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ARTICLE

Specificity profile of venlafaxine and sertraline in major depression: metaregression of double-blind, randomized clinical trials

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Abstract

Despite the well-known efficacy of selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) in the treatment of major depressive disorder, there is a lack of indications for each drug in different groups of patients. The aim of this study is to investigate the possible role of clinical sociodemographic factors as moderators of clinical response to venlafaxine (SNRI) and sertraline (SSRI). Research was performed on Medline and EMBASE for randomized control trials in English focused on sertraline and venlafaxine in the treatment of major depressive disorder and 59 studies were included. Clinical efficacy of each treatment was assessed on the basis of Hamilton Depressive Rating Scale and Montgomery–Asberg Depression Rating Scale. A metaregression analysis was performed to evaluate the role of clinical and sociodemographic factors as moderators of outcome, calculating the effect of each variable with the random-effects method. Gender, ethnicity and duration of depressive episode could have a role in prediction of clinical response to both antidepressants. Venlafaxine seems to have better effects in females and in Caucasian patients. Sertraline seems to be more efficacious in the treatment of females. Both drugs were more efficacious in patients who suffered a shorter episode of illness. Our results could represent an interesting point of view in the perspective of choosing the most suitable therapy based on clinical and social features for each patient. Metaregression is a retrospective analysis, based on the cumulative results of previous studies, so the lack of original data could represent the main limitation in this report and in the interpretation of the results obtained.

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Introduction

Major depression is the fourth most disabling illness in the world (Lepine *et al*. 2004). Despite the proven general efficacy of antidepressant drugs in major depressive disorder and the efforts to define the 'best' antidepressant in terms of efficacy and safety (Cipriani *et al*. 2009; Gartlehner *et al*. 2011), to date precise indications able to predict a patient's response to a molecule on the basis of individual characteristics are still lacking. Thus, clinicians sometimes might expose patients to different antidepressant trials before a satisfactory clinical response (Rossini *et al*. 2005). Recently, alternative meta-analytic approaches, such as sensitivity analysis or metaregression analysis, have tried to answer this unmet need, and some promising findings regarding gender, clinical history and study design were found, as in the case of paroxetine (Klemp *et al*. 2011; Serretti *et al*. 2011). In this study we address the analogue methodology to another selective serotonin reuptake inhibitor (SSRI) (sertraline) and to a serotonin–norepinephrine reuptake inhibitor (SNRI) (venlafaxine), with the aim to evaluate possible different impacts on the efficacy within and between two different classes of antidepressants of patient characteristics, as reported in randomized controlled trials (RCTs). We focused our attention on these drugs as they are two of the most prescribed compounds in clinical settings, and two of the best studied in literature. Among the commonly used SSRIs we chose to address sertraline also because of its interesting interactions with the sigma receptor, which could

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distinguish it from other SSRIs (Hoehn-Saric *et al*. 2000). Venlafaxine inhibits neuronal reuptake of both serotonin and norephinefrine and, like sertraline, has a low affinity for muscarinic, adrenergic and histaminergic receptors (Thase, 1997).

In summary, the aim of the present study is to evaluate the possible impact of clinical and sociodemographic variables on the measure of clinical outcome in patients suffering major depressive disorder in treatment with sertraline and venlafaxine, respectively. We conducted a metaregression analysis based on RCTs in order to correlate moderators with results.

