WHAT TO EXPECT FROM A THIRD STEP IN TREATMENT RESISTANT DEPRESSION: A PROSPECTIVE STUDY

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Keywords:	Major depressive disorder, Antidepressants, resistant depression, Pharmacotherapy, escitalopram

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Running title: Treatment resistant depression and third step treatment

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ABSTRACT

Objectives: Treatment resistant depression (TRD) is associated with higher dysfunction, morbidity and mortality and is more difficult and expensive to treat. However, only few studies investigated potential treatment strategies. The objective of this multicentre study was to prospectively evaluate TRD patients who previously did not respond to at least two previous antidepressants.

Methods: Four hundred seventeen patients, who failed to respond to a previous retrospectively assessed antidepressant, were firstly included in a 6-week venlafaxine treatment; secondly, those who failed to respond were treated for further 6 weeks with escitalopram.

Results: Out of 417 patients who had failed to respond to previous treatment, 334 completed treatment with venlafaxine to prospectively define TRD, with a dropout rate of 19.9%. In the intent to treat (ITT) population in the first phase of the trial, responders to venlafaxine were 151 (36.21%) while remitters were 83 (19.90%). After phase one, 170 non responders, defined as TRD, were included in the second phase and 157 completed the course, with a dropout rate of 7.65%. Of the 170 ITT entering the second phase, responders to escitalopram were 71 (41.76%) while remitters were 39 (22.94%). After the third treatment, patients showed a dropout rate of 7.65% and a rate of presence of at least one serious adverse event of 19.18%.

Conclusions: The main finding of the paper is that relevant rates of response and remission may be observed after a third line treatment in patients resistant to two previous treatments.

Key words: major depressive disorder, antidepressants, pharmacotherapy, resistant depression, escitalopram.

INTRODUCTION

Despite the available effective pharmacotherapeutic strategies to treat patients affected by Major Depressive Disorder (MDD), consistent unmet needs remain. In particular, a key issue is represented by the treatment choice for Treatment Resistant Depression (TRD) patients.

Different definitions of TRD have been suggested (Berlim and Turecki 2007), from the lack of response to a single antidepressant (Souery, Amsterdam et al. 1999; Thase 2001; Fava 2003), to the lack of response to two or more antidepressants of different classes (Thase 2001; CHMP 2002). In particular, the most widely used definition has been proposed in the Committee for Medicinal Products for Human Use (CHMP) guidelines: "a patient is considered therapy resistant when consecutive treatment with two products of different classes, used for a sufficient length of time at an adequate dose, fail to induce an acceptable effect" (CHMP 2002), though this definition is not used in the CHMP concept paper and has been under revision due to current negative evidence about defining TRD by antidepressant classes. An increasing number of reports showed no advantage in favour of switching to a different class of antidepressant in patients with MDD (Ruhe, Huyser et al. 2006; Rush, Trivedi et al. 2006; Bschor and Baethge 2010; Souery, Serretti et al. 2011; Gaynes, Dusetzina et al. 2012). The issue remains controversial.

Venlafaxine is a dual serotonin-norepinephrine reuptake inhibitor (SNRI) that has been reported to have higher efficacy in the treatment of MDD compared to selective serotonin reuptake inhibitors (SSRIs) but not to others (Stahl, Entsuah et al. 2002; Bauer, Tharmanathan et al. 2009; Cipriani, Furukawa et al. 2009). Some studies suggested that venlafaxine, due to its pharmacodynamic characteristics, could be an effective drug in TRD, with results supporting the efficacy and tolerability of venlafaxine in TRD patients who have not responded to previous treatments (de Montigny, Silverstone et al. 1999; Schweitzer,

Burrows et al. 2001; Saiz-Ruiz, Ibanez et al. 2002; Corya, Williamson et al. 2006; Fang, Yuan et al. 2010), including studies using high doses above the licensed range (450-600 mg) (Mbaya 2002).

Escitalopram (Leonard and Taylor 2010; Kirino 2012; Zhong, Haddjeri et al. 2012) is a SSRI which has shown efficacy and safety in MDD treatment as well (Burke, Gergel et al. 2002; Stamouli, Yfantis et al. 2009). Efficacy and safety remained high when using doses up to 50 mg (Wade, Crawford et al. 2011), as well as in studies with elderly populations (Chen, Huang et al. 2011). Escitalopram was found to have a superior efficacy in comparison with citalopram in particular (Cipriani, Santilli et al. 2009; Montgomery, Hansen et al. 2011) – explained by differences in the dynamics of serotonin transporter occupancy (Kasper, Sacher et al. 2009) – and in comparison with other SSRIs as well (Cipriani, Santilli et al. 2009; Kasper, Baldwin et al. 2009). The differences in efficacy appeared more clear-cut in severely depressed patients (Kennedy, Andersen et al. 2009; Ali and Lam 2011). When compared to venlafaxine or duloxetine (alone or pooled), escitalopram was found to be likewise more effective and better tolerated in MDD treatment (Montgomery and Andersen 2006; Kennedy, Andersen et al. 2009; Kornstein, Li et al. 2009). In a specific study, escitalopram was found to more likely result in remission without concurrent side effects in comparison with SNRIs (Signorovitch, Ramakrishnan et al. 2011). Moreover, escitalopram was found to be more effective than other antidepressant medications (citalopram, fluoxetine, paroxetine, sertraline, duloxetine and venlafaxine) in treating severely depressed patients (Bielski, Ventura et al. 2004; Kennedy, Andersen et al. 2009; Kilts, Wade et al. 2009; Kornstein, Li et al. 2009) and patients who had not responded to a previous antidepressant (Lam, Lonn et al. 2010).

To further evaluate the efficacy and tolerability of escitalopram in TRD, not considered in the STAR*D study, a prospective study was undertaken on a sample of 417 MDD patients resistant to at least two consecutive adequate antidepressant treatments (in terms of dose and

duration). In particular, patients who failed to respond to a previous retrospectively assessed antidepressant were entered into a multicentre multinational 2-phase trial: in the first phase patients received a 6-week venlafaxine treatment; in the second phase those who failed to respond to venlafaxine were treated for a further 6-week period with escitalopram.

