Socio-demographic and clinical predictors of treatment resistant depression: A prospective European multicenter study

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Abstract

Background: Few studies investigated socio-demographic and clinical predictors of non response and remission in treatment resistant depression (TRD) in the case of failure of more than two adequate antidepressant (AD) trial. The primary aim of this study was to investigate socio-demographic and clinical predictors of TRD defined as the lack of response to at least three adequate AD treatments, two of which prospectively evaluated. As secondary aims, we also investigated predictors of non response and remission to: (1) at least two adequate AD treatment (one of which prospectively assessed); (2) at least one adequate and retrospectively assessed AD treatment. Methods: In the context of a European multicenter project, 407 major depressive disorder (MDD) pa□tients who failed to respond to a previous AD treatment were recruited for a 2 stage trial, firstly receiving venlafaxine and then escitalopram. MINI, HRSD, MADRS, UKU, CGI-S and CGI-I were administered. Results: Ninety eight subjects (27.61%) were considered as resistant to three AD treatments. Clinical predictors were: longer duration and higher severity of the current episode (p¼0.004; ES¼0.24; p¼0.01; RR¼1.41, respectively), outpatient status (p¼0.04; RR¼1.58), higher suicidal risk level (p¼0.02; RR¼1.49), higher rate of the first/second degree psychiatric antecedents (MDD and others) (p¼0.04; RR¼1.31, p¼0.03; RR¼1.32 respectively) and side effects during treatments (p¼0.002; RR¼2.82). Multivariate analyses underlined the association between TRD and the severity of the current episode (p¼0.04). As for secondary outcomes, predicting factors were partially overlapping. Limitations: The limited sample size and specific drugs used limit present findings. Conclusion: Subjects with a high degree of resistance to AD treatments show specific features which may guide the clinicians to the choice of more appropriate therapies at baseline.

1. Introduction

Major depressive disorder (MDD) is a recurrent and hetero□geneous illness associated with significant morbidity and mortal□ity (WHO, 2012). Despite recent progress in psychopharmacolo□gical treatments, 30 to 40% of patients do not respond to a first line antidepressant therapy (Souery et al., 1999). Of these, up to 30% do not respond to multiple interventions (Cain, 2007; Berlim et al., 2008), resulting in about 10% of all MDD patients to be considered resistant to treatment. Considering remission, 60–70% of patients with a major depressive episode experience residual symptoms after treatment (Rush et al., 2006), often associated with sig□nificant occupational and psychosocial dysfunction, as well as with early relapse and increased recurrence rates (Keller et al., 1992; Trivedi et al., 2006). Taken together, these data have increased the attention on treatment resistant depression (TRD) in the last years. However, there is still some disagreement regarding TRD de□finition, which ranges from non response to a single and adequate (in terms of dosage, duration and compliance) antidepressant (AD) trial, to the lack of response to multiple ADs of different classes, including augmentation/combination strategies and electro□convulsive therapy (ECT) (for a detailed review, see Berlim and Turecki (2007a)). The lack of a univocal and universally accepted TRD definition has influenced clinical research, also in the detec□tion of socio-demographic and clinical predictors of non response and remission, leading to contrasting results. To date, most part of available studies investigated predictors of non response and re□mission to a single antidepressant, without taking into account multiple treatment failures in the same depressive episode. Among the investigated demographic factors, older age only was found to predict lower response rate (Petersen et al., 2002; Berg□man et al., 2011; Sagud et al., 2013), while melancholic subtype of depression, suicidal behavior (Papakostas et al., 2003; Souery et al., 2007) and comorbid current or lifetime generalized anxiety disorder (Petersen et al., 2001) seemed to be clinical predictors of non response. The lack of response could be also related to the AD doses and the duration of treatments (Berlim and Turecki, 2007b). As for non remission, being unmarried, higher baseline severity of illness (Fava et al., 2002; Perlis et al., 2003, 2004) and anxious symptoms (Russell et al., 2001; Howland et al., 2009) were iden□tified as significant socio-demographic and clinical predictors. The history of previous AD treatments and the administered AD doses were found to be related to non remission too (Uher et al., 2009; Nasso et al., 2011). However, only few studies reported informa□tion regarding the number of failed AD trials, with consequent difficulty in generalizing findings. Interestingly, in a previous in□vestigation, in the context of our European multicenter study named "Patterns of Treatment Resistance and Switching Strategies in Unipolar Affective Disorder", we recruited a large sample of MDD patients who failed to respond to at least two consecutive and adequate, retrospectively assessed, AD trials. Anxiety co□morbidities (in particular comorbid panic disorder and social phobia), personality disorders, suicidal risk, depression severity, melancholic features, recurrent episodes, a number of hospitali□zation more than one, early age at onset and the lack of response to the first antidepressant received lifetime have been potentially associated with TRD (Souery et al., 2007). Among them, four variables have been identified as the most discriminative ones: anxiety comorbidities, suicidal risk, melancholic features and the lack of response to the first AD received lifetime. These findings, however, require further replications in order to be considered reliable, also considering that the TRD status has been retro□spectively assessed. Prospective studies investigating clinical characteristics at each stage of the depressive episode treatment are clearly necessary to improve the knowledge on this field. We should finally consider that traditional outcomes in clinical studies on MDD mainly fo□cused on symptomatic improvement or response, rather than on full remission, failing to emphasize the substantial impact of re□sidual symptoms on psychosocial dysfunction and poor prognosis (Rush et al., 2006). Consequently, the primary aim of the present study was to in□vestigate socio-demographic and clinical predictors of TRD in a sample of prospectively assessed MDD patients. For this purpose, we focused on patients recruited in the context of a European multicenter project, who entered a 2 stage trial after the failure of at least one adequate AD treatment (retrospectively assessed), firstly receiving venlafaxine and then, in case of non response, escitalo□pram. Both treatments were prospectively evaluated. In the present study we had therefore the unique possibility to select a sample of severe resistant patients prospectively evaluated. Our primary aim was to investigate such a subsample of particularly critical subjects. TRD was

