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Depression symptom clusters and their predictive value for treatment outcomes: Results from an individual patient data meta-analysis of duloxetine trials

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ABSTRACT

We evaluated individual patient data from phase II to IV clinical trials of duloxetine in major depressive disorder (MDD) (34 studies, 13,887 patients). Our goal was to identify clusters of patients with similar depressive symptom patterns at baseline, as measured by the 17-item Hamilton Depression Rating Scale (HAMD-17), and to investigate their respective predictive value of outcomes as measured by the HAMD-17 total score.

Five clusters were identified at baseline: 1) "Lack of insight"; 2) "Sleep/sexual/somatic"; 3) "Typical MDD"; 4) "Gastrointestinal/weight loss"; and 5) "Mild MDD". However, it should be noted that cluster descriptors are not mutually exclusive. Analyses of the HAMD-17 total score results over time were performed using the 18 randomized placebo and/or actively controlled studies representing 6723 patients. At the end of acute treatment (ranging from 4 to 36 weeks), different levels of effect sizes for active therapy (64.5% duloxetine) vs. placebo were detected by cluster. In 3 out of 5 clusters (representing about 80% of the patients), the effect size was significantly different from 0, in favor of active therapy. The effect size was largest in those clusters with severe somatic symptoms ("Sleep/sexual/somatic" cluster [−0.4170], and "Gastrointestinal/weight loss" cluster [−0.338]). In conclusion, our cluster analysis identified 5 clinically relevant MDD patient clusters with specific mean treatment outcomes. Identification of MDD clusters may help to improve outcomes by adapting MDD treatment to particular clinical profiles.

1. Introduction

Despite the broad range of available therapeutic options, effective treatment of major depressive disorder (MDD) continues to be a challenge for patients and physicians, as first-line antidepressant monotherapy may only achieve remission in ≤37% of patients (Trivedi et al., 2006; Warden et al., 2007). Better treatment outcomes may be reached by identification of patients that are more or less likely to achieve positive treatment outcomes with particular treatments (Gorwood et al., 2013), depending on the clinical presentation of the patient.

Several studies have identified a number of factors associated with specific favorable or unfavorable treatment outcomes in MDD. For instance, some studies suggest that an early response to treatment leads to positive outcomes (e.g. remission), whereas a slow response to treatment often leads to poor outcomes (Henkel et al., 2009; Kuk et al., 2010; Uher et al., 2011, 2012). Clinical factors associated with negative outcomes include psychomotor retardation, executive dysfunction, hopelessness, psychiatric or medical comorbidities (e.g. hypercholesterolemia, cardiac risk factors, high body weight) (Papakostas and Fava, 2008), residual symptoms, chronicity of MDD, high number of previous MDD episodes, high number of hospitalizations (ten Doesschate et al., 2010; Kuk et al., 2010), and long episode duration (>24 months) (Riedel

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et al., 2011). Conversely, suicidality at baseline was associated with a better treatment response (Riedel et al., 2011), although other reports suggest an association does not exist or that suicidality may be associated with a worse treatment response (Malhotra et al., 2004; Serretti et al., 2007). Genetic markers (e.g. serotonin transporter, glutamate receptor genes) and neurophysiological markers (e.g. positron emission tomography changes, quantitative electroencephalography) have also been investigated as predictors of treatment outcomes (Papakostas and Fava, 2008; Uher et al., 2013). Unfortunately, the predictive value of each of these single variables is not robust enough to be of considerable value in the clinical setting. This could be partly due to the clinical heterogeneity of depression (Rush, 2007). Ultimately, heterogeneity of depression may be an important factor in the differential effects of antidepressants.

The goal of our analysis was twofold. Firstly, we wanted to define clinically meaningful homogeneous subgroups (i.e. clusters) of MDD patients from a database of randomized and non-randomized controlled studies of duloxetine in depression. Secondly, the specific treatment outcomes of patients treated with duloxetine or other antidepressants in the identified clusters were to be analyzed in all randomized studies included in the database. To this end, a meta-analytic approach of individual patient data was performed. Clusters of MDD patients were defined based on individual 17-item Hamilton Depression Rating Scale (HAMD-17) scores at baseline, as well as a number of known predictors of outcomes: number of previous episodes, duration of current episode, physical/somatic symptoms, medical comorbidities, and psychomotor retardation. Other identified predictors mentioned above (such as early response or residual symptoms) were not included in the analyses as they were not consistently measured in all studies in the database.