To the best of our knowledge, this is the first study to be primarily designed to evaluate escitalopram efficacy and tolerability in a sample of patients resistant to at least two adequate antidepressant treatments including a standardized one.

EXPERIMENTAL PROCEDURES

Study design

Four hundred seventeen MDD patients who failed to respond to a previous retrospectively assessed antidepressant (AD1, see Figure 1) were entered into an open multicentre multinational 2-phase trial: in the first phase patients received a 6-week venlafaxine treatment (AD2, Figure 1); in the second phase those who failed to respond to venlafaxine were treated for a further 6-week period with escitalopram (AD3, Figure 1).

Patients were recruited from January 2005 to December 2011 in the context of the European multicenter project. Six centers took part in the project: 1) Department of Psychiatry, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium; 2) Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy; 3) Department of Psychiatry and Psychotherapy, Medical University Vienna, Austria; 4) Department of Psychiatry, Chaim Sheba Medical Center, Tel-Hashomer, Israel; 5) Elancourt, Toulouse and Sartrouville, France; 6) 1st Department of Psychiatry, Athens University Medical School, Eginition Hospital, Greece.

Venlafaxine Treatment

To be included in the 6 week prospective treatment with venlafaxine each patient had to: 1. be able to read and understand the patient information sheet; 2. have signed the informed consent form; 3. be an in- or outpatient, male or female, of at least 18 years of age; 4. have a Current Major Depressive Episode, assessed with the Mini International Neuropsychiatric Interview (MINI), moderate or severe, according to DSM-IV-TR criteria (classification codes: 296.2x or 296.3x); 5. have been treated for the Current Episode with any antidepressant (AD1) (other than escitalopram or venlafaxine) prescribed continuously at its optimal dose (Annex 1) for at least 4 weeks (criterion verified at screening) – if at inclusion the patient was not during AD1 period of any antidepressant, this period without antidepressant should not have exceeded 4 weeks); 6. be a non-responder to this previous treatment (AD1) (Montgomery Asberg Depression Rating Scale (MADRS) improvement <50%); 7. have a total score ≥22 on the MADRS.

To be excluded from the study each patient had to: 1. have previously participated in this study; 2. be a non responder to a combination of 2 antidepressants (at least 2 weeks of treatment with an adequate dose for each of the 2 drugs) and/or to an augmentation therapy (at least 2 weeks with a potentiating agent at any dose) at the time of screening; 3. have a history of severe drug allergy or hypersensitivity, or known hypersensitivity to escitalopram or venlafaxine; 4. have one or more of the following conditions: a. any Current Psychiatric Disorder established as the principal diagnosis other than Major Depressive Disorder as defined in the DSM-IV-TR (assessed with the MINI); b. any Substance Disorder (except nicotine and caffeine) within the previous 6 months as defined in the DSM-IV-TR; c. any severe Personality Disorder according to investigator clinical judgement that might compromise the study; 5. have received one or more of the following disallowed treatments: a. oral antipsychotic drugs had to have been stopped at least 2 weeks before inclusion; the patient could be included if the antipsychotic medication had been taken at infra-therapeutic

dose (lower than the recommended dose as indicated in the notice of the product); patients were excluded if they had received a depot antipsychotic preparation within the past 6 months; b. ECT within the past 6 months; c. lithium, carbamazepine, lamotrigine, valproate or valpromide at therapeutic dose and for more than 2 weeks within the past month; d. benzodiazepines: more than 25 mg/day of diazepam or equivalent within the last week for chronic users of benzodiazepines (more than 3 months on treatment) and more than 10 mg/day of diazepam or equivalent for non chronic users (less than 3 months); e. more than 20 mg/day of zolpidem, 15 mg/day of zopiclone or 20 mg/day of zaleplon within the last week; f. any non-benzodiazepine anxiolytic within the last week; g. any serotonin agonist (e.g., triptans) within the last week; h. any other drug with potential psychotropic effects within the last week; i. any investigational product within 3 months prior to screening; j. escitalopram or venlafaxine at adequate dose and duration during the Current Episode; k. formal psychotherapy started in the month preceding inclusion; 6. have a previous history of convulsive disorder other than a single childhood febrile seizure; 7. present evidence of urinary retention or glaucoma; 8. have a serious illness and/or serious sequelae thereof, including liver or renal insufficiency, or a cardiovascular, pulmonary, gastrointestinal, endocrine, neurological, infectious, neoplastic, or metabolic disturbance; 9. have, in the opinion of the investigator (based on physical examination, medical history and vital signs), comorbid conditions(s) that would render inclusion in the study unsafe; 10. take medication that, in the opinion of the investigator, could interfere with the assessments of safety, tolerability, or efficacy; 11. in female patients, be pregnant or breastfeed at inclusion as well as during the study; 12. be, in the opinion of the investigator, unlikely to comply with the clinical study protocol or is unsuitable for any reason.

Patients meeting the above criteria and for whom the investigator considered switching to venlafaxine, were included in a 6 week prospective treatment with venlafaxine (AD2) prescribed continuously at its optimal dose.

Initial venlafaxine daily dose was 75 mg; the daily dose could be further increased to 150 mg after 1 week, on the basis of an unsatisfactory response as judged by the investigator. If necessary, the dose could be increased up to a maximum of 225 mg, since in many countries this dose is the highest allowed and since there is no specific evidence that higher doses are more effective than 225 mg one.

The aim of the venlafaxine phase of the trial was to prospectively define TRD.

Escitalopram Treatment

Patients considered as non responders at the end of the venlafaxine treatment were evaluated for inclusion in the second phase of the trial. To be eligible for inclusion in the 6-week prospective treatment with escitalopram (AD3) each patient had to meet 1 of the 2 following inclusion criteria:

1. At day 28: the patient has a total score ≥20 on the MADRS and a decrease from start of the venlafaxine treatment in MADRS total score <25%;
2. At day 42: patient has a total score ≥20 on the MADRS or a decrease from start of the venlafaxine treatment in MADRS total score <50%.

Exclusion Criteria: any patient who met the following criteria at the end of the venlafaxine treatment was not included in the escitalopram treatment: 1. The patient had not taken AD2 medication for three consecutive days or more, or overall compliance was less than 80% during the venlafaxine treatment; 2. any of the previously described exclusion criteria that appeared since the initiation of the venlafaxine treatment.