thereby defined as the lack of response to at least three adequate AD treatments, two of which prospectively evaluated (venlafaxine and escitalopram). As secondary aims, in the same sample, we also investigated: (1) sociodemographic and clinical predictors of non response and remission in patients who failed to respond to at least two adequate AD treatment, one of which pro□spectively assessed (venlafaxine); (2) sociodemographic and clinical predictors of non response and remission in patients who failed to respond to at least one adequate and retrospectively assessed AD treatment (not specified). We finally evaluated differences in socio□demographic and clinical features between early responders and severe non responders.

2. Methods

2.1. Sample and study design

407 MDD patients who failed to respond to the previous and adequate, retrospectively assessed, AD treatment have been re□cruited from January 2005 to December 2011, in the context of an European multicenter project. They entered a 2 stage open trial: in the first stage, they received a 6 week treatment with venlafaxine; in the second stage, 170 patients who failed to respond to venla□faxine received escitalopram for 6 weeks more. As for the first stage (venlafaxine treatment), we included in□outpatients of at least 18 years old with a current major depressive episode as assessed with the Mini International Neuropsychiatric Interview (MINI), moderate or severe, according to DSM-IV-TR criteria. Each patient had to: (1) have been treated for the current MDE with any antidepressant at its optimal dose for at least 4 weeks; (2) be a non-responder to this previous treatment (Montgomery Asberg Depression Rating Scale (MADRS) improvement o50%); (3) have a MADRS total score Z22. Exclu□sion criteria were: (1) non response to a combination of 2 anti□depressants and/or to an augmentation therapy; (2) any current psychiatric disorder established as the principal diagnosis other than MDD as defined in the DSM-IV-TR; (3) any Substance Dis□order (except nicotine and caffeine) within the previous 6 months as defined in the DSM-IV-TR; (4) any severe Personality Disorder according to investigator clinical judgement that might compro□mise the study; (5) any treatment with other psychotropic medi□cations (es. oral antipsychotic drugs or depot preparations, ECT within the past 6 months, mood stabilizer within the past month, benzodiazepines or other anxiolytic/hypnotic drugs at high doses); (6) any serious physical illness which could have rendered inclu□sion in the study unsafe or interfered with the assessments of tolerability or efficacy. As for the second stage (escitalopram treatment), patients who failed to respond to venlafaxine were included. Patients who had not taken venlafaxine for three or more consecutive days or whose compliance was less than 80% during the venlafaxine treatment were excluded from the present study; any of the previously de□scribed exclusion criteria that appeared since the initiation of the venlafaxine treatment was considered as well. Inclusion/exclusion criteria of both stages were detail reported in our previous study as well as a detailed description of the study design and recruitment procedures (Souery et al., 2014) (See also Fig. 1). The study protocol was approved by the Ethical Committees of all participating centers 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 parti□cipants prior to their inclusion in the study.

