender group	Unstandardized coefficients		95% CI	*P* value
	B	SE		
Males compared with females < 50 years	8.66	3.88	1.05 to –16.28	0.027
Females < 50 years compared with males	–8.66	3.88	–16.28 to –1.05	0.027
Males compared with females ≥ 50 years	4.78	3.20	–1.50 to 11.06	0.138
Females ≥ 50 years compared with males	–4.78	3.20	–11.06 to 1.50	0.138
Females ≥ 50 years compared with females < 50 years	3.88	3.60	–3.18 to 10.94	0.284
Females < 50 years compared with females ≥ 50 years	–3.88	3.60	–10.94 to 3.18	0.284

Abbreviations: *B*, beta; SE, standard error; CI, confidence interval.

Table 4. Differences in trial effect between groups, all results were adjusted for baseline HRSD.

Contrast	Mean difference in trial effect	*P* value
Group 1 – Group 2	8.05	0.046
Group 1 – Group 3	4.19	0.21
Group 2 – Group 3	–3.86	0.30

Group 1: men, group 2: women < 50, group 3: women ≥ 50 years. The overall P-value for the between group differences in trial effect is 0.13; HRSD, Hamilton Rating Scale of Depression.

DISCUSSION

The present study investigated the effect of gender and menopausal status on treatment response to imipramine and fluvoxamine in depressed inpatients. In depressed inpatients, men respond more favourably to imipramine than fluvoxamine. Premenopausal women respond more frequently to fluvoxamine than men.

Men versus premenopausal women

For men, there was a significant difference in treatment response to imipramine and fluvoxamine, and men responded more favourably to imipramine. When comparing men with premenopausal women, men responded more favourably to imipramine than premenopausal women, and premenopausal women responded more favourably to fluvoxamine than men. These conclusions are in agreement with some earlier studies,[6-14] but in contrast to others.[15-20]

Many studies have concluded that gender and menopausal status do not influence antidepressant treatment response,[15-20] which contradicts the conclusions of the present study. There are several possible explanations for this discrepancy, the most important being the difference in patient populations. For example, Quitkin et al.[15] included mainly patients with atypical depression, and Wohlfarth et al.[18] included relatively large numbers of men and relatively more premenopausal women, whereas the present study included inpatients with major depression. In addition, the study by Scheibe et al.[16] included outpatients with varying levels of severity, chronicity and recurrence, which could also account for the overall low response to antidepressant medication that they found. Other possible explanatory factors are that one study covered a period of 20 years,[15] another study did not use randomization and grouped the data of several different TCAs together, which could have diluted the results,[16] and yet another study prescribed rather low doses of antidepressant.[19] Furthermore, the fluoxetine study by Quitkin et al.[15] was an open trial and lacked data on menopausal status, and Wohlfarth et al.[18] performed a meta-analysis of 32 small randomised controlled trials, which means that their conclusions depend on the quality of the studies involved, which was difficult to assess. Thus, there are several explanations as to why an existing difference in treatment response based on gender and menopausal status could have been missed by some earlier studies. These factors are differing in patient population and differences in trial design.

A major advantage of the present study is that the patients included were all depressed inpatients,[21] whereas other studies included mainly depressed outpatients. Besides the differences in the studied populations, some methodological aspects of the present study can account for results differing from those of previous studies. Our patient group was supervised more closely, which reduces noncompliance. Additionally, this study differs from other studies due to optimization of drug dosage according to a predefined blood level;[21] the close monitoring of plasma levels further reduced noncompliance and rules out pharmakinetic explanations for response differences.

Men versus postmenopausal women

In the present study, there was no significant difference in treatment response to either imipramine or fluvoxamine when comparing men with postmenopausal women. This conclusion corresponds with the hypothesis that men and postmenopausal women show similar treatment response to imipramine and fluvoxamine.

Pre versus postmenopausal women

Finally, this study shows that pre and postmenopausal women do not respond better to either imipramine or fluvoxamine. Similarly, comparison of pre versus postmenopausal women reveals no significant difference in treatment response to either antidepressant. These findings are in contrast to the conclusion of Kornstein et al.[6] and Martényi et al.[7] amongst others and do not correspond with the hypothesis of the present study.

The limitations of the present study are also possible explanations for the lack of a significant difference in treatment response between pre and postmenopausal women. The arbitrary age limit chosen to define menopausal status and not taking into account the symptoms of oligomenorrhea and amenorrhea together with the small sample size in the premenopausal groups compared with the larger number of inpatients in the postmenopausal groups due to non-randomization of the gender groups is the most probable explanation for not finding a significant difference in treatment response between pre and postmenopausal women.

