Journal of Affective Disorders 196 (2016) 171–180

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Trajectories of depression symptom improvement and associated predictor analysis: An analysis of duloxetine in double-blind placebo-controlled trials

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ARTICLE INFO

Article history:
Received 19 September 2015
Received in revised form
14 January 2016
Accepted 13 February 2016
Available online 17 February 2016

Keywords:
Duloxetine
Trajectory
Depression
Remission
Predictor
Placebo

ABSTRACT

Background: In the treatment of major depressive disorder (MDD), it is not fully understood how individual symptoms improve over time (trajectory) in remitters. This study compared symptom improvement trajectories, as measured with the 17-item Hamilton Depression Rating Scale (HAM-D17), in remitters and nonremitters.

Methods: This analysis is based on 10 placebo-controlled, randomized, double-blind trials of duloxetine (40–60 mg/day) for treatment of MDD from baseline up to week 8. Remission was defined as a HAM-D17 total score ≤ 7 at week 8 (last observation carried forward). Trajectories of HAM-D17 items were assessed by mixed model repeated measures analysis for treatment and remitter-nonremitter comparisons. Grouping of the trajectories was performed by factor analysis. Predictor analysis using HAM-D17 items was conducted by logistic regression.

Results: There were 1555 patients in the duloxetine group (489 [31.4%] remitters) and 1206 patients in the placebo group (290 [24.0%] remitters; $P < .0001$). For most items, the difference in trajectories between remitters and nonremitters appeared at early time points and increased over time. Treatment response trajectories were very similar for duloxetine and placebo remitters, while duloxetine nonremitters improved more than placebo nonremitters. For duloxetine remitters, we found 3 trajectory groups of HAM-D17 items. The predictor analysis showed that improvement in 6 individual items at week 1 or 2 was significantly associated with remission at week 8.

Limitations: Generalizability of these results may be limited by the relatively short observation period used to define remission.

Conclusions: Early monitoring of some symptoms of depression may prove useful in guiding treatment decisions.

1. Introduction

For recovery from major depressive disorder (MDD), remission is a critical treatment goal. Failure to reach remission leads to higher probability of relapse (Pintor et al., 2003). Reaching remission is, moreover, needed to recover psychosocial functioning comparable to nondepressed people (Miller et al., 1998).

However, remission is not readily achieved. Trivedi et al. (2006), reporting results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, found that only 27.5% of patients treated with a selective serotonin reuptake inhibitor (SSRI) reached remission in 14 weeks when assessed with

Abbreviations: AE, adverse events; AUC, area under the curve; CI, confidence interval; DLX, duloxetine; DSM-IV-TR, Diagnostic and Statistical Manual-IV-Text Revision; HAM-D, Hamilton Depression Rating Scale; HAM-D17, 17-item Hamilton Depression Rating Scale; HAM-D21, 21-item Hamilton Depression Rating Scale; HAM-D24, 24-item Hamilton Depression Rating Scale; LOCF, last observation carried forward; MDD, major depressive disorder; MMRM, mixed model repeated measures; OR, odds ratio; PLA, placebo; QIDS-C16, 16-item Quick Inventory of Depressive Symptomatology, Clinician Rating; QIDS–SR16, 16-item Quick Inventory of Depressive Symptomatology, Self-Report; ROC, Receiver Operating Characteristic; SSRI, selective serotonin reuptake inhibitor; STAR*D, Sequenced Treatment Alternatives to Relieve Depression

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http://dx.doi.org/10.1016/j.jad.2016.02.039

the HAM-D. Therefore, it has been investigated what baseline characteristics of patients with MDD are associated with remission. For example, in the STAR*D study, gender, employment status, education history, baseline function, and quality of life were shown to affect remission rates (Trivedi et al., 2006).

Another question regarding remission is whether or not early symptom improvement is predictive of remission. Lack of early (at 2 weeks) response to fluoxetine has been shown to predict a poor outcome at 8 weeks (Nierenberg et al., 1995, 2000). Furthermore, early improvement in the first 2 weeks as measured by Hamilton Depression Rating Scale (HAM-D) total score or subscale scores may predict later remission (Henkel et al., 2009; Katz et al., 2009; Szegedi et al., 2009). However, it is not clear whether some HAM-D items are better predictors than others.

Depressive disorders show many different types of symptoms. Accordingly, it is interesting to compare the degree of symptom improvement over time (trajectory) in patients who eventually reach remission (remitters) with those who do not (nonremitters). For example, responses on some items could improve faster or better than others in remitters, but not in nonremitters. Trajectories of individual symptoms in remitters and nonremitters were examined by secondary analysis of the STAR*D trial data (Sakurai et al., 2013). In that study, patients were treated with citalopram, and symptoms were evaluated using the16-item Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR16) and the 16-item Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C16) versions. Analysis of trajectories of symptoms revealed substantial separation between remitters and nonremitters for almost all symptoms. However, the differences between trajectories of remitters and nonremitters when assessed with the HAM-D, a more broadly used depression scale for clinical trials, are not known. Moreover, trajectories may depend on the antidepressant used, as each of them has its own pharmacological profile.