2.2. Assessment

At the time of screening, socio-demographic and clinical fea□tures of the MDD patients were collected using “TRD.COM”, a centralized server consisting on a structured examination tool with immediate data capture, divided in several modules, some of these specifically developed for this study: (1) socio-demographic data; (2) Mini International Neuropsychiatric Interview (MINI), version 5.0.0 modified for the group for the study of resistant depression (Souery et al., 2007); (3) severity scales (MADRS (Montgomery and Asberg, 1979)), Hamilton Rating Scale for De□pression (HRSD) 17-item version (Hamilton, 1960), and Clinical Global Impression Severity (CGI-S) (Guy, 1976)); (4) somatic ill□nesses; (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; (9) functional impairment (Sheehan Disability Scale (SDS) (Shee□han, 1983)). Patients were subsequently evaluated at specific time points (baseline, day 14, 28, and 42 (venlafaxine treatment), and day 56, 70, 84 (escitalopram treatment)) administering the fol□lowing modules: (1) MADRS; (2) HRSD; (3) CGI-S; (4) CGI-I (Clinical Global Impression Improvement); (5) current medication (AD doses, benzodiazepine use, concomitant psychotherapy); (6) UKU.

2.3. Outcomes

2.3.1. Primary outcome

The primary outcome was to detect available socio-demo□graphic and clinical predictors of TRD (for the complete list see tables). As our aim was to study the severe resistance, we com□bined the data from the two stagess. For this purpose, we focused on the patients who did not respond to any of the 2 prospective consecutive AD trials (venlafaxine and escitalopram). They were compared with the remaining part of the sample (i.e. all the pa□tients who responded to either the venlafaxine stage and to the escitalopram stage combined). So, TRD patients were defined in this case as non responders to at least three adequate and con□secutive AD treatments and compared to subjects who responded to a second or third treatment.

2.3.2. Secondary outcomes

As for secondary outcomes, we considered separately the two stages of the trial, analyzed according to standard methodologies. First, we focused on the second stage of the trial (escitalopram treatment). In particular, we evaluated predictors of non response and remission of only the patients who did not respond to the venlafaxine stage and were included in the escitalopram stage. Second, we focused on the first stage of the trial (venlafaxine stage). In particular, we evaluated predictors of non response and remission in patients who failed to respond to at least one pre□vious and adequate AD treatment (patients who entered the first stage of the trial and received venlafaxine). Finally, we evaluated differences in socio-demographic and clinical features between Early Responders and Severe Non responders.

2.4. Definitions

First stage (venlafaxine treatment): Non Responders to venla□faxine were patients with a MADRS total score 420 and a de□crease in MADRS total score r50% from the start of the venla□faxine treatment. Non Remitters to venlafaxine were patients with a MADRS total score 410 at the end of the venlafaxine treatment. Early Responders were patients with a decrease in MADRS total score Z50% after 2 weeks of venlafaxine treatment, while Severe Non Responders were patients with a decrease in MADRS total score o20% at the end of the venlafaxine treatment. Second stage (escitalopram treatment): Non Responders to escitalopram (Resistants) were patients with a MADRS total score 420 and a decrease in MADRS total score r50% from the start of the escitalopram treatment. Non Remitters to escitalopram were patients with a MADRS total score 410 at the end of the escita□lopram treatment. Early Responders were patients with decrease in MADRS total score Z50% after 2 weeks of escitalopram treat□ment, while Severe Non Responders were patients with a decrease in MADRS total score o20% at the end of the escitalopram treatment. For better understanding of primary and secondary outcomes see Fig. 2a and Supplementary Fig. 2b.

2.5. Statistical analyses

The number of Non Responders and Remitters was previously assessed (Souery et al., 2014) with a repeated-measure ANOVA analysis of variance focused on MADRS change from baseline (day 0) to day 14, 28, 42, 56, 70 and 84. Here, chi-square and t-test were applied, on the basis of categorical or continuous variables, to evaluate the possible impact of socio-demographic and clinical features on the different outcomes. All the investigated socio-de□mographic and clinical features were reported in Tables 1, S3–S6.