2. Methods

This cluster analysis is based on individual patient data from a database including all patients from 34 clinical trials of duloxetine, used as an antidepressant, performed by Eli Lilly & Co. Studies were included in the meta-analysis if all HAMD-17 items were available at baseline.

To select studies for further analyses, the following additional criteria were used:

- Randomized controlled studies (either with placebo or active comparator).
- Investigating efficacy and safety of duloxetine in patients with MDD.
- Doses of duloxetine $\geq$60 mg/day (standard dose approved for MDD in most countries).

The list of 34 studies included in the analysis defining the clusters at baseline, with their key study-design features, is provided in Online Table 1.

2.1. Parameters analyzed

The following individual patient parameters were extracted from studies in the database: standard demographics (age, gender, ethnicity), location of the patient during the study (United States [US], Europe, Other), pre-existing clinical conditions, number of previous depressive episodes, duration of current depressive episode, and pre-treatment for depression. Severity of depressive symptoms was assessed by the HAMD-17 total score and the Clinical Global Impression of Severity (CGI-S). Co-morbid symptoms of anxiety were assessed by the Hamilton Anxiety Scale (HAMA). The cluster definitions were based on all individual HAMD-17 items.

2.2. Statistical analyses

Clusters were defined by grouping patients based on similar HAMD-17 individual item scores at baseline. In Ward's minimum-variance method (implemented in PROC CLUSTER; SAS 9.2), the distance between 2 clusters is the analysis of variance sum of squares between the 2 clusters added up over all the variables. At each generation of the program, the within-cluster sum of squares is minimized over all partitions obtainable by merging 2 clusters from the previous generation. The sum of squares are easier to interpret when they are divided by the total sum of squares to give proportions of variance (squared semipartial correlations). Based on this method 5 clusters were identified.

Once the 5 clusters were identified, the baseline characteristics of patients in the clusters were analyzed descriptively, including: HAMD total score, HAMD-17 subscales (Maier, retardation, sleep), HAMD items, HAMA total, age, gender, ethnicity, variables related to the history of depression (e.g. time since onset), and other baseline variables such as CGI-S, Sheehan Disability Scale (SDS) total score, SDS items and Visual Analog Scale for pain. Subscores of the HAMD-17 were also evaluated but provided little additional insight and thus are not presented. Some variables were only available for a subset of studies. No statistical tests were done to compare the clusters as one would need to present either overall p-values (which are not appropriate to detect differences between specific cluster pairs), or pairwise comparison p-values (resulting in an excessive number of tests: 10 tests per variable).

In order to compare the efficacy of antidepressants across clusters (based on randomized controlled trials in MDD patients with a duloxetine dose of $\geq$60 mg/day), a meta-analytical approach was used in which, firstly, the results were obtained for each study and an analysis of covariance was calculated, with treatment, cluster, and their interaction as fixed effects and baseline HAMD-17 total score as covariate. In a second step, these results were pooled with weights accounting for the precision of the contributing studies. Effect sizes in each model were calculated for differences, divided by the standard deviation of the residuals provided by the model of this study. Overall estimates and effect sizes were calculated as a weighted mean of the corresponding estimates in all studies, with weights based on within study variance, assuming a fixed study effect. The analyses were done separating duloxetine, active comparator, and placebo (with and without, including the head-to-head studies against venlafaxine [study codes HMCQ and HMBU], as well as pooling the active arms and excluding studies with no placebo arms). The results of these sensitivity analyses did not reveal any additional relevant information and are therefore not reported here. Only the combined active treatment efficacy results are presented, as patient numbers for comparators were quite small. Heterogeneity was assessed via visual inspection of the forest plots.

The data analysis for this paper was generated using SAS® software version 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Cluster definition

Overall, 13,887 patients with MDD from 34 clinical trials with duloxetine (phases II-IV; Online Table 1) were included in the analysis for defining the clusters based on the baseline HAMD-17 individual item scores. Five clusters of patients were identified,