Methods

We searched Medline, EMBASE and the Cochrane Library using the keywords 'sertraline', 'venlafaxine' and 'major depressive disorder' as primary diagnosis. The search was restricted by study design (randomized trials), language (English), year of publication (from 1993 to 2011) and age (all adults: 19+yr). The search was refined through the analysis of relevant review and meta-analysis on sertraline (Cipriani *et al*. 2009; Murdoch and McTavish, 1992). Initial and periodic assessment of efficacy, as based on the Hamilton Depression Rating Scale (HDRS) or the Montgomery–Asberg Rating Scale (MADRS), was evaluated. In order to evaluate the efficacy of each drug we considered the global improvement of depressive symptoms, as standardized mean difference (SMD) of HDRS and MADRS score, without taking into account clinical outcome in terms of response and remission. In order to maximize power both in terms of available data and magnitude of effect, we used an improvement of the methodology of our previous analysis focusing on paroxetine (Serretti *et al*. 2011). We excluded studies that covered both dysthymia and bipolar depression and articles that took into account electroconvulsive therapy (ECT). Two independent investigators (A.M., S.G.) analysed studies according to inclusion criteria from the former sources. Data were extracted by one (A.M.) and checked for accuracy by a second author (S.G). The quality of included reporting was assessed using a validated quality scale (Jadad *et al*. 1996) by two investigators, independently, under the supervision of a reviewer, who also checked for accuracy (A.S.). All disagreements were resolved through discussion. We collected the sociodemographic data (age, sex, job, educational level, marital status) and clinical data (age of onset, duration, type, family history). The sample size was gathered from the intent to treat (ITT) data, when available, otherwise by analysing patients who had completed the trial. Data of categorized variables (gender, marital status, employment, education level, duration of present episode, single/recurrent episodes) were expressed as a percentage of patients for each study. We performed metaregression analysis, evaluating standardized mean differences for each study according to the available data at baseline *vs.* week 6 and at baseline *vs.* week 8 and each of the former variables. We performed a preliminary analysis using the Jaded scale score as moderator to verify that the quality of the paper did not have an independent impact on results. We then performed metaregression analysis, testing each moderator clinical variable on efficacy results. We considered as primary results metaregression of the score between baseline and week 6, since most clinical trials we collected were conducted up to week 6. Only in a few studies were data concerning week 8 of treatment available, so results from baseline to week 8 are reported as supplementary material. We chose to include variables reported in at least six papers for each drug, and we performed a preliminary correlation analysis (data not shown) between variables of interest and standardized mean difference to check the validity of the results. We used the R statistics environment (http://www.R-project.org) version 2.10.0., package 'metafor' to perform the metaregression, choosing the random-effect method. We assessed publication bias through funnel plots (supplementary material Figures 1 and 2).

Results

59 RCTs were included for sertraline (Fig. 1), for a total sample 6029 patients treated with sertraline and 57 for venlafaxine (Fig. 2) for a total sample 6375 patients treated with venlafaxine. More details of characteristics of samples (age, gender and ethnicity) are reported in the supplementary material, Tables S1 and S2 for sertraline and Tables S3 and S4 for venlafaxine.

Female gender seems to be related to a better clinical outcome during venlafaxine treatment ($p=0.007$ and $p=0.004$ at weeks 6 and 8, respectively), whilst for sertraline a definite gender specificity was not found, even if a positive direction of response in females has been observed at week 6. About age, a slightly significant result for venlafaxine was found, with a possible worse trend in older patients. In our study we observed a possible effect of ethnicity as a possible moderator of efficacy for venlafaxine, as demonstrated in results assessed on secondary outcome: a positive trend was in fact found for Caucasians at week 8 ($p=0.0212$). Further, the duration of depressive episode was found as a possible moderator of response: we