Focus was on Intent To Treat (ITT) patients, but analyses on Completers were also performed. In case of significance, crude effect size (ES) and relative risk (RR) were also determined. We hypothesized, however, that some of the identified variables were likely to be reciprocally correlated (e.g. the severity of the current MDE, the administered AD doses and side effects). Thus the po□tential correlations were evaluated using both the correlation matrix model and clinical judgement (i.e. clinical features which are logically and clinically more relevant). In particular, all sig□nificant socio-demographic and clinical features entered the cor□relation matrix model. If predictors were significantly related to each other, we selected, according to clinical judgement, the most relevant and independent ones. In this way, we identified a list of predictors to test in relation to the different outcomes with mul□tiple regression analysis. On the basis of the results, we also pre□liminarily investigated if AD doses and side effects were in□dependently associated with non response, in order to exclude that higher sides effects were caused by higher AD doses. In order to do this, we created two subsamples (Responders vs Non Re□sponders or Remitters vs Non Remitters) matching patients by AD doses, separately considering the two stages of the trial. All p va□lues were 2-tailed and statistical significance was exploratorily set at 0.05. With these parameters, we had sufficient power (0.80) to detect a small effect size (ω¼0.15) that, as an example, corres□ponds to an OR of 1.86 between Resistant and Non-resistant, considering the severity of the current MDD episode. Statistical analyses were performed using "Statistica" package (StatSoft, 1995). Power analysis has been performed using G*Power 3.1 (Faul, 2007).

3. Results

3.1. Sample description

417 MDD patients were originally included in the study; however, 10 patients did not complete the first week treatment and were excluded from the present analyses. Considering ITT patients, of a total of 407 MDD patients, 222 (54.55%) did not re□spond to venlafaxine. Out of 222 patients, 170 received escitalo□pram. Indeed, 39 did not complete the venlafaxine stage (con□sidered venlafaxine non responders), while 13 did not meet in□clusion criteria for the escitalopram stage. However, these 52 pa□tients did not differ from the 170 ones included. Of these 170, 98 (57.65% of the escitalopram treated patients and 27.61% of the total sample respectively) did not respond to escitalopram treatment and were considered as Resistant (to at least 3 treatments). The detailed flow chart of patient inclusion/exclusion process was re□ported in Fig. 2a (see also our previous work Souery et al. (2014)). In the present study, drop outs were considered as Non Re□sponders-Remitters/Responders-Remitters on the basis of the Last Observation Carried Forward. Socio-demographic and clinical features of the ITT sample are shown in Tables 1, S3–S6. 3.2.

Primary outcome

Predictors of TRD (non response to at least 3 adequate treat□ments including venlafaxine and escitalopram prospectively evaluated) Results for ITT patients were reported in Table 1. TRD was related to: (1) outpatient status (p¼0.04; RR¼1.58); (2) longer duration of the current MDD episode (p¼0.004; ES¼0.24); (3) its higher severity as assessed with the MINI (p¼0.01; RR¼1.41); (4) higher CGI and MADRS scores (p¼0.03; ES¼0.23 and p¼0.04; ES¼0.24 respectively); (5) moderate to high suicidal risk level (p¼0.02; RR¼1.49); (6) first/second degree psychiatric antecedents (MDD: p¼0.04; RR¼1.31; other psychia□tric disorders (no mood disorders): p¼0.03; RR¼1.32); (7) higher rates of side effects during treatments (p¼0.002; RR¼2.82). Fo□cusing on anxiety comorbidities, a higher prevalence of anxiety disorders (excluding obsessive-compulsive disorder (OCD)) was observed in Resistant patients; however, this association did not reach the statistical significance. On the basis of both the corre□lation matrix and the clinical judgment, we selected some in□dependent TRD predictors: (1) severity of the current MDD epi□sode as assessed with the MINI; (2) suicidal risk level; (3) ante□cedents with MDD or other psychiatric

disorders (others than mood disorders). Results were reported in Table 2. In particular, the severity of the illness was found to be independently asso□ciated with TRD (p¼0.04).

