What to expect from a third step in treatment resistant depression: A prospective open study on escitalopram

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Abstract

Objectives. Only few studies investigated treatment strategies for treatment resistant depression (TRD). The objective of this multicentre study was to evaluate TRD patients who did not respond to at least two antidepressants. Methods. A total of 417 patients, who failed to respond to a previous retrospectively assessed antidepressant (AD1), were firstly included in a 6-week venlafaxine treatment (AD2); secondly, those who failed to respond were treated for further 6 weeks with escitalopram (AD3). Results. Out of 417 patients who had failed to respond to previous treatment (AD1), 334 completed treatment with venlafaxine to prospectively define TRD. In the intent to treat (ITT) population in the first phase of the trial (AD2), responders to venlafaxine were 151 (36.21%) out of which 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. Of the 170 ITT entering the second phase (AD3), responders to escitalopram were 71 (41.76%) out of which 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. Relevant rates of response and remission may be observed after a third line treatment in patients resistant to two previous treatments. A relevant limitation of this study was represented by the design: naturalistic, non-randomized, open-label, without a control sample and with unblinded raters.

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 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” (Committee for Medicinal Products for Human Use 2002), though this definition has been revised in the more recent CHMP document (Committee for Medicinal Products for Human Use 2013) 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 et al. 2006; Rush et al. 2006; Bschor and Baethge 2010; Souery et al. 2011a,b; Gaynes 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 some selective serotonin reuptake inhibitors (SSRIs; Stahl et al. 2002; Bauer et al. 2009; Cipriani 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 et al. 1999; Schweitzer et al. 2001; Saiz-Ruiz et al. 2002; Corya et al. 2006; Fang 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 et al. 2012) is a SSRI which has shown efficacy and safety in MDD treatment as well (Burke et al. 2002; Stamouli et al. 2009). Efficacy and safety remained high when using doses up to 50 mg (Wade et al. 2011), as well as in studies with elderly populations (Chen et al. 2011). Escitalopram was found to have a superior efficacy in comparison with citalopram in particular (Cipriani et al. 2009; Montgomery et al. 2011) – explained by differences in the dynamics of serotonin transporter occupancy (Kasper et al. 2009) – and in comparison with some other SSRIs as well (Cipriani et al. 2009; Kasper et al. 2009). The differences in efficacy appeared more clear-cut in severely depressed patients (Kennedy 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 et al. 2009; Kornstein 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 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 et al. 2004; Kennedy et al. 2009; Kilts et al. 2009; Kornstein et al. 2009) and patients who had not responded to a previous antidepressant (Lam et al. 2010), however this was a retrospective study and resistance was defined as non-response to only one previous treatment.

The aim of the present paper was therefore to evaluate the clinical effectiveness and tolerability of a third treatment in TRD, with a design based on the above-mentioned evidence, in a prospective study 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 naturalistic two-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 a third treatment clinical effectiveness 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 and seventeen MDD patients who failed to respond to a previous retrospectively assessed antidepressant (AD1) were entered into an open multicentre multinational two-phase naturalistic trial: in the first phase patients received a 6-week venlafaxine treatment (AD2); in the second phase those who failed to respond to venlafaxine were treated for a further 6-week period with escitalopram (AD3).

Patients were recruited from January 2005 to December 2011 in the context of the European multicenter project. Six centres 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; and (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: 296.2× or 296.3×); (5) have been treated for the Current Episode with any antidepressant (AD1) (other than escitalopram or venlafaxine) prescribed continuously at its optimal dose 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%); and (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 two antidepressants (at least 2 weeks of treatment with an adequate dose for each of the two 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 MDD 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., tryptans) 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.