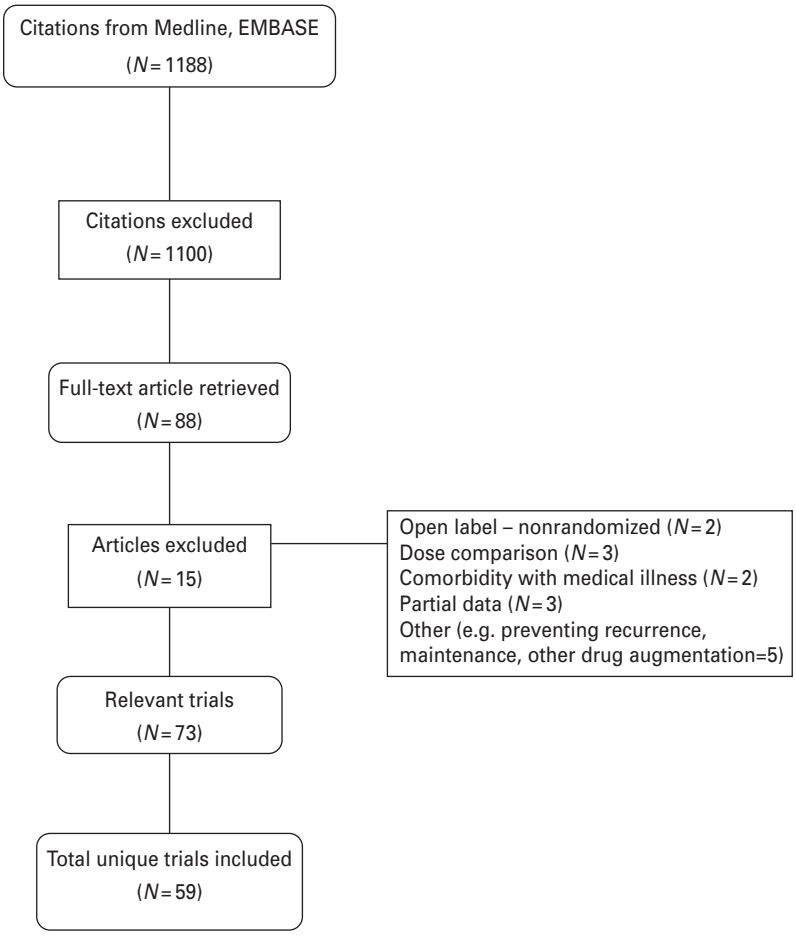

Fig. 1. Study flow chart for sertraline.

noticed a general positive correlation in the clinical response for all the drugs investigated when the duration of the depressive episode was shorter than 6 months; in particular there was a significant reduction of depressive symptoms in patients treated with venlafaxine at both week 6 and week 8 of treatment (p=0.001; p=0.004). On the contrary, duration of depressive episode longer than 6 months was associated, for both venlafaxine and sertraline, with a worse outcome of depressive symptoms. All results are synthesized in Tables 1 and 2, and more relevant results are shown graphically in Figs. 3 and 4. Relative results at baseline-to-week 8 are reported in the supplementary material Tables 5 and 6. Other moderators did not prove a significant effect on the outcome.

DISCUSSION

One of the most intriguing fields of research in depression is the possibility of finding the best antidepressant on the basis of the patient's characteristics, in order to optimize time of response and to minimize side effects. The attempt to find the most effective and most tolerable antidepressant among the modern drugs has led to controversial and inconclusive findings (Cipriani *et al.* 2009; Gartlehner *et al.* 2011), and in recent years interest had been re-addressed to study of the possible role of the patient's clinical features in predicting response to therapy. In our study we collected papers from 1993 to 2011 and we verified that the year of publication of articles analysed did not impact on our results. One of the most studied factors in recent years is age: in several papers age was proposed to have a role in prediction of clinical outcome in depressed patients (Ezquiaga *et al.* 2004; Grigoriadis and Robinson, 2007; O'Leary *et al.* 2000), while in other studies no influence of age on clinical response was reported (Bagby *et al.* 2002; Gartlehner *et al.* 2011). We took into account a possible relationship between age and response to antidepressant drugs, but we found no significant association in response for sertraline and only a slightly significant