3.3. Secondary outcomes

3.3.1. Predictors of non response and remission to venlafaxine and at least a previous retrospective AD treatment (escitalopram stage only) Significant results for ITT patients were reported in Supple□mentary Table 3. Non response to treatment was found to be associated with a longer duration of the current MDD episode (p¼0.003; ES¼0.80) and higher rates of side effects after 6 weeks of escitalopram treatment (day 84) (p¼0.04; RR¼1.46). Multiple regression ana□lysis revealed an association with side effects only (p¼0.05). We also investigated if side effects were independently asso□ciated with non response. Controlling for doses, we observed higher rates of side effects in Non-responders, although no sig□nificant relationship was found (X2¼2.77; p¼0.10). A small range of escitalopram doses and a relatively small sample size may ac□count for the lack of significance. As for predictors of non remission, we observed: (1) recurrent vs single episodes (p¼0.048; RR¼0.69); (2) a higher mean age at the last MDD episode (current episode) (p¼0.02; ES¼0.48); (3) longer duration of the current MDD episode (p¼0.001; ES¼0.91); (4) its higher severity as assessed with the MINI (p¼0.02; RR¼1.58); (5) higher CGI and MADRS scores (p¼0.002; ES¼0.58 and p¼0.0002; ES¼0.77 respectively); (6) suicidal risk (p¼0.04; RR¼1.49); (7) second degree Bipolar Disorder ante□cedents (p¼0.01), even if the small sample size of the affected antecedents (n¼2) should be considered as a consistent limitation of this finding; (8) disabilities in both work (p¼0.01; ES¼0.49) and family life or home responsibilities (p¼0.05; ES¼0.37); (9) higher AD doses after 2 and 6 weeks of escitalopram treatment (day 56 and 84) (p¼0.02; ES¼0.52 and p¼0.02; ES¼0.43 re□spectively); (10) higher rates of side effects after 6 weeks of esci□talopram treatment (day 84) (p¼0.02; ES¼2.79). Focusing on anxiety co-morbidities, a higher prevalence of anxiety disorders (excluding OCD) (p¼0.01; RR¼1.77) was observed in Non Re□mitters. Multiple regression analysis results were reported in Ta□ble 2. In particular, severity of the illness and comorbid anxiety disorders were found to be independently associated with non remission (p¼0.03 and p¼0.008 respectively). We also investigated if AD doses and side effects were in□dependently associated with non remission. Controlling for doses, we observed higher rates of side effects in Non-remitters, although no significant relationship was found (X2¼2.14; p¼0.14). Again, a small range of escitalopram doses and a relatively small sample size should be considered. Finally, we compared non responders with remitters to venla□faxine and at least a previous retrospective AD treatment founding the same predictors.

3.3.2. Predictors of non response and remission to at least one ret□rospective AD treatment (venlafaxine stage only) Significant results for ITT patients were reported in Supple□mentary Tables 4 and 5. Non-responders were more frequently employed (p¼0.04; RR¼1.26). Regarding clinical predictors, we identified: (1) higher severity of the current MDD episode as assessed with the MINI (p¼0.03; RR¼1.28); (2) higher CGI and MADRS scores (p¼0.003; ES¼0.32 and p¼0.0001; ES¼0.41 respectively); (3) moderate to high suicidal risk level (p¼0.03; RR¼1.35); (4) first/second degree psychiatric antecedents (others than mood disorders) (p¼0.009; RR¼1.43); (5) higher AD doses after 6 weeks of venlafaxine treatment (day 42) (p¼0.006; ES¼0.31); (6) higher rates of side effects after 6 weeks of venlafaxine treatment (day 42) (po0.0000001; RR¼2.78). Focusing on anxiety co-morbidities, no significant association was found. Higher frequency of psychiatric antecedents was found to be independently associated with TRD (p¼0.02) in multiple regression analysis as well (Table 2). We also investigated if AD doses and side effects were in□dependently associated with non response. Controlling for doses, we confirmed the relationship between non response and side effects (X2¼50.79; po0.00001). As for non remission, we found similar results. Moreover, Non Remitters more frequently had a family history of MDD, in parti□cular of first degree MDD antecedents (p¼0.02; RR¼1.35). We also investigated if AD doses and side effects were in□dependently associated with non remission. Controlling for doses, we confirmed the relationship between non response and side effects (X2¼24.77; po0.00001). Finally, we compared non responders with remitters to at least a previous

retrospective AD treatment founding the same predictors. 3.3.3. Socio-demographic and clinical differences between early re□sponders and severe non-responders in both subsamples Results for significant associations in ITT patients are shown in Supplementary Table 6. When all analyses were preformed considering only Com□pleters, no significant difference appeared (data not shown).