Theories

Various theories have been introduced to explain the influence of gender and menopausal status on antidepressant treatment response; Kornstein mentions several of these.[6,22] First, the inhibition of the reuptake of serotonin by sertraline (SSRIs) may be important for younger women, since it is also effective as treatment for premenstrual dysphoric disorder. Second, the difference in treatment response may be due to the depressive subtype: atypical depressions (which are treated more effectively with SSRIs or MAOIs), which are more common among women. A final theory is that female sex hormones may affect treatment response: women' gonadal hormones may either increase the response to SSRIs or decrease the response to TCAs and estrogen may improve serotonergic activity. As Grigoriadis et al.[10] discuss, oestrogen may enhance serotonergic responsivity and enable receptor down-regulation or normalize weakened serotonergic responsivity. Rasgon et al.[2] showed that postmenopausal women who were randomised to sertraline (SSRI) combined with oestrogen therapy (OT) showed significantly earlier treatment response compared with postmenopausal women who were randomised to sertraline and placebo; however, there was no significant difference in the overall remission rates. The addition of OT to SSRI was therefore explained by Rasgon et al.[2] as having a synergistic effect on treatment response, possibly due to improved serotonergic response early in the treatment phase.

In future research on the influence of gender and menopausal status on treatment response in depressed inpatients, we suggest that the patients should be selected beforehand for gender and menopausal status instead of using an existing database; also, the patients should be randomised for treatment with either antidepressant after the selection. Furthermore, the menopausal status of women should be defined based on symptoms of menopause instead of based on age alone. If these results are replicated in such a randomised trial, this could have consequences for treatment of depressed patients with antidepressants. Male patients should preferably be treated with a TCA before being called treatment resistant. Treatment of depressed female patients should be influenced by their menopausal status before being labelled having a treatment resistant depression.

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CHAPTER 7

Summary and general discussion

In this thesis we investigated the efficacy of three phases of a treatment algorithm of inpatients with severe depression: *phase I* optimal antidepressant monotherapy (plasma level-targeted dose imipramine or high-dose (375 mg/day) venlafaxine); *phase II* subsequent lithium addition in case of insufficient improvement of antidepressant monotherapy; *phase III* subsequent ECT in case of insufficient improvement of antidepressant-lithium treatment. Furthermore, we investigated several predictive factors of antidepressant treatment response in severely depressed inpatients. The main findings and clinical implications of our findings are discussed below. Lastly, recommendations for future research are made.

MAIN FINDINGS

Chapter 2 presents a randomized double-blind clinical trial comparing the efficacy of 7-weeks treatment with predefined plasma level-targeted dose imipramine (200-300 ng/ml) versus high-dose venlafaxine (300-375 mg/day) in inpatients diagnosed with a major depressive episode. The patient population of this study consists of a homogeneous group of severely depressed inpatients with a mean age of 54 years, a mean baseline HAM-D score of 26.7, almost all with melancholic features (96%) and the majority having a recurrent episode (60%). Although it may be considered a major strength, the homogeneous study sample limits the generalizability of the results. Both the proportion of responders (50.0% vs. 39.5%), defined as a ≥ 50% reduction on the HAM-D score, and the proportion of remitters (35.7% vs. 23.3%), defined as a HAM-D score ≤ 7, are non-significantly larger in patients treated with venlafaxine. The mean reduction in HAM-D score (12.3 vs. 10.8 points) is also non-significantly larger in patients treated with venlafaxine. Even though the present study was slightly underpowered, which is considered a limitation, these results imply venlafaxine to be at least equal in efficacy compared with imipramine for the treatment of severely depressed inpatients.

This thesis emphasizes the importance of adequate antidepressant treatment in depressed inpatients. In this context, the term "adequate treatment" means having an accurate diagnosis of major depressive disorder and assuring treatment being given in an adequate dosage for a sufficient duration in time. This is considered a major strength of the present study. Accurate diagnosis was achieved by both a routine drug-free observation period and diagnosis confirmation using the SCID-I interview conducted by clinicians. For the imipramine-treated group, adequate dosage was achieved by using predefined plasma level-targeted dosing, preventing underdosing and assuring treatment compliance. Therapeutic drug monitoring is considered state-

of-the-art for imipramine.[1-2] For the venlafaxine-treated group, adequate dosage was achieved by gradually increasing to maximum dosage (300-375 mg/day) whereby all study medication was taken in the presence of the nursing staff to maximize treatment compliance. Previous research has shown the efficacy of venlafaxine to be higher at dosages ≥ 225 mg compared with dosages ≤ 150 mg.[3] Finally, all patients in this study were treated over a period of 7 weeks, with either venlafaxine or imipramine, resulting in sufficient duration in time. Thus in this thesis, adequate antidepressant treatment, as described above, was accomplished. The broad inclusion criteria, the relatively low overall drop-out rate (7%) and the low concurrent use of benzodiazepines (14%) further contribute as strengths of this study. The homogeneous patient group of this thesis limits the generalizability of the results, but contributes to benefit the reliability and validity of the results.