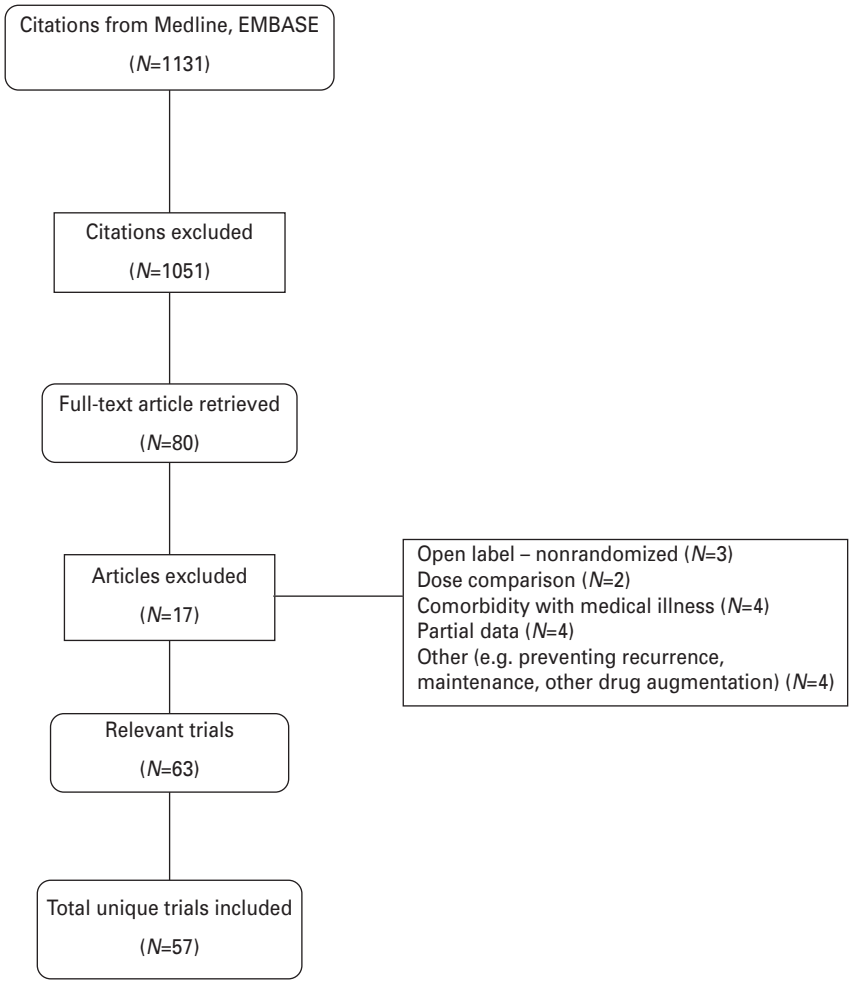

Fig. 2. Study flow chart for venlafaxine.

result for venlafaxine, in our opinion not sufficiently reliable for clinical relevance. Our finding could represent a real absence of a relevant role in a clinical setting for age as a predictor of response, or it could be a limitation of our study due to the lack of variability in the mean age of patients in the papers we analysed. In the literature there are several reports aimed at studying the possible role of gender in the prediction of response (Gartlehner *et al*. 2011; Simmons and Allen, 2011), with the result that gender was *not* found to be an influencing factor in predicting response to both SSRIs and SNRIs (Gorman, 2006; Steiner *et al*. 2005). If gender has never been clearly related to a different response rate in patients treated with SSRIs as a group (Serretti *et al*. 2009), nonetheless, in a recent meta-analysis, a possible better response to paroxetine (Serretti *et al*. 2011) and to sertraline (Morishita and Kinoshita, 2008) was proposed for females. In our meta-analysis we just hint at a possible better trend in females treated with sertraline at week 6. As far as SNRIs are concerned, we observed a significant positive response to venlafaxine at both week 6 and week 8 in females, but we cannot exclude the possibility that this result could be distorted by the larger number of females in the reports we analysed. Nevertheless, this latter finding could be interesting because antidepressants with noradrenergic activity (such as tricyclics) have been traditionally associated with a better response in males. This result could be due to dose-dependent effects of venlafaxine; in fact, it shows noradrenergic effects (which maybe responsible for better response in males) only at doses of 150 mg/d or higher (Shelton *et al*. 2006). In the reports we analysed the mean daily dose of venlafaxine was 160 mg, and it is possible that serotoninergic effects predominate at this dose, related to a better response in females. Our data did not contain sufficient information to test the possible effect at higher doses.

Table 1. Sertraline (SMD for interval: Bsl-6 week)

	Estimate	S.E.	*z*	*p*	*N*
Gender (male)	−7.92	5.27	−1.50	0.133	25
Age	0.01	0.06	0.12	0.906	25
Caucasian	−0.60	1.03	−0.59	0.558	11
Duration of episode (1–6 months)	6.24	6.20	1.01	0.314	9
Duration of episode (6–12 months)	−0.25	0.88	−0.28	0.778	8
Duration of episode (>1 year)	−1.06	0.86	−1.23	0.220	8
Recurrent depression	0.00	0.00	11.09	0.268	29
Year of publication	0.07	0.14	0.50	0.621	25
Main dose	−0.02	0.03	−0.61	0.541	14
Baseline severity (HAM-D score)	−0.09	0.16	−0.55	0.585	25
No patients	1.75	0.76	2.29	0.022	29
Drop outs	−1.78	1.60	−1.11	0.266	18

Legend: SE=standard error; *z*=*z* value; *p*=*p* value; *N*=number of studies analysed.