Initial escitalopram daily dose was 10 mg; the daily dose had to be increased to 20 mg after 1 week; after 2 weeks, the daily dose could be further increased to 30 mg on the basis of an unsatisfactory response as judged by the investigator.

The study protocol was approved by the Ethical Committees of all participating centres and it has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all participants prior to their inclusion in the study.

Assessment

To any patient meeting criteria for inclusion, once they had signed the inform consent, a baseline interview including the following modules was administered: 1. socio-demographic data; 2. MINI, version 5.0.0 modified for the group for the study of resistant depression (Souery, Oswald et al. 2007); 3. severity scales (baseline MADRS (Montgomery and Asberg 1979), Hamilton Rating Scale for Depression (HRSD) 17-item version (Hamilton 1960), and Clinical Global Impression Severity (CGI-S) (Guy 1976)); 4. somatic illnesses; 5. current and 6. previous medications; 7. side effects (Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale (Lingjaerde, Ahlfors et al. 1987)); 8. psychiatric familial antecedents; 9. functional impairment (Sheehan Disability Scale (SDS) (Sheehan 1983)). The assessment was completed using "TRD.COM", a centralized server consisting on a structured examination tool and immediate data capture. The MINI was administered to all patients. The MADRS, the HRSD, the CGI-S and CGI-I (Clinical Global Impression Improvement) scales, and the UKU were administered to all patients at each time point (Day 0, 14, 28, 42, 56, 70, 84).

Concomitant medications

The use of psychotropic drugs was not allowed during the period of the study except for:

a. Chronic use of benzodiazepines (more than 3 months):

1. Daily use of 25 mg of diazepam or equivalent was allowed, with the possibility to increase to 35 mg per day.

2. Zolpidem, zopiclone or zaleplon were allowed, no more than zolpidem 20 mg/day, zopiclone 15 mg/day or zaleplon 20 mg/day.

b. Patients free/non chronic users of benzodiazepines at inclusion:

1. Daily use of up to 10 mg of diazepam or equivalent was allowed.

2. Zolpidem, zopiclone or zaleplon were allowed, no more than zolpidem 20 mg/day, zopiclone 15 mg/day or zaleplon 20 mg/day.

c. Deviation from these criteria was allowed up to 2 days, only once and at any time during the study.

Switching strategies and therapeutic windows

From AD1 to AD2: a maximum of 3 days of bitherapy was allowed. A maximum of 3 days of therapeutic window was allowed (except for MAOI: 2 weeks).

From AD2 to AD3: Bitherapy was not allowed (venlafaxine + escitalopram). A maximum of 3 days of therapeutic window was allowed.

Procedures

In the venlafaxine phase of the trial, responders were defined in presence of: 1. at day 28: MADRS <20 and decrease from start of the venlafaxine treatment in MADRS total score ≥25%; or 2. at day 42: MADRS <20 or decrease from start of the venlafaxine treatment in MADRS total score ≥50%.

In the escitalopram phase of the trial, responders were defined in two ways: 1. at day 84, if both of the following criteria were met: a. MADRS <20; b. decrease from start of the escitalopram treatment in MADRS total score >25%; 2. at day 84, if both of the following criteria were met: a. MADRS <20; b. decrease from start of the escitalopram treatment in MADRS total score ≥50%. As primary outcome a MADRS decrease ≥50% has been considered while MADRS decrease >25% has been described in Supplementary materials (Supplementary table 3).

In both phases remitters were defined as having a MADRS score <10.

MADRS ratings have been collected by independent researchers blinded to the study hypotheses and clinicians were not raters of response/remission.

Objectives

Primary aim

To evaluate the efficacy of escitalopram in TRD, assessed by 2 consecutive failed antidepressant treatments. The considered primary outcome was the MADRS score.

Secondary aims

To evaluate efficacy of escitalopram considering further scales: the HRSD, CGI-S and CGI-I.

To assess safety and tolerability of escitalopram.

Statistical analyses

The primary analysis was a repeated-measure ANOVA analysis of variance focused on Day 14, 28, 42, 56, 70 and 84 MADRS change from baseline (Day 0). Focus was on Intent To Treat (ITT) patients, but analyses on completers were also performed.

The secondary analyses of HRSD, CGI-S and CGI-I change scores from baseline were carried out in line with the primary analysis.

P-value was set at 0.05 level. The sample had sufficient power (0.80) to detect a small effect size (f=0.07) that, as an example, corresponds to a final difference in the total MADRS score of 0.59 points.

RESULTS

Sample description

Four hundred seventeen patients were initially included, the flow chart of patient inclusion/exclusion process is reported in Figure 2. Baseline socio-demographic and clinical features of the ITT sample are shown in Table 1 (more data are reported in Supplementary tables 1 and 2). The sample was mainly composed of outpatients (81.60%). Melancholic features were present in 55.80% of patients while current anxiety disorder comorbidity was present in 23.26%.

Primary outcome

Table 2 shows main outcome data of ITT patients in the two phases of the trial.

In the first phase of the trial, responders to venlafaxine were 151 (36.21%) while remitters were 83 (19.90%). MADRS mean scores at baseline were 31.45±6.24 and at the end of this phase of the trial were 19.98±12.20.

Out of the 183 (43.89%) non responders to venlafaxine, 170 patients (92.90%) were included in the second phase of the trial (13 non responders (7.10%) were not included because of clinician's choice or patient refusal to continue the study).

In the second phase of the trial, responders to escitalopram were 71 (41.76%) while remitters were 39 (22.94%). MADRS mean scores at baseline were 29.82±7.82 and at the end of this phase were 18.42±11.09.

MADRS mean scores at each time-point in both phases of the trial are shown in Figure 3, with a significant effect of time in the change from baseline scores in both phases (venlafaxine phase: F=220.83; d.f.=3, 942; p<0.0001; escitalopram phase: F=98.21; d.f.=3, 438; p<0.0001).

Data on completers are provided in Supplementary table 3: in particular, in the first phase of the trial 334 (80.10%) of 417 patients were completers while in the second phase completers were 157 (92.35%) of 170 patients. Considering completers, the mean dosage at the end of the venlafaxine phase of the trial was mg 186.79±43.67 while at the end of the escitalopram phase was mg 26.43±4.80.