4. Discussion

The present study primarily aimed to investigate socio-demo□graphic and clinical predictors of severe TRD in a large sample of MDD patients assessed both prospectively and retrospectively. TRD was defined by the lack of response to at least three adequate AD treatments, two of which prospectively evaluated. Therefore, in a two stage approach, patients first received venlafaxine and consecutively escitalopram if necessary. Thus the study also aimed to evaluate predictors of non response and remission for both stagess separately. Some clinical features were associated with TRD: outpatient status, longer duration and higher severity of the current MDD episode, moderate to high suicidal risk level, first/second degree psychiatric antecedents (MDD and others) and higher rates of side effects during treatments. Among them, the severity of the illness (as assessed with the MINI) was identified as the most dis□criminative one, featuring the highest independent predictive va□lue as assessed with multivariate analysis. Similar findings were also observed for secondary outcomes. To our knowledge, this is the first study evaluating predictors of treatment resistance to two adequate and prospectively assessed AD treatment (after the failure of a previous, retrospectively as□sessed, AD), providing a large database of MDD patients for whom a Resistant status could be suggested on the basis of prospective data collected during the last MDD episode. Pertaining to the primary outcome, the most important TRD predictor seemed to be the severity of the current MDE, which also resulted as significant predictor in early stages of resistance. In particular, we considered the severity of the illness as assessed with the MINI, which may allow a better and comprehensive clinical evaluation of patients compared to rating scales. However, also the latter, which investigate different aspects of MDD, showed associations with TRD. Comparing these findings with literature is very difficult, because of the unique level of resistance shown by our TRD sample. Interestingly, literature data showed that pre□treatment severity of depressive symptoms was associated with both better and worse response to AD treatments (Tedlow et al., 1998; Khan et al., 2005). Nevertheless, when only MDD patients who failed to respond to at least one previous AD treatment were considered, almost all studies did not find any association with non response (Petersen et al., 2002; DeBattista et al., 2003; Nasso et al., 2011; Rosso et al., 2012; Sagud et al., 2013). On the contrary, most part of the studies focusing on non remission reported po□sitive results, suggesting a substantial predictive role of severe symptoms on treatment outcome. In our previous retrospective investigation, the severity of the current MDD episode was found to be associated with higher risk of treatment resistance (as con□sidered by the failure of at least two consecutive and adequate AD treatment; Souery et al., 2007). This finding, however, disappeared when the second-step Cox regression analysis was performed, indicating the presence of a possible confounding factor mediating this relationship (e.i., Axis II diagnosis). Also the lack of a clear distinction between treatment non response and remission, in term of HRSD scores, and the retrospective assessment of patients could have affected our previous result. In the present study, we observed the severity of the illness as the principal predictor of both TRD, and non response and remission to at least one or two previous AD trials. Severity probably conditions the duration of the current MDD episode and the higher administered AD doses, with possible higher rates of side effects during treatment (another variables found to be associated with TRD). The latter could be also independently associated with TRD as the results of the individual sensitivity to the AD drugs of this specific group of patients. In fact, literature data considering the duration of MDD episode and side effects as separately associated with TRD seemed to be in line with our results (Petersen et al., 2002; Howland et al., 2009; Sagud et al., 2013). So, the severity of the illness should be considered as a consistent TRD predictor and deeper investigated in order to clearly dissect its role in both short and long term response to treatment. Moreover, its influence on non remission seemed to be stronger, with consequent effects on the functional impairment and poor prognosis. Although not