Subsequently, **chapter 3** presents a two-phase double-blind randomized non-inferiority trial comparing the efficacy of two 11-week antidepressant treatment strategies in inpatients diagnosed with a major depressive episode. The two antidepressant treatment strategies being compared were the following: *strategy A* predefined plasma level-targeted dose imipramine (200-300 ng/ml) and subsequent lithium addition in case of non-response to imipramine; *strategy B* high-dose venlafaxine (300-375 mg/day) and subsequent lithium addition in case of non-response to venlafaxine. As a result of the two-phase study design, whereby adequate antidepressant monotherapy (the results are previously described in chapter 2) was given prior to lithium addition, the efficacy of subsequent lithium addition in case of non-response to antidepressant monotherapy could be accurately assessed. When comparing the two antidepressant treatment strategies, initially, non-inferiority was established, and thereafter, a significant difference was found in the proportion of responders (HAM-D score reduction ≥ 50%) in favor of the venlafaxine-lithium treatment strategy (77% vs. 52%). Both the proportion of remitters (50% vs. 34%), defined as a HAM-D score ≤ 7, and the mean reduction in HAM-D score (16.1 vs. 13.5 points) are non-significantly larger in the venlafaxine-lithium treatment strategy. These results imply the venlafaxine-lithium treatment strategy, which has only rarely been studied prior to this thesis, to be a useful treatment strategy in inpatients diagnosed with a major depressive episode.

Several theories have been proposed regarding the underlying mechanisms of the therapeutic effects of lithium addition to an antidepressant for the treatment of major depressive disorder. It has been suggested that lithium addition in treatment-resistant depression may alter serotonin transmission to achieve treatment response.[4] Lithium on its own was shown to enhance the synthesis and release of serotonin in animals, i.e. rats and cats.[5] An alternative explanation is that the treatment effect of lithium

addition is caused by the antidepressant effect of lithium itself.[6] Alongside these theories, based on other animal studies, it is assumed that the increased serotonin sensitization of postsynaptic neurons as a result of long-term TCA treatment might account for the synergistic effect of lithium combined with a TCA in non-responding patients.[7] Also, it has been suggested that a pharmacokinetic interaction of lithium addition to an antidepressant does not explain the treatment effect observed, since antidepressant plasma levels remain constant after lithium addition.[8] However, the exact pharmacological effect of lithium addition to antidepressant treatment remains to be established.

The results of this study are in favor of the venlafaxine-lithium treatment strategy and we have no straightforward explanation for these results. Although meta-analyses conclude that lithium addition is effective with various types of antidepressants (both TCAs and second-generation antidepressants),[9-10] the generally accepted hypothesis is that lithium addition works preferentially with serotonergic and mixed reuptake inhibitors but it may be less effective with noradrenergic reuptake inhibitors.[11] Imipramine is a TCA characterized by the inhibition of both serotonin and noradrenaline reuptake[12] and venlafaxine at high doses (375 mg/day), as used in the present study, works in a similar way by also inhibiting both serotonin and noradrenaline reuptake.[13] However, most TCAs (i.e. imipramine) are more potent at the human norepinephrine transporter than at the serotonin transporter, whereas venlafaxine is more potent at the serotonin transporter and weakly potent at the human norepinephrine transporter.[14] The exact pharmacology of venlafaxine and imipramine is not entirely clear but, assuming the latter hypothesis, a stronger affinity of venlafaxine for the serotonin transporter might explain the favorable efficacy results in the venlafaxine-lithium treatment group of this thesis. However, the literature appears inconclusive whether lithium addition works preferentially with mixed reuptake inhibitors that have a potent effect on serotonin. There are previous studies contradicting the above-mentioned hypothesis, i.e. in these studies of patients with severe depression, lithium addition to a serotonergic agent, compared to lithium addition to a TCA, was shown to have inferior efficacy in treatment response.[15-16]

When considering adverse events, it is reported that lithium addition to venlafaxine carries a higher risk of serotonin toxicity. Two case reports described that lithium has a serotonin-intensifying effect when concomitantly used with venlafaxine causing serotonin syndrome,[17-18] a potentially life-threatening drug-related condition of increased serotonergic activity causing mental, autonomic and neuromuscular changes as tremor, diarrhea, delirium, rigidity and hyperthermia.[19] In the present study, despite high-dose venlafaxine (mean daily dose 371.4 mg/day) and adequate lithium dosing

(mean daily dose 968.4 mg/day and mean plasma level 0.77 mmol/L), no patients dropped out due to (serious) adverse events and no cases of serotonin syndrome were reported. In addition, no significant differences in common adverse events (i.e., tremor, transpiration, dry mouth, diarrhea, myoclonus, nausea and agitation) were found between the venlafaxine-lithium treatment group and the imipramine-lithium treatment group. We found no evidence for developing (serious) adverse events (e.g. serotonin syndrome) due to an interaction between venlafaxine and lithium. Based on the results of this thesis, and in contrast to the above-mentioned case reports,[17-18] we consider that there is no increased risk of developing (serious) adverse events when lithium is concomitantly used with venlafaxine.