When missing values were taken into account by using the last observation carried forward (ITT - LOCF), and LOCF patients were compared with completers in terms of rates of responders/remitters, results did not change (data not shown). Results also showed no change when mean MADRS scores of LOCF patients were compared with the ones of completers.

Secondary outcomes

The repeated-measure ANOVA showed similar results on the change from baseline on HRSD, CGI-S and CGI-I scores in both phases of the trial (venlafaxine phase, respectively: F=186.20, p<0.0001; F=20.27, p<0.0001; F=60.47, p<0.0001; escitalopram phase, respectively: F=78.81, p<0.0001; F=89.72, p<0.0001; F=82.73, p<0.0001).

In the venlafaxine phase of the trial, dropouts were 83 (19.90%) and in the escitalopram phase of the trial dropouts were 13 (7.65%).

At the end of both phases, patients reporting at least one severe side effect (psychic, neurologic, autonomic, or another effect) were 80 (19.18%) in the first phase and 35 (20.59%) in the second one (Table 2 for ITT and Supplementary table 4 for completers).

In both phases the most frequent side effects were asthenia/lassitude/increased fatigability and diminished sexual desire. In the first phase another frequent side effect was reduced sleep duration, while in the second phase was increased dream activity.

In more detail, patients reporting at least one severe psychic side effect were 48 (15.09%) in the first phase and 18 (11.46%) in the second one; in particular, patients on venlafaxine reported higher rates of concentration difficulties, tension and reduced sleep duration, while patients on escitalopram reported higher rates of increased dream activity. Patients reporting at least one severe neurologic side effect (dystonia) were only 3 (0.94%), all in the first phase of the trial. Patients reporting at least one severe autonomic side effect were 10 (3.14%) in the first phase and 8 (5.09%) in the second one; in particular patients on escitalopram reported higher rates of increased tendency to sweating. Patients reporting at least one other kind of severe side effect were 40 (12.58%) in the first phase and 17 (10.83%) in the second one, patients on venlafaxine reporting higher rates of diminished sexual desire.

DISCUSSION

This study was designed to evaluate efficacy and tolerability in a sample of patients resistant to at least two adequate (in terms of dose and duration) antidepressant treatments. The main finding of the paper is the relevant efficacy of a third treatment in subjects who were resistant to two previous treatments. Escitalopram has been suggested in the treatment of severe depression (Montgomery, Baldwin et al. 2007), and only one study previously investigated this issue in TRD (Lam, Lonn et al. 2010); however this was a retrospective study and resistance was defined as non response to only one previous treatment.

Contrastingly to the STAR*D study, which showed a progressive decrease in treatment efficacy with subsequent antidepressant treatments but which focused on chronic depression (mean duration of depressive episode was over 150 weeks), the third treatment was numerically higher than the second treatment, with the response/remission rates of 36.21/19.90% for venlafaxine and 41.76/22.94% for escitalopram, which was the third treatment.

Regarding dosage, patients were adequately treated with both venlafaxine (mean dose at the end: 186.79±43.67 mg) and escitalopram (mean dose at the end: 26.43±4.80 mg). Dropout rate in the escitalopram phase (7.65%) was lower than the one previously reported in MDD patients treated with escitalopram compared with nortriptyline in the GENDEP study (Power, Muthen et al. 2012).

Regarding side effect rate, escitalopram appeared to be associated with high tolerability in TRD patients. In those with mild side effect severity, the rate in the escitalopram phase was lower than previously reported (Bose, Tsai et al. 2012). However, it has to be taken under consideration that the method of assessing side effects varies from study to study. Moreover, this was an open trial, where side effects are usually lower than in double-blind controlled

trials. In the large post-marketing surveillance study by Laux et al., in which patients with comorbid depression and anxiety were treated for 16 weeks with escitalopram, results similar to the present were reported regarding higher frequency of fatigue (Laux, Friede et al. 2013).

There are a number of design issues that may weaken our findings. First of all the open nature of the study could be criticised since it may allow physician bias to influence results. Secondly, the retrospective assessment of the first antidepressant treatment (AD1) could be considered as a limitation. However, the present study is the only naturalistic study which used a prospectively defined last venlafaxine treatment to define TRD before treatment with escitalopram (the paper is not a comparative study to venlafaxine). The restrictions of the exclusion criteria in the patient selection might have led to a well defined study population that might not be completely comparable to other patients receiving antidepressants. Another limitation is represented by the responder definition in both phases of the trial (MADRS decrease from baseline ≥50%). Although this is the most widely used criterion of responders, this definition could have reduced response rates in the second phase of the trial and may not be the most appropriate definition in a population with defined resistance to treatment. Furthermore, the 4 week criteria for the duration of the first antidepressant treatment (AD1) might be criticised as being too short in TRD. Some authors suggested to consider a treatment period of at least 6 weeks for the initial antidepressant (Bschor and Baethge 2010), particularly in TRD to evaluate possible late effects of the treatment. However, guidelines (e.g., NICE, United Kingdom) propose that the decision on treatment for TRD should not be delayed and should be made at 3 to 4 weeks. Moreover, the possibility to establish efficacy within this period in TRD has been previously reported (Rapaport, Gharabawi et al. 2006). Moreover, the six week venlafaxine trial may have been insufficient to show eventual improvement, considering that venlafaxine may require multiple dose increases to achieve multi-receptor effectiveness. Finally, the dosage heterogeneity among patients from different

European countries for both venlafaxine and escitalopram, due to different treatment guidelines, could have biased the results.

The results of the present study showed high response rates and tolerability for a third treatment in TRD patients who previously did not respond to at least two previous antidepressants. Our results suggest that treatment response and remission may be still relevant after a third line antidepressant.

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URL for the registry: http://www.ANZCTR.org.au/ACTRN12613000256774.aspx.