significant in multiple regression analysis, we identified other TRD predictors: moderate to high suicidal risk and higher rate of the first/second degree psychiatric antecedents (MDD and others). As for the first one, our primary results were confirmed by secondary ones, strengthening the association be□tween suicidal risk and non response and remission to treatment. As complex clinical syndrome, related to several biological, so□ciological, and psychological factors (Olin et al., 2012), suicidal behavior cannot be considered as exclusively depended on the severity of the illness and deserves a separate investigation. We should underline that the evaluation of suicidal risk trough the MINI includes a combination of different suicidal aspects, such as the presence of current suicide ideation, plan and attempt as well as of suicidal attempts during lifetime. However, we could not discriminate if only a specific aspect was involved and to what extent. Indeed, a history of suicidal attempts was considered as predictor of non response in a sample of TRD patients (Sagud et al., 2013); in the same study, current suicidal risk seemed not to in□fluence response. Opposite results emerged from our previous retrospective investigation (Souery et al., 2007). Similarly, TRD patients were also found to more likely report current suicidal thoughts and wishes (Papakostas et al., 2003). All these findings suggest to consider suicidal behavior as a possible predictor of non response to ADs in TRD patients. Its influence on non remission deserve further attention as the only study examining a history of suicidal attempts in TRD found no association (Dudek et al., 2010). As for psychiatric antecedents, most part of the studies recruiting MDD patients who failed to respond to at least one AD trial showed no relationship between a family history of mood dis□orders and non response (Agid and Lerer, 2003; Souery et al., 2007; Fang et al., 2010; Nasso et al., 2011) or non remission (Bock et al., 2009; Dudek et al., 2010; Fang et al., 2010). On the other hand, in line with our results, some studies showed that a family history of depression may be directly or indirectly associated with TRD (Nelsen and Dunner, 1995; Klein et al., 1999). Indeed, it was frequently related to early onset of MDD and chronicity, both linked to treatment resistance (Klein et al., 1999). While literature data suggest that a more endogenous type of depression, with a stronger biological substrate, is more frequently associated with treatment response, several confounding factors, both biological and environmental, could be present when investigating TRD. These factors could also explain why melancholic features were frequently found to influence non response (Souery et al., 2007; Maron et al., 2009). However, in our sample, we did not observe a higher prevalence of melancholic features in TRD patients com□pared to non TRD ones. Because of these contrasting results, fur□ther studies are obviously necessary. Regarding a family history of other psychiatric disorders (e.g. suicide, alcoholism or schizo□phrenia), our positive results in both TRD and non response and remission to at least one or two previous AD treatment seemed to be in contrast with literature data (Agid and Lerer, 2003; Bock et al., 2009; Dudek et al., 2010; Fang et al., 2010). Although iso□lated, they deserve a further investigation as confirmed by mul□tiple regression analysis in secondary analysis. Indeed, we could speculate that an unfavorable family environment or the lack of family support, due to psychopathologies, may increase the risk of developing TRD (George et al., 1989; Leskela et al., 2006). Pertaining to primary results, we should finally consider that Responders to at least three AD treatments represent a hetero□geneous sample, composed by Responders to both at least one and at least two AD treatments. As for secondary results, the association between anxiety dis□orders and non remission to at least two adequate AD treatments (one of which prospectively assessed) deserves particular atten□tion. Indeed, comorbid anxiety disorders were widely associated with poorer or delayed response to ADs, chronicity, higher severity of both depression and anxiety, and psychosocial impairment (Alpert and Lagomasino, 2001). Interestingly, in two large samples of MDD patients who failed to respond to at least one AD trial, anxious symptoms were associated with higher rates of non re□mission (Russell et al., 2001; Howland et al., 2009). Similarly, current or lifetime generalized anxiety disorders was considered as predictors of non response in TRD (Petersen et al., 2001), while panic disorder has been associated with poor treatment outcome and chronicity in elderly (Fava et al., 1997; Flint and Rifat, 1997). In the present work, while a trend for association was observed for all our outcomes, a stronger relationship emerged for MDD pa□tients who failed to respond to venlafaxine. The reason for this is not clear. The fact that we selected patient subgroups after each AD failure should be considered when interpreting this and other

