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Research report

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) patients 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 ($p=0.004$; ES=0.24; $p=0.01$; RR=1.41, respectively), outpatient status ($p=0.04$; RR=1.58), higher suicidal risk level ($p=0.02$; RR=1.49), higher rate of the first/second degree psychiatric antecedents (MDD and others) ($p=0.04$; RR=1.31, $p=0.03$; RR=1.32 respectively) and side effects during treatments ($p=0.002$; RR=2.82). Multivariate analyses underlined the association between TRD and the severity of the current episode ($p=0.04$). 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 heterogeneous illness associated with significant morbidity and mortality (WHO, 2012). Despite recent progress in psychopharmacological 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 significant 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 definition, 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,

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including augmentation/combination strategies and electroconvulsive 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 detection 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 remission 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; Bergman 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 identified 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 information regarding the number of failed AD trials, with consequent difficulty in generalizing findings. Interestingly, in a previous investigation, 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 comorbidities (in particular comorbid panic disorder and social phobia), personality disorders, suicidal risk, depression severity, melancholic features, recurrent episodes, a number of hospitalization 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 retrospectively 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 focused on symptomatic improvement or response, rather than on full remission, failing to emphasize the substantial impact of residual symptoms on psychosocial dysfunction and poor prognosis (Rush et al., 2006).

Consequently, the primary aim of the present study was to investigate 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, escitalopram. 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 prospectively 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 sociodemographic 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 recruited 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 venlafaxine 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 $< 50\%$); (3) have a MADRS total score ≥ 22. Exclusion criteria were: (1) non response to a combination of 2 antidepressants 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 Disorder (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 compromise the study; (5) any treatment with other psychotropic medications (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 inclusion 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 described 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 participants prior to their inclusion in the study.

2.2. Assessment

At the time of screening, socio-demographic and clinical features of the MDD patients were collected using "TRD.COM", a centralized server consisting on a structured examination tool