Conflict of interest

Dr. Souery D. has received grant/research support from GlaxoSmithKline and Lundbeck; has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen and Lundbeck. Dr. Calati R., Dr. Juven-Wetzler A., Dr. Gailledreau J., Dr. Modavi D., Dr. Sentissi O., and Dr. Pitchot W. declares no conflict of interest. K. Papageorgiou received honoraria from RB Pharmaceuticals. Prof. Papadimitriou G.N. has served on speakers/advisory boards and/or has received consultancy fees for participation in research and in clinical expert groups, as well as unrestricted grants for the 1st Department of Psychiatry of Athens University Medical School of which he is the Chairman, from various Pharmaceutical Industry Companies including Eli Lilly, Bristol Myers Squibb, Sanofi,

Wyeth, AstraZeneca, Servier, GAP, Specifar, Elpen, Pfizer, Organon, Janssen and Lundbeck. Prof. Dikeos D. has been on speakers or advisory boards for, and/or has received consultancy fees for participation in research and for participation in clinical expert groups from various Pharmaceutical Industry Companies including AstraZeneca, Boehringer, Bristol Myers Squibb, Eli Lilly, Genesis Pharma, GlaxoSmithKline, Janssen, Lundbeck, Organon, Sanofi, UniPharma, and Wyeth; he has also received unrestricted grants from Lilly and AstraZeneca for the Sleep Research Unit of Eginition Hospital (Athens University), of which he is director. Prof. Montgomery S. has been a consultant or served on Advisory boards: AstraZeneca, Bionevia, Bristol Myers Squibb, Forest, GlaxoSmithKline, Grunenthal, Intellect Pharma, Johnson & Johnson, Lilly, Lundbeck, Merck, Merz, M's Science, Neurim, Otsuka, Pierre Fabre, Pfizer, Pharmaneuroboost, Richter, Roche, Sanofi, Sepracor, Servier, Shire, Synosis, Takeda, Theracos, Targacept, Transcept, UBC, Xytis and Wyeth. Prof. Kasper S. has received grant/research support from Eli Lilly, Lundbeck, Bristol-Myers Squibb, GlaxoSmithKline, Organon, Sepracor and Servier; has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Lundbeck, Pfizer, Organon, Schwabe, Sepracor, Servier, Janssen, and Novartis; and has served on speakers' bureaus for AstraZeneca, Eli Lily, Lundbeck, Schwabe, Sepracor, Servier, Pierre Fabre, Janssen and Neuraxpharm. Prof. Zohar J. has received grant/research support from Lundbeck, Servier and Pfizer, has served as a consultant or on advisory boards for Servier, Pfizer, Solvay and Actelion, and has served on speakers' bureaus for Lundbeck, GSK, Jazz and Solvay. Prof. Mendlewicz J. is a member of the Board of the Lundbeck International Neuroscience Foundation and of Advisory Board of Servier. Prof. Serretti A. is or has been consultant/speaker for: Abbott, Astra Zeneca, Clinical Data, Boheringer, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Pfizer, Sanofi, Servier.

Figure 1. Study design schema (AD1: first antidepressant treatment; AD2: second antidepressant treatment; AD3: third antidepressant treatment; TRD: treatment resistant depression).

Figure 2. Flow chart of the patient inclusion/exclusion process (ITT: intent to treat patients; AD1: first antidepressant treatment; AD2: second antidepressant treatment; AD3: third antidepressant treatment).

Figure 3. MADRS mean scores of ITT patients in both phases of the trial.

Socio-demographic and clinical features	ITT patients n=417 Mean±SD/n(%)
Age (years, n=416)	47.29±12.51
Males	140 (33.57)
Caucasians	386 (92.57)
Outpatients (n=413)	337 (81.60)
Onset (years, n=334)	33.22±13.16
Duration current episode (days, n=375)	169.00±194.16
Melancholia (n=414)	231 (55.80)
Current anxiety disorder	97 (23.26)

Table 1. Socio-demographic and clinical features of the Intent To Treat patients (n=417) at baseline.

Clinical features	ITT Venlafaxine Phase (n=417) Mean±SD/n(%)	ITT Escitalopram Phase (n=170) Mean±SD/n(%)
Response		
Responders	151 (36.21)	71 (41.76)
Non responders	183 (43.88)	86 (50.59)
Dropouts	83 (19.90)	13 (7.65)
Remission		
Remitters	83 (19.90)	39 (22.94)
Non remitters	251 (60.19)	118 (69.41)
Dropouts	83 (19.90)	13 (7.65)
MADRS		
Day 0 – baseline	31.45±6.24	
Day 14 (n=406)	26.85±9.45	
Day 28 (n=366)	22.01±10.67	
Day 42 – end of the venlafaxine phase (n=318)	19.98±12.20	
Day 42 – end of the venlafaxine phase LOCF (n=407)	20.59±12.31	
Day 42 – baseline of the escitalopram phase (n=170)		29.82±7.82
Day 56 (n=169)		25.67±9.80
Day 70 (n=163)		21.63±10.31
Day 84 – end of the escitalopram phase (n=157)		18.42±11.09
Day 84 – end of the escitalopram phase LOCF (n=170)		19.32±11.39
UKU		
Presence of at least one side effect (severe)		
Day 42 – end of the venlafaxine phase (n=318)	80 (19.18)	
Day 84 – end of the escitalopram phase (n=157)		35 (20.59)

Table 2. Main outcome measures of the Intent To Treat patients in the two phases of the trial (n=417 and n=170, respectively).

Supplementary tables

Socio-demographic and clinical features	Intent To Treat MDD patients n=417 Mean±SD/n(%)
Age (years, n=416)	47.29±12.51
Males	140 (33.57)
Caucasians	386 (92.57)
Education	
Below Compulsory	58 (13.91)
Compulsory Education	125 (29.98)
Secondary School	142 (34.05)
University	92 (22.06)
Marital Status	
Single	97 (23.26)
Married/Cohabiting	209 (50.12)
Separated/Divorced	98 (23.50)
Widowed	13 (3.12)
Occupation	
Employee	236 (56.59)
Unemployed	98 (23.50)
Student/Retired	60 (14.39)
Unknown/Others	23 (5.52)
Outpatients (n=413)	337 (81.60)
Onset (years, n=334)	33.22±13.16
Severity current episode (n=403)	
Moderate	182 (45.16)
Severe without psychotic features	216 (53.60)
Severe with psychotic features	5 (1.24)
Duration current episode (days, n=375)	169.00±194.16
Number of lifetime episodes (n=310)	