Chapter 4 presents the single center treatment algorithm under study in this thesis, i.e. the overall feasibility and efficacy of a 3-phase treatment algorithm of severely depressed inpatients. *Phase I:* 7 weeks optimal antidepressant monotherapy (either imipramine or venlafaxine; also described in chapter 2); *phase II:* 4 weeks subsequent plasma level-targeted dose lithium addition in case of non-response in phase I (also described in chapter 3); *phase III:* subsequent electroconvulsive therapy (ECT) in case of non-response in phase II. The results show an overall dropout rate of 28% during the course of the three treatment phases. This dropout rate is fairly high, but it does not seem to be a result of low tolerability since dropout was shown primarily high in between the different treatment phases and not during the treatment phases. The data was analyzed using both a modified intention-to-treat analysis and a completers analysis; the proportion of patients achieving complete remission (HAM-D score ≤ 7) by the end of the 3-phase algorithm was 46% and 64%, respectively. Similarly, the proportion of patients that were responder (HAM-D score reduction ≥ 50%) by the end of the 3-phase algorithm was 71% and 93%, respectively. These favorable overall results emphasize the importance of following stepwise treatment algorithms, to optimize and enhance treatment outcome for the treatment of MDD.

Additionally, we evaluated the effects of the different baseline demographic and clinical characteristics of the study population on the likelihood to achieve remission during the 3-phase treatment algorithm. The baseline characteristics evaluated were: age, gender, educational level, duration of the index period, first episode, psychotic type and adequate pre-treatment with antidepressants. Three baseline characteristics showed a significant difference and were identified as possible predictors of achieving remission: a duration of the index episode ≤ 1 year, not having received an adequate pre-treatment with antidepressants and an education less than high school. The last, i.e. the educational level, does not seem a plausible predictor. In the literature, insight on predictors of antidepressant treatment response is scarce. A systematic review and

meta-analysis reviewed the evidence of the effects of duration of untreated major depression on clinical outcomes; they conclude that a shorter duration of untreated illness had an overall positive effect on both treatment response and treatment remission.[20] Furthermore, the authors conclude that, especially in a first episode of major depression, reducing the duration of untreated depression is important to prevent worse outcomes and chronicity.[20] These results correlate to the possible predictors of achieving remission identified in this thesis. Although we did not find a positive predictability of the variable first episode on achieving remission during the 3-phase treatment algorithm, we did find an index episode ≤ 1 year and not having an adequate pre-treatment with antidepressants as positive predictors of achieving remission. Altogether, this suggests that a longer duration of untreated depression and chronicity of symptoms have an unfavorable effect on antidepressant treatment outcome.

Presented in **chapter 5**, in line with the previous chapter, the predictive value of early improvement on antidepressants is assessed. It is assumed that a longer duration of non-response to antidepressant treatment may increase the likelihood of eventual non-response.[21] In this thesis we conducted a post hoc analysis to evaluate the predictive value of early improvement, i.e. early drug response defined as a ≥ 25 % reduction on HAM-D score occurring within the first two weeks of antidepressant treatment, in the course of treatment with imipramine or venlafaxine in severely depressed inpatients. Early improvement was found to be a modest sensitive predictor of eventual antidepressant treatment response (≥ 50% reduction on HAM-D score). Of the severely depressed inpatients achieving early improvement 59% became responder after 6 weeks of treatment, whereas only 27% of the patients not achieving early improvement became responder after 6 weeks of treatment. Taking into account the severity of clinical symptoms, the presence or absence of early improvement to antidepressant treatment may influence the stepwise treatment course of MDD, e.g. the absence of early improvement may result in switching treatment at an earlier stage than customary. However, the literature is inconclusive whether early improvement shortly after initiating treatment of major depressive disorder is a placebo effect[22] or a true early drug response.[23] Moreover, since the time of onset of response was not the primary objective of the two pooled clinical trials, the results of this post hoc analysis can be interpreted as preliminary results.

Chapter 6 presents a post hoc multivariate analysis evaluating the influence of gender and menopausal status on antidepressant treatment response in severely depressed inpatients, treated with either imipramine (TCA) or fluvoxamine (SSRI).

Women are more likely than men to develop MDD; the estimated lifetime prevalence of MDD is 13% in men and 24% in women, as reported in NEMESIS-2.[24] The risk to develop MDD is even higher during menopausal transition, in association with hormonal changes;[25-26] the likelihood of depressed mood in the menopausal transition is approximately three times greater compared with that during premenopause.[27]

In the literature, several studies address the topic of gender differences and menopausal status in terms of response to antidepressant treatment. A previous study in an outpatient population with chronic depression found men to respond significantly more favorably to imipramine (TCA) and women (especially premenopausal women) to respond significantly more favorably to sertraline (SSRI).[28] Other studies found similar results.[29-30] However, complementary studies failed to find a difference in antidepressant treatment response based on gender and menopausal status.[31-32]

