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Clinical features and drug induced side effects in early versus late antidepressant responders

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ABSTRACT

Early antidepressant response (2nd week) has been reported as the result of a true antidepressant effect and a predictor of subsequent stable response.

With the purpose to study the clinical profile of early response/remission (2nd week) compared to late response/remission (4th–6th weeks), two independent major depressive disorder (MDD) samples (the Sequenced Treatment Alternatives to Relieve Depression or STAR*D $n = 1922$ and an Italian sample $n = 171$) were investigated. Patients were treated with citalopram in the STAR*D while in a naturalistic setting in the Italian sample. Depressive symptomatology was assessed by the Hamilton Depressive Rating Scale weekly in the Italian sample and biweekly by the Quick Inventory of Depressive Symptomatology Clinician Rated in the STAR*D. Logistic regression was used to investigate possible predictors of early response and the Bonferroni correction was applied.

In the STAR*D, higher levels of baseline core depressive symptoms (Bech subscale) were associated with early response ($p = 0.00017$), as well as lower baseline insomnia ($p = 0.003$) and higher work and social functioning ($p = 0.001$). In the Italian sample none of these variables were associated with the phenotype, but a non significant trend of lower baseline quality of life ($p = 0.078$) was observed in late remitters.

In the STAR*D late responders reported higher levels of antidepressant induced side effects, especially difficulty in sleeping ($p = 5.68e\text{-}13$), with a non significant trend in the same direction in the Italian sample ($p = 0.09$). The identification of late versus early antidepressant responders at the beginning of the treatment may be useful to guide therapeutic choices in clinical settings.

1. Introduction

Major depressive disorder (MDD) is a common disease involving high functional morbidity, increased rate of suicide, high risk of recurrence, and considerable health service utilization (Judd et al., 2000). Currently several classes of antidepressant drugs are available, but only half of patients shows a satisfying response and about the 70% fails to achieve complete remission (Kemp et al., 2008). No clear predictors of treatment response are available, thus guidelines currently recommend a trial of 3–4 weeks before switching (Taylor et al., 2009) and the belief that the efficacy of antidepressant therapy could not be manifest until 4 weeks is still widespread. Nevertheless, consistent findings support that a specific antidepressant effect is already evident at the 2nd week: recent meta-analysis demonstrated that clinical improvement is highest by the end of the 1st week of treatment (Taylor et al., 2006) and drug-placebo differences are most pronounced during the first 2 weeks and diminished in a stepwise fashion thereafter (Posternak and Zimmerman, 2005). Consistently, early improvement (2nd week) can be considered a reliable predictor of later and stable response (Szegedi et al., 2009). A number of previous studies investigated both clinical, cognitive, psychophysiological, neuroimaging, and genetic predictors of MDD treatment outcome (Kemp et al., 2008), but they were mainly focused on the comparison response/remission versus non response/non remission, while predictors of response/remission rapidity were marginally considered (Kim et al., 2010). On the other hand, clinical trials showed that both early and late patterns of response are possible (Uher et al., 2011), thus the identification of predictors of early vs late response may be useful to guide the choice of switching at the 2nd week or continuing therapy up to week 4. The result could be the optimization of trial duration, without subjecting patients to vain, if not harmful, treatments.

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Clinical-demographic predictors of early and late response have been already investigated, but the direct comparison of these clinical profiles of response was only marginally investigated (Kim et al., 2010). The usefulness of studying early response also results from the hypothesis that it may represent a specific phenotype of antidepressant response compared to late response, since drug-placebo differences are more pronounced during the first 2 weeks of treatment (see above). Consistently, early responders (2nd week) to citalopram may show a specific genetic background when compared to late responders in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (Fabbri et al., 2012).

Given the provided picture, the primary aim of the present study was to investigate clinical-demographic predictors of early (2nd week) versus late (4th–6th week) antidepressant response and remission. Early response/remission was defined at week 2 since previous trials suggested that switch to another antidepressant at this time point may be beneficial at least in some groups of patients (Nakajima et al., 2011). The temporal cut-off of late response was set at week 6 since it is the upper duration limit of an antidepressant trial according to the current guidelines and clinical trials demonstrated that symptom improvement is scarce after week 6 (Taylor et al., 2006). Secondly, drug-related adverse events (DRAEs) were compared between early and late responders/remitters. Indeed, early and late response may be determined by differences at pharmacokinetic/pharmacodynamic level. Moreover, drug tolerance is a critical point when deciding if switching or continuing treatment.