Range 1-10	3.04±2.22
>10	27 (8.01)
Duration hospitalization (weeks, n=84)	13.80±21.02
Age first hospitalization (n=74)	38.30±13.50
Melancholia (n=414)	231 (55.80)
Major depressive episode features (n=413)	
With full inter-episode recovery	71 (17.19)
Without full inter-episode recovery	52 (12.59)
Seasonal pattern	15 (3.63)
Atypical features	24 (5.81)
Catatonic features	12 (2.91)
Post partum onset	2 (0.48)
No features	237 (57.39)
Dysthymia (n=414)	3 (0.72)
Suicide risk	230 (55.16)
Suicide risk level (n=230)	
Low	115 (50.00)
Moderate	69 (30.00)
High	46 (20.00)
Current anxiety disorder	97 (23.26)
Current panic disorder	34 (8.15)
Current social phobia	26 (6.23)
Current obsessive compulsive disorder	12 (2.88)
Current post traumatic stress disorder	8 (1.92)
Generalized anxiety disorder	56 (13.43)
Current alcohol dependence	3 (0.72)
Current alcohol abuse	2 (0.48)
Current substance dependence	2 (0.48)
Current substance abuse	0 (0.00)
Current anorexia nervosa	1 (0.24)

Current bulimia nervosa	3 (0.72)
Psychiatric antecedents (n=415)	
Unipolar depressive disorder in 1st degree relatives	207 (49.88)
Unknown	31 (7.47)
Unipolar depressive disorder in 2nd degree relatives	69 (16.63)
Unknown	111 (26.75)
Bipolar disorder in 1st degree relatives	17 (4.10)
Unknown	50 (12.05)
Bipolar disorder in 2nd degree relatives	2 (0.48)
Unknown	102 (24.58)
Antecedents affected by any other psychiatric disorder	146 (35.18)
Unknown	49 (11.81)
Suicide or suicidal attempt in 1st and 2nd degree relatives	73 (17.51)
Unknown	61 (14.63)
Suicide in 1st and 2nd degree relatives	42 (10.12)
Unknown	43 (10.36)
Suicidal attempt(s) in 1st and 2nd degree relatives	48 (11.57)
Unknown	60 (14.46)
Sheehan Disability Scale (n=415)	
Work	6.55±2.48
Social life	6.80±1.92
Family life/home responsibilities	6.29±1.99

Supplementary table 1. Socio-demographic and clinical features of the Intent To Treat patients (n=417) at baseline.

Antidepressant treatments at inclusion	Intent To Treat MDD patients n=378 n(%)
Paroxetine	76 (20.11)
Sertraline	62 (16.40)
Citalopram	40 (10.58)
Fluoxetine	40 (10.58)
Fluvoxamine	19 (5.03)
Mirtazapine	33 (8.73)
Amytriptiline	3 (0.79)
Clomipramine	11 (2.91)
Imipramine	2 (0.53)
Nortriptiline	5 (1.32)
Trimipramine	2 (0.53)
Maprotiline	2 (0.53)
Dosulepine	3 (0.79)
Reboxetine	2 (0.53)
Trazodone	7 (1.85)
Bupropion	4 (1.06)
Mianserine	7 (1.85)
Others	60 (15.87)
Number of previous antidepressants prescribed for current or past episode (n=270)	1.39±1.28
Number of adequate* previous antidepressants prescribed for current or past episode (n=165)	1.35±0.89

Supplementary table 2. Antidepressant treatments at inclusion of the Intent To Treat patients (n=378; n=39 were missing).

* Duration of at least 4 weeks and a score ≥2 at the Modified Antidepressant Treatment History Form (ATHF).

Clinical features	Completers Venlafaxine Phase (n=334) Mean±SD/n(%)	Completers Escitalopram Phase (n=157) Mean±SD/n(%)
Response		
Responders	151 (45.21)	71 (45.22) (MADRS≥50%) 86 (54.78) (MADRS>25%)
Non responders	183 (54.79)	86 (54.78) (MADRS≥50%) 71 (45.22) (MADRS>25%)
Remission		
Remitters	83 (24.85)	39 (24.84)
Non remitters	251 (75.15)	118 (75.16)
Doses		
Day 0 – baseline	75.00±0.00	
Day 14 (n=406)	122.84±37.96	
Day 28 (n=366)	166.60±42.11	
Day 42 – end of the venlafaxine phase (n=318)	186.79±43.67	
Day 42 – baseline of the escitalopram phase (n=170)		10.00±0.00
Day 56 (n=169)		22.19±4.15
Day 70 (n=163)		25.15±5.01
Day 84 – end of the escitalopram phase (n=157)		26.43±4.80
HDRS 17 item		
Day 0 – baseline (n=416)	22.34±5.31	
Day 14 (n=406)	18.80±7.03	
Day 28 (n=366)	15.61±7.78	
Day 42 – end of the venlafaxine phase (n=318)	14.43±8.82	
Day 42 – baseline of the escitalopram phase (n=154)		21.40±6.13
Day 56 (n=169)		18.22±6.94
Day 70 (n=163)		15.40±7.50
Day 84 – end of the escitalopram phase (n=157)		13.69±8.33
CGI-S		
Day 0 – baseline (n=415)	3.05±3.54	
Day 14 (n=406)	4.42±1.11	
Day 28 (n=366)	3.85±1.29	

Day 42 – end of the venlafaxine phase (n=318)	3.47±1.58	
Day 42 – baseline of the escitalopram phase (n=154)		4.78±0.86
Day 56 (n=169)		4.28±1.15
Day 70 (n=163)		3.79±1.25
Day 84 – end of the escitalopram phase (n=157)		3.30±1.48
CGI-I		
Day 14 (n=406)	3.47±1.03	
Day 28 (n=366)	2.94±1.15	
Day 42 – end of the venlafaxine phase (n=318)	2.79±1.37	
Day 42 – baseline of the escitalopram phase (n=154)		3.84±0.87
Day 56 (n=169)		3.30±0.95
Day 70 (n=163)		2.82±1.08
Day 84 – end of the escitalopram phase (n=157)		2.55±1.28

Supplementary table 3. Main outcome measures of Completers in the two phases of the trial (n=334 and n=157, respectively).