In this thesis, the results showed severely depressed men to respond significantly more favorable to imipramine compared with fluvoxamine. For severely depressed premenopausal (< 50 years) and postmenopausal (≥ 50 years) women, we found no significant difference in response to imipramine and fluvoxamine. Analyzing differences in antidepressant treatment response between the groups, men showed a significantly higher response rate to imipramine than premenopausal women, and premenopausal women showed a significantly higher response rate to fluvoxamine than men. No significant difference in response to imipramine and fluvoxamine was shown when comparing men with postmenopausal women nor when comparing premenopausal with postmenopausal women. Limitations of the present study include defining menopausal status based solely on women's age and the small sample size of premenopausal women. In spite of the results of this post hoc analysis being preliminary, they offer promising new insights to enhance antidepressant efficacy.

One proposed theory regarding the underlying mechanism of the gender differences in antidepressant treatment response is that women's gonadal hormones may either enhance response to SSRIs or inhibit response to TCAs and estrogen may promote a greater response to SSRIs through enhancement of serotonergic activity.[28] Few preliminary studies investigated the effect of adjunct hormone replacement therapy (HRT) especially to SSRIs in peri- and postmenopausal women with treatment resistant depression[26,33] and found it to enhance antidepressant efficacy.

CLINICAL IMPLICATIONS OF THE FINDINGS

Altogether, the results of this thesis provide new and clinically useful insights for clinicians to guide the choice for specific antidepressants in the treatment of MDD. Even so, the results of this thesis have limited generalizability and only apply to a homogeneous group of inpatients diagnosed with major depressive disorder (MDD) with melancholic features. This thesis emphasizes the importance of accurate diagnosis of major depressive disorder prior to initiating adequate antidepressant treatment, consisting of optimal dosage for a sufficient duration in time. The results add to the current knowledge on antidepressant treatment and imply high-dose venlafaxine to be at least equal in efficacy, and therefore a useful alternative, compared to plasma level-targeted dose imipramine for the treatment of severely depressed inpatients. Subsequently, in case of non-response to antidepressant monotherapy, lithium addition both to venlafaxine and to imipramine is advised as relevant second-line treatment of severely depressed inpatients. Moreover, to optimize treatment outcome for the treatment of MDD, it is essential to follow stepwise treatment algorithms in nonresponders to the first antidepressant. Treatment algorithms help clinicians by step-wise categorizing the different treatments and guide the implementation of these treatments, which will enhance treatment outcome. Even though the patient population of this thesis consisted only of inpatients, we also consider these results to be useful for clinicians treating patients diagnosed with MDD with melancholic features in outpatient settings.

Predictors of antidepressant treatment response will contribute to further optimize treatment outcome for the treatment of MDD, e.g. early drug improvement is proposed as a possible predictor. In case of severe depression in which early improvement is not achieved after 2 weeks of treatment with imipramine or venlafaxine, the treating clinician and the patient it concerns can seriously contemplate switching treatment in advance instead of traditionally awaiting for a delayed therapeutic effect of antidepressants. This will prevent treatment delay, which will subsequently very likely result in increased treatment compliance, increased patient wellbeing and decreased morbidity, benefiting the overall mental health care. Furthermore, clinicians should take into account the higher vulnerability of women in the menopausal transition to develop MDD, which is associated with the hormonal changes of the perimenopause. Clinicians should be aware of the potential differences in antidepressant treatment response based on gender and women's menopausal status. Gender and menopausal status should be taken into consideration when treating patients diagnosed with MDD.

FUTURE RESEARCH DIRECTIONS

Major depressive disorder is highly prevalent and treatment of MDD in clinical practice can be challenging. Many different antidepressants are available and it is necessary to continue research on the efficacy and tolerability of these antidepressants to further add to the current knowledge on antidepressant treatment. It is also necessary to replicate research on adapted treatment algorithms in various patient populations, e.g. in- and outpatient settings, to enhance the generalizability of the study results. Likewise, research should be replicated in patient populations with mild vs. severe depression to investigate whether the results also apply for mild depression. E.g. in an outpatient population with major depression without melancholic features, future research should focus on investigating an adapted treatment algorithm consisting of second-generation antidepressants and psychotherapy. The present thesis is unique in being the first to compare the different treatment phases of the venlafaxine-lithium treatment strategy and the imipramine-lithium treatment strategy in a population of severely depressed inpatients. This implies that the study needs replication, since it was a first and a slightly underpowered study. Moreover, the precise underlying mechanism of the therapeutic effects of lithium addition to an antidepressant for the treatment of MDD remains unclear and future research should address this topic. It is of clinical interest to investigate lithium addition to a mixed reuptake inhibitor, e.g. imipramine, vs. lithium addition to a noradrenergic reuptake inhibitor, e.g. nortriptyline. This would clarify some of the working mechanisms of lithium addition to an antidepressant.