2. Materials and methods

2.1. Samples

2.1.1. Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

Detailed descriptions of the study population, phenotypic definitions and clinical outcomes of STAR*D Level 1 are detailed elsewhere (Trivedi et al., 2006). In brief, non psychotic MDD (DSM-IV criteria) patients were enrolled from primary care or psychiatric outpatient clinics and a current 17-item Hamilton Depression Rating score of $\geq$14 by independent raters was obtained. Severity of depression was assessed using the 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C) (Trivedi et al., 2004) at baseline, week 2, 4, 6, 9, and 12. All patients received citalopram in level 1. Anxiolytics, sedative hypnotics, and other medications for concomitant general medical conditions were the only additional medications allowed. Patient-reported DRAEs were entered into the Patient-Rated Inventory of Side Effects (PRISE) at each postbaseline visit (Rush et al., 2004). This instrument was used to categorize any common side effect experienced in 8 organ systems. Within each organ system, specific side effects and the severity (e.g. tolerable, distressing) of the worst side effect were reported. DRAEs were documented also using the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) (Wisniewski et al., 2006) at each postbaseline visit. The FIBSER is composed of three 7-point subscales that measure the frequency, intensity, and burden of side effects, respectively.

Functioning was evaluated according to the work and social adjustment scale (WSAS) (Mundt et al., 2002).

Data were obtained from the National Institute of Mental Health.

2.1.2. Italian sample

Patients aged 18 years or older with diagnosis of non psychotic MDD (DSM-IV criteria) and with a score $\geq$13 on Hamilton Depression Rating Scale (HDRS, 21-item version) were eligible for inclusion. Any other psychiatric disorder as primary diagnosis (bipolar disorder included), comorbidity for substance abuse, cognitive impairment (Mini Mental State Evaluation $<$28), poor ability to participate to evaluations and current pregnancy or feeding were exclusion criteria. Eligible patients were treated with antidepressants according to the current clinical practice in a naturalistic setting (114 [66.66%] SSRIs, 40 [23.39%] SNRIs, 5 [2.92%] TCAs, 5 [2.92%] NaSSAs, 5 [2.92%] SARIs, 2 [1.17%] other antidepressants). Antidepressant dose was adjusted accordingly to clinical response, but always within the therapeutic range. Anxiolytics, sedative hypnotics, and other medications for concomitant general medical conditions were the only additional medications allowed. Patients were evaluated for depressive symptomatology (21-item HDRS) by trained psychiatrists at baseline and weekly until week 8, and a further visit followed at week 17. Drug related adverse events were assessed by the Dosage Record & Treatment Emergent Symptom scale (DOTES) (Guy, 1976) at every visit after baseline. Functioning and quality of life were evaluated by the social adjustment scale (SAS) (Weissman and Bothwell, 1976) and the World Health Organization Quality of Life Instrument (WHOQOL) (WHO, 1998) at baseline.

Patients were outpatients recruited at the Department of Biomedical and NeuroMotor Sciences, Bologna University. Patients were carefully informed about all study procedures before signing written informed consent. Ethical approval was obtained from local research ethic committee.

2.2. Hypothesis under investigation

The primary aim of the present study was to identify clinical-demographic predictors of early (2nd week) versus late (4th–6th week) antidepressant response (reduction of HDRS or QIDS-C score of at least 50%) and remission (HDRS $\leq$ 7 or QIDS-C $\leq$ 5). The choice to compare early response/remission versus late response/remission (and not early response/remission versus early non response/non remission) is due to the hypothesis that early responders, late responders and non responders to antidepressants may represent specific clinical patterns due to distinct biological backgrounds (see Introduction). Thus, the comparison of these 3 response patterns 2 at a time may be more informative. This study was focused on the comparison early response/remission versus late response/remission because we thought it is clinically relevant to give suggestions to decide if switch to another antidepressant at the 2nd week of treatment. In order to provide support to our approach, we compared clinical-demographic characteristics of late responders versus non responders in the largest sample (STAR*D) with the aim to demonstrate they are different phenotypes.

The secondary aim was to evaluate possible differences in antidepressant induced side effects between early and late responders/remitters.

2.3. Choice of variables under analysis

Clinical-demographic variables under analysis were chosen according to previous studies about predictors of antidepressant response (Serretti et al., 2009). Other than more widely investigated clinical-demographic predictors, anxious MDD was included among the variables under study. Anxious MDD is defined as a score $\geq$7 of the HDRS anxiety/somatization factor (anxiety psychic, anxiety somatic, somatic symptoms gastrointestinal, somatic symptoms general, hypochondriasis and insight) and it was reported to affect treatment outcome in the STAR*D (Fava et al., 2008). Given this finding and the observation that MDD is a multidimensional phenomenon made up of a number of discrete clinical features, the hypothesis that specific MDD symptom