Side effects (UKU)	Completers Venlafaxine Phase (n=318) n(%)	Completers Escitalopram Phase (n=157) n(%)
At least a psychic side effect (moderate-severe)		
Day 42 – end of the venlafaxine phase	120 (37.74)	
Day 84 – end of the escitalopram phase		52 (33.12)
At least a psychic side effect (severe)		
Day 42 – end of the venlafaxine phase	48 (15.09)	
Day 84 – end of the escitalopram phase		18 (11.46)
Psychic side effects (severe)		
Concentration Difficulties	25 (7.86)	8 (5.10)
Asthenia/Lassitude/Increased Fatigability	27 (8.49)	10 (6.37)
Sleepiness/Sedation	22 (6.92)	9 (5.73)
Failing Memory	0 (0.00)	0 (0.00)
Depression	23 (7.23)	8 (5.10)
Tension/Inner Unrest	10 (3.14)	1 (0.64)
Increased Duration of Sleep	2 (0.63)	4 (2.55)
Reduced Duration of Sleep	29 (9.12)	7 (4.46)
Increased Dream Activity	1 (0.31)	10 (6.37)
Emotional indifference	2 (0.63)	3 (1.91)
At least a neurologic side effect (moderate-severe)		
Day 42 – end of the venlafaxine phase	38 (11.95)	
Day 84 – end of the escitalopram phase		14 (8.92)
At least a neurologic side effect (severe)		
Day 42 – end of the venlafaxine phase	3 (0.94)	
Day 84 – end of the escitalopram phase		0 (0.00)
Neurologic side effects (severe)		
Dystonia	3 (0.94)	0 (0.00)
Rigidity	0 (0.00)	0 (0.00)
Hypokinesia/Akinesia	0 (0.00)	0 (0.00)
Hyperkinesia logic	0 (0.00)	0 (0.00)
Tremor	0 (0.00)	0 (0.00)
Akathisia	0 (0.00)	0 (0.00)

Epileptic Seizures	0 (0.00)	0 (0.00)
Paraesthesias	0 (0.00)	0 (0.00)
At least an autonomic side effect (moderate-severe)		
Day 42 – end of the venlafaxine phase	114 (35.85)	
Day 84 – end of the escitalopram phase		46 (29.30)
At least an autonomic side effect (severe)		
Day 42 – end of the venlafaxine phase	10 (3.14)	
Day 84 – end of the escitalopram phase		8 (5.09)
Autonomic side effects (severe)		
Accommodation Disturbances	1 (0.31)	0 (0.00)
Increased Salivation	0 (0.00)	0 (0.00)
Reduced Salivation	3 (0.94)	0 (0.00)
Nausea/Vomiting	0 (0.00)	0 (0.00)
Diarrhoea	0 (0.00)	1 (0.64)
Constipation	0 (0.00)	0 (0.00)
Micturition Disturbances	0 (0.00)	0 (0.00)
Polyuria/Polydipsia	0 (0.00)	0 (0.00)
Orthostatic Dizziness	0 (0.00)	0 (0.00)
Palpitations/Tachycardia	1 (0.31)	0 (0.00)
Increased Tendency to Sweating	5 (1.57)	7 (4.46)
At least another side effect (moderate-severe)		
Day 42 – end of the venlafaxine phase	117 (36.79)	
Day 84 – end of the escitalopram phase		65 (41.40)
At least another side effect (severe)		
Day 42 – end of the venlafaxine phase	40 (12.58)	
Day 84 – end of the escitalopram phase		17 (10.83)
Other side effects (severe)		
Rash	0 (0.00)	0 (0.00)
Pruritus	1 (0.31)	0 (0.00)
Photosensitivity	0 (0.00)	0 (0.00)
Increased Pigmentation	0 (0.00)	0 (0.00)
Weight gain	0 (0.00)	2 (1.27)

Weight loss	1 (0.31)	0 (0.00)
Menorrhagia	1 (0.31)	0 (0.00)
Amenorrhoea	1 (0.31)	0 (0.00)
Galactorrhoea	0 (0.00)	0 (0.00)
Gynaecomastia	0 (0.00)	0 (0.00)
Increased Sexual Desire	0 (0.00)	0 (0.00)
Diminished Sexual Desire	30 (9.43)	11 (7.01)
Erectile Dysfunction	6 (1.89)	4 (2.55)
Ejaculatory Dysfunction	6 (1.89)	2 (1.27)
Orgasmic Dysfunction	12 (3.77)	8 (5.09)
Dry Vagina	0 (0.00)	0 (0.00)
Headache	6 (1.89)	1 (0.64)
Physical Dependence	0 (0.00)	0 (0.00)
Psychic Dependence	0 (0.00)	0 (0.00)

Supplementary table 4. Side effects of Completers in the two phases of the trial (n=318 and n=157, respectively).

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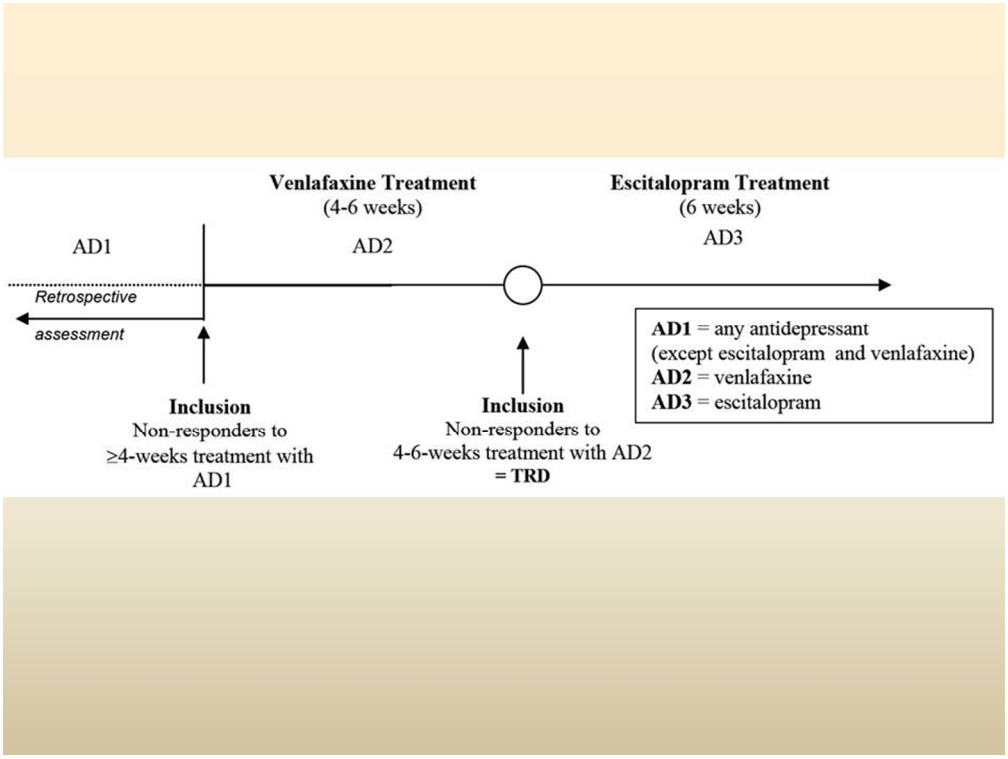