Table 2. Venlafaxine (SMD for interval: Bsl-6 week)

	Estimate	S.E.	*z*	*p*	*N*
Gender (male)	−1.43	0.53	−2.71	0.007	42
Age	−0.01	0.01	−2.05	0.040	43
Caucasian	2.21	1.44	1.53	0.125	11
Duration of episode (1–6 months)	0.98	0.30	3.25	0.001	17
Duration of episode (6–12 months)	0.69	1.25	0.55	0.581	17
Duration of episode (>1 year)	−1.09	0.31	−3.53	0.0004	16
Recurrent depression	1.58	1.70	0.93	0.352	6
Year of publication	0.00	0.01	−0.21	0.835	44
Main dose	−0.06	0.13	0.10	0.921	43
Baseline severity (HAM-D score)	0.02	0.26	0.09	0.930	43
Baseline severity (MADRS score)	0.00	0.13	0.03	0.973	44
No patients	0.00	0.00	1.35	0.177	44
Drop outs	−1.57	0.73	−2.17	0.030	23

Legend: SE=standard error; *z*=*z* value; *p*=*p* value; *N*=number of studies analysed.

Not only gender may have implications for drug efficacy; ethnicity also could have a role in the different response among different groups of patients, at least on the basis of genetic differences in enzymes involved

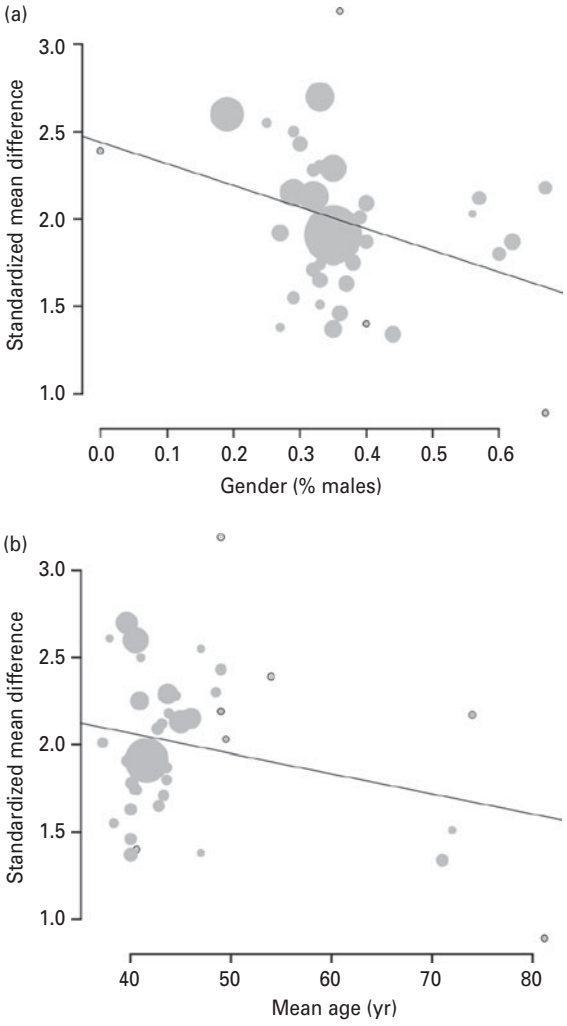

Fig. 3. Significant results of metaregression in venlafaxine: effects on outcome of per cent of males (a), mean age (b). Black circles underline studies of low numerosity.

in drug metabolism (Serretti *et al*. 2009). In some previous reports ethnicity seemed not to be associated with clinical response (Bagby *et al*. 2002; Lesser *et al*. 2011; Spillmann *et al*. 1997), while in others ethnicity does appear to be involved in response to antidepressants (Lesser *et al*. 2007; Varner *et al*. 1998; Weissman *et al*. 2011). In our analysis we observed a positive impact of Caucasian ethnicity as a moderator of response to venlafaxine at week 8, while the response to sertraline showed a positive, but not significant, trend. However, these results should be reconsidered because of the large prevalence of Caucasian subjects over other ethnicities in the reports considered, confirming the necessity of further studies in this area.