findings concerning each step resistance. Alternatively, comorbid anxiety disorders may define a heterogeneous sample with sub□groups having anxiety secondary to stressful life events or per□sonality traits which present a higher degree of resistance. Finally, the association between non response and remission and both higher escitalopram/venlafaxine doses and higher rates of side effects at the end of each treatment deserve a brief dis□cussion, also considering primary results. Indeed, higher rates of side effects were commonly related to higher AD doses. However, when we removed the effect of AD doses on outcomes, a re□lationship between non response and remission and higher rates of side effects was in general confirmed, reaching statistical sig□nificance for patients treated with venlafaxine. Interestingly, this association did not depend on the number of drop-outs as con□firmed by the analysis on Completers. In other words, higher rates of side effects seemed not to be totally conditioned by higher AD doses and could be identified as independent predictor of non response and remission in MDD patients. In the light of these findings, we could speculate that raising the dose of ADs versus keeping lower dose when treating non-responder MDD patients should be considered with caution in clinical practice, as 230 M. Balestri et al. / Journal of Affective Disorders 189 (2016) 224–232 previously underlined by some Authors (Dornseif et al., 1989; Licht and Qvitzau, 2002). However, the reason for this should not be completely related to the fact that higher rates of side effects were connected to higher AD doses. So, increasing the AD doses could be justified until side effects appear. Nevertheless, some limitations should be underlined. First, the present study was designed to evaluate efficacy and tolerability of a third treatment in TRD as defined by the failure of at least two adequate AD trials. However much evidence suggest that the switch to a new AD compared to simply continuing the so far not effective first AD does not show any advantage in favor of switching (Souery et al., 2011). Unfortunately, the present study design was designed before these strong evidence come into light, but it still represents a common practice. Second, some clinical data (e.g., age of MDD onset, number of MDD episodes and the duration of the current illness) were obtained by participant self reports and may not be considered as consistently valid. Similarly, also the retrospective assessment of the first AD could have led to recollection bias. Nevertheless, we also evaluated socio-demo□graphic and clinical features of MDD patients who failed to re□spond to a lower number of AD trials, thus avoiding to focus only on severe resistant patients. Third, although the evaluation of the severity of the current MDD episode through the MINI allows a better and comprehensive clinical evaluation of patients, the clinician ratings of depressive symptoms could have been affected by cultural context, alliance, personality style, age, and prior or current life experiences. However, also CGI and MADRS scales were considered. Interestingly, although evaluating some different aspects of MDD, results for MINI severity, CGI and MADRS scales were similar. Fourth, the restrictive exclusion criteria in the patient selection (e.g. personality disorders, substance abuse) might have led to a well defined study population that might not be com□pletely representative to other patients receiving ADs. Fifth, the Responder definition in both stages of the trial (MADRS decrease from baseline Z50%), also if widely used, could have reduced the response rates in the second stages and may not be the most ap□propriate definition in a population with defined resistance to treatment. The dosage heterogeneity among patients from differ□ent European countries for both venlafaxine and escitalopram, due to different treatment guidelines, could have biased the results as well. Further, the variance explained by single predictors and their combination is quite low, ranging from 4% to 8%. The relatively small number of patients attending the second stage of the trial could have biased multiple regression analysis results as well. Fi□nally, we did not consider recent adverse life events, childhood trauma, specific personality features as well as psychotic symp□toms as possible TRD predictors. As for the latter, however, psy□chotic features were not found be associated with TRD in a large sample of severely depressed patients (Zaninotto et al., 2013). Also concomitant psychotherapy was not taken into account. In conclusion, considering also the numerous above mentioned limitations and the need of caution in the generalizability of the results, some clinical variables were associated with severe treat□ment resistant depression, which has never been properly ex□amined before, as well as with non response and remission to a different number of AD treatments, such as severity of the illness, suicidal risk, psychiatric antecedents and comorbid anxiety dis□orders. Some of these variables were previously identified as

predictor of resistance in a sample of retrospectively assessed MDD patients, strengthening the present findings. The early identification of MDD patients at high risk for treatment resistance could guide clinicians in selecting optimal setting and intensity of care. Indeed, individuals at high TRD risk could benefit from an early more aggressive treatment. Moreover, they could represent important subjects to test for new antidepressants, which target different neurotransmitter systems outside the monoaminergic one (e.g. glutamatergic modulators, acetylcholine receptor drugs, infliximab and anti-inflammatory agents).

Contributors

All authors were actively involved in the design of the study, the analytical method of the study, the selection and review of all sci□entific content. All authors had full editorial control during the writing of the manuscript and finally approved it. Trial registry name: Australian New Zealand Clinical Trials Registry; (ANZCTR). Registra□tion identification number: ACTRN12613000256774; URL for the registry: http://www.ANZCTR.org.au/ACTRN12613000256774.aspx.

Role of founding source

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Conflict of interests

Dr. Souery D. has received grant/research support from Glax□oSmithKline and Lundbeck; has served as a consultant or on ad□visory boards for Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Janssen and Lundbeck. Prof. Montgomery S. has been a consultant or served on Advisory boards: Astra Zeneca, 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 Astra Zeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Lundbeck, Pfizer, Organon, Schwabe, Sepracor, Servier, Janssen, and Novartis; and has served on speakers' bureaus for Astra Zeneca, 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, Abbvie, Angelini, Astra Zeneca, Clinical Data, Boheringer, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polipharma, Sanofi, Servier. The other authors declare no potential conflict of interest.

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