Ultimately, predictors of antidepressant treatment response for the treatment of MDD, in the broader sense, can help differentiate and personalize treatment strategies. Future research should focus on identifying and interpreting such predictors of antidepressant treatment response. Controlled prospective trials are necessary to further investigate if the absence of early improvement is a predictor of nonresponse to antidepressant treatment; these studies should compare a switch strategy with a continuation strategy in early nonresponse to antidepressant treatment. Also, the influence of gender and menopausal status on the efficacy of antidepressant treatment has not yet been thoroughly investigated; future randomized controlled trials are necessary and should stratify eligible patients according to gender and menopausal status. Aside from optimizing antidepressant outcome for the treatment of MDD, in future research efforts should also be made to implement early intervention programs for depression to reduce delay in receiving treatment by stimulating patients with MDD to seek timely therapy. Efforts to overcome stigma's may also be helpful to reduce treatment delay and, thereby, reduce chronicity of depression.

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APPENDICES

Samenvatting (summary in Dutch)
List of abbreviations
Dankwoord (acknowledgements)
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SAMENVATTING

Hoofdstuk 1 betreft de introductie van dit proefschrift. De prevalentiecijfers voor depressieve stoornissen zijn hoog. Depressieve stoornissen hebben een grote impact op het leven van patiënten en op de samenleving. Het effectief behandelen van depressieve stoornissen door middel van farmacotherapie is moeilijk, circa 30-40% van de patiënten zijn non-responder in de eerste stap van behandeling met alleen een antidepressivum. Het volgen van behandelschema's (algoritme) draagt bij aan het optimaliseren van de behandeling en het verbeteren van het behandelresultaat bij patiënten met een depressieve stoornis.

In dit proefschrift wordt de effectiviteit van een 3-fase behandelalgoritme onderzocht bij opgenomen patiënten met een depressieve stoornis. Het behandelalgoritme bestaat uit een aantal stappen: *fase I* monotherapie met een antidepressivum (de vergelijking van imipramine, een tricyclisch antidepressivum, en venlafaxine, een serotonine-norepinefrine heropname remmer); *fase II* lithium additie bij onvoldoende respons op monotherapie met een antidepressivum; *fase III* electroconvulsietherapie (ECT) bij onvoldoende respons op farmacotherapie. Vervolgens wordt gekeken naar voorspellende factoren voor respons op behandeling met antidepressiva bij opgenomen patiënten met een depressieve stoornis, o.a. vroege verbetering op het antidepressivum, geslacht en menopauzale status. De belangrijkste bevindingen en klinische implicaties van onze bevindingen worden hieronder besproken.

In **hoofdstuk 2** wordt een dubbelblind gerandomiseerd onderzoek beschreven waarin imipramine (gedoseerd op geleide van bloedspiegel) en venlafaxine (hoog gedoseerd) met elkaar worden vergeleken in een onderzoekspopulatie van opgenomen patiënten met een depressieve stoornis (fase I). Opgenomen patiënten met een depressieve stoornis werden gedurende tenminste één week medicatievrij geobserveerd alvorens ze, indien toestemming werd gegeven, werden behandeld met studiemedicatie. De onderzoekspopulatie was een homogene groep van opgenomen patiënten met een depressieve stoornis, met een gemiddelde leeftijd van 54 jaar, gemiddelde ernstscore volgens de HAM-D van 26.7 bij het intreden van de studie, bijna allemaal met melancholische kenmerken (96%) en het merendeel met een recidiverende episode (60%). De homogeniteit van de onderzoekspopulatie wordt beschouwd als een groot voordeel maar beperkt tegelijkertijd de generaliseerbaarheid van de resultaten. Zowel de proportie van patiënten met respons (50.0% vs. 39.5%), een daling van ≥ 50% op de HAM-D score, en de proportie van patiënten met remissie (35.7% vs. 23.3%), een HAM-D score ≤ 7, waren wel groter maar niet significant verschillend bij de patiënten

behandeld met venlafaxine. Hoewel de huidige onderzoekspopulatie ietwat klein was om definitieve conclusies te trekken, kan venlafaxine wel beschouwd worden als ten minste even effectief in vergelijking met imipramine voor de behandeling van opgenomen patiënten met een depressieve stoornis. De onderzoeksresultaten benadrukken het belang van adequate behandeling, met andere woorden, het belang van nauwkeurige diagnostiek alvorens behandeling te starten met optimale dosering van antidepressiva en adequate tijdsduur.