In previous work baseline severity of depressive symptoms, evaluated by the Hamilton Depression

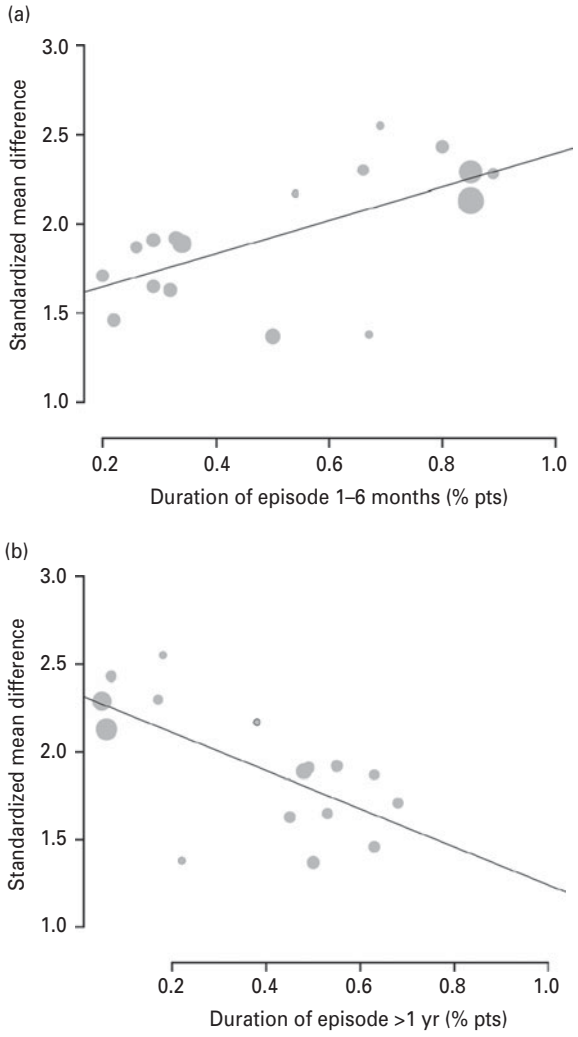

Fig. 4. Significant results of metaregression in venlafaxine: effects on outcome of per cent of patients with duration of episode 1–6 months (a) and of per cent of patients with duration of episode >1 yr (b). Black circles underline studies of low numerosity.

Rating Scale, has been considered as a clinical predictor of antidepressant response (Serretti *et al*. 2007), but no significant findings were found in our analysis. Duration of illness represents another interesting element in the clinical assessment of patients: it is well known that a longer duration of illness is associated with a worse outcome (Serretti *et al*. 2009). In another report, patients identified as non-remitters after an appropriate time of treatment were found to have a longer duration of episode before undertaking antidepressant therapy (Hennings *et al*. 2009). Although the role of a longer depressive episode as a negative predictor is well established, no one had ever estimated a temporal limit of illness associated with a bad outcome. In our review of the literature, a brief depressive episode (1–6 months) is associated with a good remission of depressive symptoms, with a specific response to venlafaxine at both week 6 and week 8. Response to SSRIs showed a possible trend in the same direction. If duration of illness is higher than 6 months the outcome gets worse: there is a negative response to venlafaxine at week 8 of treatment, to sertraline and to paroxetine (Serretti *et al*. 2011) at week 6. Nevertheless, we recognize that in most studies duration of illness was included as standard intervals and not as precise durations, and this could represent a limitation in the interpretation of the original data. However, the existence of a temporal cut-off which could foretell response to these drugs may have relevance in guiding the choice of a more aggressive antidepressant treatment on the basis of this anamnestic data.

Our study has several limitations, some due to the meta-analytic method itself: analysing a series of reports is not the same as analysing the raw data for each patient. For these reasons this paper has to be considered as an observational study, with all the limitations in the interpretation of results that this kind of analysis involves (Thompson and Higgins, 2002). To cope with this limitation we asked the authors of the articles we collected for databases of individual patient data, but the limited amount of original data retrieved was insufficient to perform reliable analyses. This paper, however, can pave the way for further studies focused on specificity of antidepressants on the basis of results obtained analysing a great number of previous reports with metaregression methods. In conclusion, we are conscious that research for the best antidepressant is doomed to failure, but, if our results can be replicated, we believe that clinical features which are easily investigated in every patient could lead to the selection of the most effective specific drug.

Supplementary material

For supplementary material accompanying this paper, visit http://dx.doi.org/10.1017/S1461145713000746.

Acknowledgments

None.

Statement of Interest

S. Gibiino and A. Marsano have no conflict of interest. A. Serretti has been a consultant/speaker for: Abbott, Astra Zeneca, Clinical Data, Boheringer,

Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Pfizer, Sanofi and Servier.

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