Duloxetine (DLX) is a potent inhibitor of serotonin (5-hydroxytryptamine) and norepinephrine reuptake and is relatively balanced in its binding affinity for serotonin and norepinephrine transporter sites (Bymaster et al., 2003; Wong and Bymaster, 2002). Acute administration of DLX increases extracellular monoamine levels (Karpa et al., 2002), thereby enhancing monoaminergic tone. DLX has demonstrated efficacy in the acute treatment of MDD in multiple randomized, double-blind, placebo (PLA)-controlled trials (Detke et al., 2002; Goldstein et al., 2002; Nemeroff et al., 2002). Moreover, a recent comparison of DLX and SSRIs suggested DLX has good efficacy for the core symptoms of MDD (Harada et al., 2015). However, despite the large amount of data supporting the efficacy of DLX as an antidepressant, it is not yet known precisely how DLX-treated patients experience improvement of symptoms. In addition, given the fact that a substantial number of patients experience remission even with PLA, it is still unknown whether there are any differences in the trajectories of improvement of individual symptoms between remitters treated with PLA and those treated with antidepressants.

In this analysis of PLA-controlled trials of DLX, we examined the trajectories of depression symptoms (items on the 17-item Hamilton Scale of Depression [HAM-D17]) in remitters, compared with nonremitters, treated with DLX. Furthermore, we examined these trajectories in PLA-treated patients, remitters versus nonremitters. A factor analysis (principal component analysis) was performed to determine if there are patterns of symptom improvement in DLX and remitters. Finally, a predictor analysis was utilized to assess if early improvement on any HAM-D17 items predict remission at endpoint.

2. Methods

2.1. Data sources

The data used in the present *post-hoc* analysis (Supplementary Table 1) were extracted from the integrated database of DLX clinical trials, which includes all clinical trials for MDD with DLX conducted by Eli Lilly and Co. The number of clinical trials included in the database is 39. This database allowed us to conduct a patient-level analysis. From the database, we included all of the trials which met the following inclusion criteria: acute (at least 6 weeks in duration), PLA-controlled, randomized, double-blind trials of DLX for the treatment of MDD; at least 1 DLX arm of ≥ 40 mg/day and ≤ 60 mg/day; and use of the 17-, 21-, or 24-item version of the Hamilton Depression Rating Scale (HAM-D17, HAM-D21, and HAM-D24, respectively). We excluded relapse-prevention and nonresponder trials.

As a result of screening, 10 trials met all criteria; they were used in the present *post-hoc* analysis (Supplementary Table 1). For the DLX group, only patients treated with ≥ 40 and ≤ 60 mg/day DLX were included in this analysis since this dose range has been confirmed as effective in the treatment of MDD and is commonly used globally (Ball et al., 2013; Cowen et al., 2005). Only data from the acute treatment phases of the studies throughout week 8 (up to day 70) were included in the analyses. No maintenance treatment phases were included in the analyses.

For the individual trials included in this analysis, patients were required to meet several inclusion criteria, including meeting the criteria for MDD, as defined by the Diagnostic and Statistical Manual-IV-Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000), and were required to sign an informed consent document. Exclusion criteria typically included having any current Axis I disorder other than MDD, having a current or previous diagnosis of bipolar disorder or any psychotic disorder, having any organic mental disorder, dementia, or mental retardation, being at serious suicidal risk (in the judgment of the investigator), and having a recent history of substance abuse or dependence. Study protocols permitted minimum anxiolytic use by the patients.

The protocols for the individual studies were reviewed and approved by the applicable organizational ethical review boards. The studies were conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice, and applicable laws and regulations.

The clinical trials included in this analysis were registered at ClinicalTrials.gov. Study Identifiers are as follows: NCT00036335; NCT00073411; NCT00406848 and NCT00536471. Studies HMAQa, HMAQb, HMATa, HMATb, HMBHa and HMBHb predate the registration requirement.

2.2. Time frame of analysis

The time frame of data collection was restricted to the acute phase of the clinical trial, beginning with the baseline visit and ending with the endpoint visit of the acute phase or 70 days after baseline, whichever occurred first. The time frame start definition excluded any “lead-in phase,” and the definition of time frame end excluded the data in any open-label trial extension. Analysed data included baseline (week 0), week 1 (day 7, range 1–10 days postbaseline), week 2 (day 14, range 11–21 days postbaseline), week 4 (day 28, range 22–35 days postbaseline), and week 8 (day 56, range 43–70 days postbaseline). If there were more than 2 data points within the allowance range of a specific time point for a patient, the data nearest the date of the specific time point was used. If there were more than 2 data points at the nearest date of the specific time point for a patient, the average of these data points was used for the specific time point for that patient.