In **hoofdstuk 3** wordt de effectiviteit van twee behandelstrategieën met elkaar vergeleken bij opgenomen patiënten met een depressieve stoornis; imipramine gevolgd door lithiumadditie voor patiënten met onvoldoende respons op imipramine, of venlafaxine eveneens gevolgd door lithiumadditie voor patiënten met onvoldoende respons op venlafaxine (fase I en II gecombineerd). De effectiviteit van lithium additie kon nauwkeurig worden geëvalueerd als gevolg van de twee-fase onderzoeksopzet waarbij voorafgaand aan lithium additie alle patiënten adequate behandeling kregen met alleen een antidepressivum (beschreven in hoofdstuk 2). In eerste instantie, op basis van de resultaten, is gebleken dat de venlafaxine-lithium behandelstrategie niet minder werkzaam ("non-inferiority") is in vergelijking met de imipramine-lithium behandelstrategie. Vervolgens was de proportie van patiënten met respons (77% vs. 52%), een daling van ≥ 50% op de HAM-D score, significant groter in de venlafaxine-lithium behandelstrategie. De venlafaxine-lithium behandelstrategie is, voorafgaand aan dit proefschrift, zelden onderzocht. De onderzoeksresultaten impliceren dat venlafaxine-lithium behandelstrategie een zinvolle behandelstrategie is voor opgenomen patiënten met een depressieve stoornis.

Aan de hand van de literatuur op dit gebied worden verschillende theorieën besproken met betrekking tot de onderliggende mechanismen van de therapeutische effecten van lithium additie bij een antidepressivum. Een gangbare hypothese is dat lithium additie met name werkzaam is in combinatie met antidepressiva die de heropname van serotonine remmen. Er is geen duidelijke verklaring voor de onderzoeksresultaten ten gunste van de venlafaxine-lithium behandelstrategie, doch een mogelijke verklaring zou kunnen zijn de sterkere affiniteit van venlafaxine voor de serotonine transporter. Helaas geeft de literatuur hier geen uitsluitsel over, immers eerdere onderzoeksresultaten zijn in tegenspraak met bovengenoemde hypothese. Tot slot hebben we, ondanks hoge dosering venlafaxine en lithium gedoseerd op geleide van bloedspiegel, geen evidentie gevonden voor een verhoogd risico op het ontwikkelen van ernstige bijwerkingen (zoals een serotonine syndroom) als gevolg van een mogelijke interactie tussen venlafaxine en lithium.

In **hoofdstuk 4** wordt ingegaan op de verdraagbaarheid en effectiviteit van het 3-fase behandelalgoritme in zijn geheel bij opgenomen patiënten met een depressieve stoornis (fase I, II en III gecombineerd). Het totale uitvalspercentage gedurende de drie fases van behandeling was 28%, wat tamelijk hoog is. Aangezien de uitval met name plaats vond in de overgang tussen de fases van behandeling (en niet zozeer tijdens de behandelfases), lijkt het niet een gevolg te zijn van een matige verdraagbaarheid. De data werd geanalyseerd met behulp van zowel een gemodificeerde intention-to-treat analyse als een completers-analyse; de proportie van patiënten met remissie (HAM-D score ≤ 7) aan het einde van het 3-fase behandelalgoritme was respectievelijk 46% en 64%. Eveneens, de proportie van patiënten met respons (HAM-D score daling ≥ 50%) aan het einde van het 3-fase behandelalgoritme was respectievelijk 71% en 93%. Deze gunstige onderzoeksresultaten benadrukken het belang van het stapsgewijs volgen van een behandelalgoritme om de behandeling te optimaliseren en de behandelresultaten bij opgenomen patiënten met een depressieve stoornis te verbeteren. Tot slot hebben we het effect van verschillende demografische en klinische kenmerken van de onderzoekspopulatie geëvalueerd op de kans op remissie gedurende het 3-fase behandelalgoritme. Drie kenmerken toonden een significant verschil en werden geïdentificeerd als mogelijke voorspellers voor remissie: een huidige episode duur van ≤ 1 jaar, het ontbreken van een adequate voorbehandeling met antidepressiva en een opleiding lager dan middelbare school. Echter, het opleidingsniveau lijkt geen plausibele voorspeller. Zowel de literatuur als bovenstaande onderzoeksresultaten impliceren dat een langere duur van onbehandelde depressieve stoornis en chronische symptomen een ongunstig effect hebben op de behandelrespons met antidepressiva.

In **hoofdstuk 5** wordt ingegaan op de voorspellende waarde van vroege verbetering tijdens de behandeling met antidepressiva. Vroege verbetering op antidepressiva wordt gedefinieerd als een daling van ≥ 25% op de HAM-D score gedurende de eerste twee weken van behandeling met antidepressiva (imipramine of venlafaxine) bij opgenomen patiënten met een depressieve stoornis. Op basis van de resultaten blijkt vroege verbetering binnen twee weken een matig sensitieve voorspeller voor uiteindelijke behandelrespons (HAM-D score daling ≥ 50%) na zes weken behandeling met een antidepressivum bij opgenomen patiënten met een depressieve stoornis. Van de studiepatiënten met vroege verbetering was uiteindelijk 59% responder na zes weken behandeling met een antidepressivum, terwijl van de studiepatiënten zonder vroege verbetering was uiteindelijk maar 27% responder na zes weken behandeling met een antidepressivum. De afwezigheid van vroege verbetering, rekening houdend met de ernst van de depressieve klachten, kan reden zijn om te switchen van behandeling

in een eerder stadium dan op dit moment gebruikelijk is. Desalniettemin, omdat dit een post hoc analyse betreft, dient dit beschouwd te worden als een preliminair onderzoeksresultaat.