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 and for whom the investigator considered switching to escitalopram 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 one of the 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 were that 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 and (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 could 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 protocols of the subjects were approved by the Ethical Committees of participating centres and were 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 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 et al. 1987); (8) psychiatric familial antecedents; and (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 inclusion of subjects treated with other psychotropic drugs was not allowed during the period of the study except for:

a. Chronic use of benzodiazepines (more than 3 months): daily use of 25 mg of diazepam or equivalent was allowed, with the possibility to increase to 35 mg/day; 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: daily use of up to 10 mg of diazepam or equivalent was allowed; 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 allowed for inclusion:

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

From AD2 to AD3: no bitherapy (venlafaxine + escitalopram). A maximum of 3 days of therapeutic window.

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 ≥ 50%;
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 the supplementary material available online (see Supplementary Table III to be found online at http://informahealthcare.com/doi/abs/10.3109/15622975.2014.987814).

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 clinical effectiveness of a third treatment (escitalopram) in TRD, assessed by two consecutive failed antidepressant treatments. The considered primary outcome was the MADRS score.

Secondary aims. To evaluate further scales: the HRSD, CGI-S and CGI-I. To assess safety and tolerability of the treatments.

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. 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 and seventeen patients were initially included, the flow chart of patient inclusion/exclusion process is reported in Figure 1. Baseline socio-demographic and clinical features of the ITT sample are shown in Table I (more data are reported in Supplementary Tables I and II to be found online at http://informahealthcare.com/doi/abs/10.3109/15622975.2014.987814). 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 II 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%) out of which remitters were 83 (19.90%).

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, there were 71 responders to escitalopram (41.76%) of which there were 39 remitters (22.94%).

MADRS mean scores at each time-point in both phases of the trial are shown in Figure 2, with a

Figure 1. Study design schema (AD1: first antidepressant treatment; AD2: second antidepressant treatment; AD3: third antidepressant treatment; TRD: treatment resistant depression).
significant effect of time in the change from baseline scores in both phases (venlafaxine phase: \( F = 220.83; \) df = 3, 942; \( P < 0.0001 \); escitalopram phase: \( F = 98.21; \) df = 3, 438; \( P < 0.0001 \)).

Data on completers are provided in Supplementary Table III to be found online at http://informahealthcare.com/doi/abs/10.3109/15622975.2014.987814: in particular, in the first phase of the trial 334 (80.10%) of 417 patients were completers, while in the second phase there were 157 completers (92.35%) out of 170 patients.

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: \( F = 186.20, P < 0.0001; F = 20.27, P < 0.0001; \) escitalopram phase, respectively: \( F = 78.81, P < 0.0001; F = 89.72, P < 0.0001; F = 82.73, P < 0.0001 \)) (Figure 3).

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

At the end of both phases, there were 80 patients reporting at least one severe side effect (psychic, neurological, autonomic or another effect) (19.18%) in the first phase, and 35 (20.59%) in the second (Table II for ITT and Supplementary Table IV for completers to be found online at http://informahealthcare.com/doi/abs/10.3109/15622975.2014.987814).

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 it was increased dream activity.

Table II. Main outcome measures of the intent to treat patients in the two phases of the trial (\( n = 417 \) and \( n = 170 \), respectively).

| Clinical features               | ITT venlafaxine phase (\( n = 417 \)) | ITT escitalopram phase (\( n = 170 \)) |
|--------------------------------|----------------------------------------|----------------------------------------|
| **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 56 (\( n = 169 \))         | 29.82 ± 7.82                           |                                        |
| Day 70 (\( n = 163 \))         | 25.67 ± 9.80                           |                                        |
| Day 84 – end of the escitalopram phase (\( n = 157 \)) | 21.63 ± 10.31 |                                        |
| Day 84 – end of the escitalopram phase LOCF (\( n = 157 \)) | 18.42 ± 11.09 |                                        |

**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) |
adequate (in terms of dose and duration) antidepressants. The main finding of the paper is the relevant clinical effectiveness of a third treatment in subjects who were resistant to two previous treatments.

In contrast to the STAR*D study, which showed a progressive decrease in treatment effectiveness 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 the second (venlafaxine) and 41.76/22.94% for the third (escitalopram).