Study design schema (AD1: first antidepressant treatment; AD2: second antidepressant treatment; AD3: third antidepressant treatment; TRD: treatment resistant depression).
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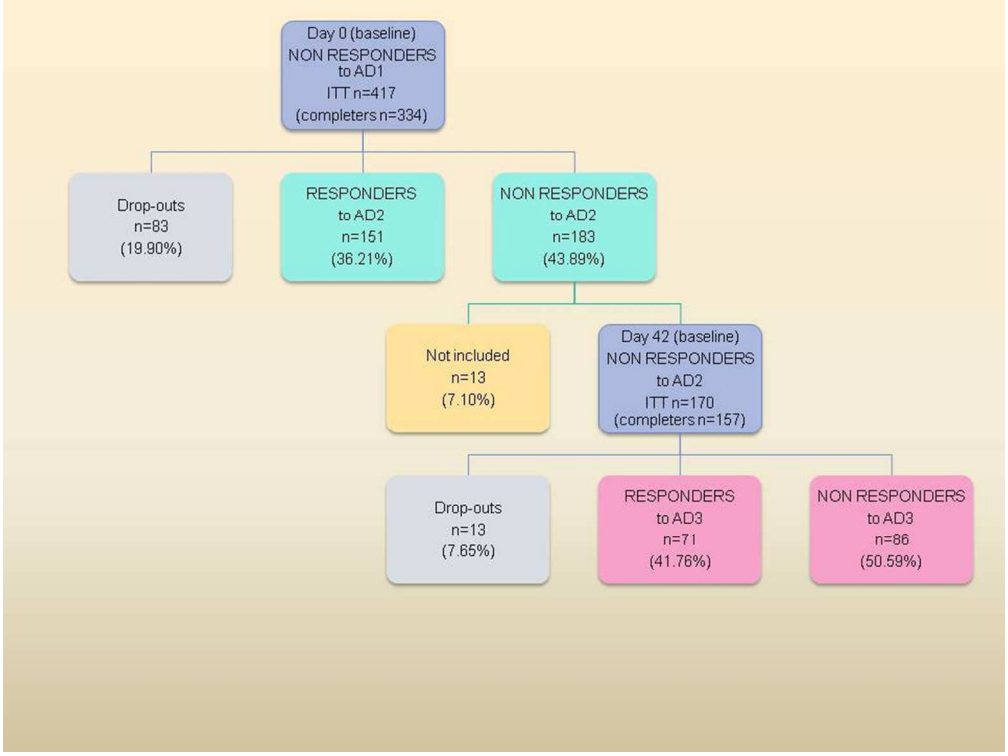

Flow chart of the patient inclusion/exclusion process (ITT: intent to treat patients; AD1: first antidepressant treatment; AD2: second antidepressant treatment; AD3: third antidepressant treatment).
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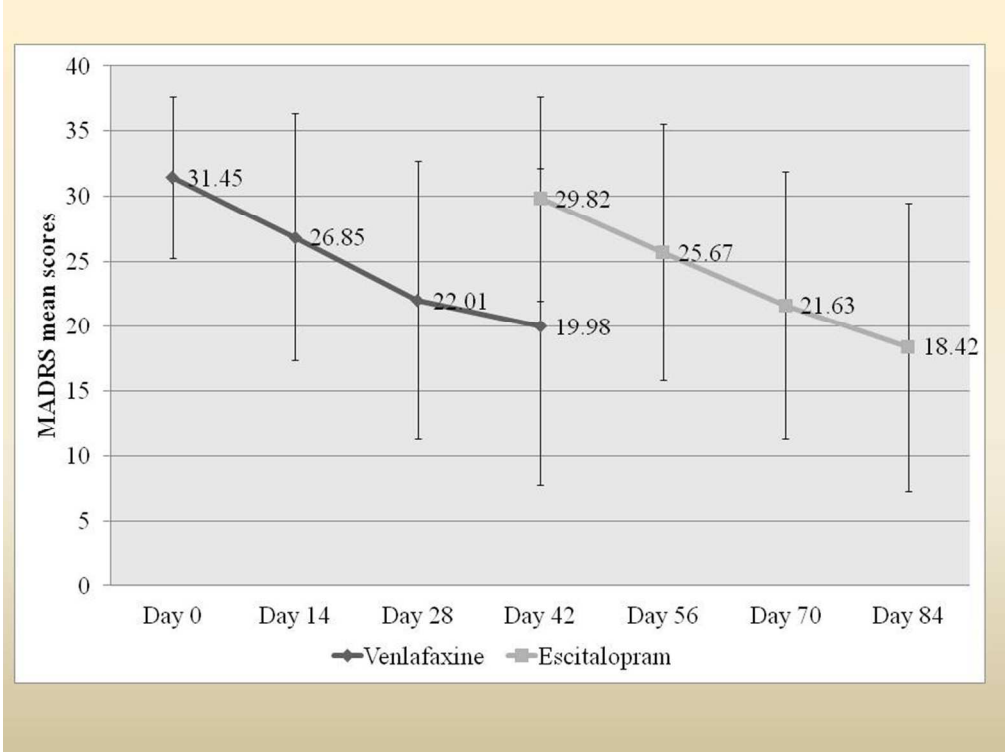

MADRS mean scores of ITT patients in both phases of the trial.
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