In **hoofdstuk 6** wordt een post hoc analyse beschreven waarbij er wordt ingegaan op de invloed van geslacht en menopauzale status op de behandelrespons met antidepressiva (imipramine, een tricyclisch antidepressivum, of fluvoxamine, een selectieve serotonine heropname remmer) bij opgenomen patiënten met een depressieve stoornis. De kans bij vrouwen op het ontwikkelen van een depressieve stoornis is meer dan twee keer zo groot als bij mannen en deze kans is, als een gevolg van hormonale veranderingen, nog groter tijdens de menopauzale transitie. De onderzoeksresultaten van dit proefschrift laten zien dat de groep depressieve mannen significant hogere respons hadden met imipramine in vergelijking met fluvoxamine. Er werden geen significante verschillen in respons gezien voor de groep depressieve premenopauzale vrouwen (< 50 jaar) noch voor de groep depressieve postmenopauzale vrouwen (≥ 50 jaar) behandeld met imipramine of fluvoxamine. De proportie van mannen met respons op imipramine was significant hoger in vergelijking met premenopauzale vrouwen; daarentegen, de proportie van premenopauzale vrouwen met respons op fluvoxamine was significant hoger in vergelijking met mannen. Er werden geen significante verschillen gezien in respons op imipramine en fluvoxamine tussen de mannen en de postmenopauzale vrouwen, noch tussen de pre- en postmenopauzale vrouwen. Zowel de literatuur als bovenstaande onderzoeksresultaten impliceren dat de verschillen in behandelrespons op antidepressiva op basis van geslacht en menopauzale status mogelijk verklaard kan worden door de vrouwelijke gonadale hormonen, d.i. door de respons op een selectieve serotonine heropname remmer te versterken ofwel door de respons op een tricyclisch antidepressivum te onderdrukken. Ondanks het feit dat dit, wederom, preliminaire onderzoeksresultaten zijn, bieden de resultaten veelbelovende nieuwe inzichten ter verbetering van de effectiviteit van behandeling met antidepressiva bij opgenomen patiënten met een depressieve stoornis.

Hoofdstuk 7 bevat de samenvatting en discussie van dit proefschrift, inclusief de klinisch implicaties van onze bevindingen. De resultaten van dit proefschrift hebben betrekking op een homogene groep opgenomen patiënten met een depressieve stoornis met melancholische kenmerken; de resultaten hebben een beperkte generaliseerbaarheid. Dit proefschrift benadrukt het belang van nauwkeurige diagnostiek alvorens behandeling te starten met optimale dosering van antidepressiva en adequate tijdsduur. De resultaten dragen bij aan de huidige kennis van psychofarmaca en impliceren, voor de behandeling van opgenomen patiënten met een depressieve stoornis, hoge dosering venlafaxine als ten minste even effectief en derhalve een zinvol alternatief

in vergelijking met imipramine gedoseerd op geleide van bloedspiegel. Vervolgens is gebleken dat, bij onvoldoende respons op monotherapie met een antidepressivum, lithium additie zowel bij venlafaxine als bij imipramine een zinvolle tweede stap is in de behandeling voor opgenomen patiënten met een depressieve stoornis. Daarbij benadrukt dit proefschrift het belang van stapsgewijs behandelalgoritmen te volgen om de behandeling te optimaliseren en het behandelresultaten bij opgenomen patiënten met een depressieve stoornis te verbeteren. Hoewel de onderzoekspopulatie bestond uit opgenomen patiënten, beschouwen wij de resultaten ook bruikbaar voor behandelaren van ambulante patiënten met een depressieve stoornis met melancholische kenmerken. Naast het optimaliseren van behandeling met antidepressiva o.a. door voorspellende factoren voor respons verder te onderzoeken, zouden we ons ook moeten inzetten om vroege interventie programma's voor depressie te implementeren. Dit kan de vertraging in het zoeken naar professionele psychiatrische hulp doen afnemen en kan patiënten met een depressieve stoornis stimuleren om initieel behandelcontact te zoeken. Eveneens is het bestrijden van stigma's zinvol om behandeluitstel en chroniciteit van depressieve stoornissen te verminderen.

LIST OF ABBREVIATIONS

APA	American Psychiatric Association
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth Edition
ECT	Electroconvulsive therapy
HAM-D	Hamilton Rating Scale for Depression
HRT	Hormone replacement therapy
MDD	Major depressive disorder
NEMESIS-2	Netherlands Mental Health Survey and Incidence Study-2
SCID-I	Structural Clinical Interview for DSM-IV Axis I disorders
SNRIs	Serotonin-norepinephrine reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
TCAs	Tricyclic antidepressants
WHO	World Health Organization
WMH	World Mental Health

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