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). Drop-out 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 et al. 2012).

Regarding side effect rate, escitalopram appeared to be associated with good tolerability in TRD patients. In those with mild side effect severity, the rate in the escitalopram phase was lower than previously reported (Bose 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. (2013), 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.

### Discussion

This study was designed to evaluate clinical effectiveness and tolerability of a third treatment in a sample of patients resistant to at least two adequate (in terms of dose and duration) antidepressants. The main finding of the paper is the relevant clinical effectiveness of a third treatment in subjects who were resistant to two previous treatments.

In contrast to the STAR*D study, which showed a progressive decrease in treatment effectiveness 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 the second (venlafaxine) and 41.76/22.94% for the third (escitalopram).

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Moreover the low drop-out rate during the AD3 treatment may also be due to a selection criteria as a number of patients had already dropped out during previous treatments.

There are a number of design issues that may weaken our findings. First of all, the lack of a placebo-controlled arm or of an active treatment arm limits the interpretation of the results. Moreover, the open nature of the study could be limiting also because it may allow physician bias to influence results. However, randomized placebo-controlled studies are important in providing specific answers in limited populations, but have the disadvantage of having a limited representativity. The exclusion criteria used and the defined protocol helped to ensure that the population studied suffered from treatment-resistant MDD using licensed and antidepressant doses. The results from this study should not be generalised to less well-defined groups. 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 antidepressant treatment (venlafaxine) to define TRD before treatment with a third compound (escitalopram). The paper is not therefore a comparative study to venlafaxine: venlafaxine treatment was only used for having a prospective antidepressant trial in order to assess if patients are treated as non-responders or not. The following switch to escitalopram was decided on the basis that this compound has been reported to have a synergistic action compared to other SSRIs (Sanchez et al. 2014). 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, and thus explaining the high response rate. Another limitation is represented by the responder definition in both phases of the trial (MADRS decrease from baseline $\geq 50\%$). 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. Also, compliance was not assessed through plasma level monitoring, and poor compliance has been suggested by many to be a confounding factor; however, this issue was taken into consideration during clinical assessments. Moreover, augmentation strategies are commonly used in clinical practice and in other studies, while the present study excluded subjects receiving augmentation, this also limits generalizability. Similarly, the dose escalation we observed for both treatments may have influenced results; however, this may reflect the common clinical use in the collaborating centres. 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, UK) propose that the decision on treatment for TRD should not be delayed and should be made at 3–4 weeks. Moreover, the possibility to establish effectiveness within this period in TRD has been previously reported (Rapaport et al. 2006). Moreover, the 6-week venlafaxine trial may have been insufficient to show eventual improvement, considering that venlafaxine may require multiple dose increases to achieve multi-receptor effectiveness. In fact in the present study the average titration schedule of venlafaxine we observed did not allow it to reach manufacturer’s recommendation for the first 2 weeks, this slow dose escalation could have influenced the responder rate during the AD2 treatment. Furthermore, the dosage heterogeneity among patients from different European countries for both venlafaxine and escitalopram, due to different treatment guidelines, could have biased the results, though in a non-clear direction since high antidepressant doses are not more effective and may also lead to poorer tolerability (Licht and Qvitzau 2002; Adli et al. 2005). Finally, the treatment algorithm applied in this study was not optimal: in fact, recent studies comparing switching to a new antidepressant with continuing the so far not effective first antidepressant failed to show any advantage of switching (Bschor and Baethge 2010; Souery et al. 2011a,b); consequently, further studies assessing a continuation of the second antidepressant would be useful for a deeper evaluation of present findings.

In conclusion, 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. However, present results should be considered with caution since a number of design issues could have biased them.

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URL for the registry: http://www.ANZCTR.org.au/ACTRN12613000256774.aspx.
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Supplementary material available online

Supplementary Table I–IV.