



Individual residual symptoms and functional impairment in patients with depression



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ABSTRACT

The aim of treatment of depression is remission of symptoms and functioning. Although there is a relationship between remission of symptoms and remission of functioning, it is not known how individual residual symptoms are related to functioning. Here we report a post-hoc analysis of two studies which treated depressed patients with duloxetine in an open fashion for 10–12 weeks. We evaluated the association of individual residual symptoms and functional impairment in patients who remitted or partially remitted after acute treatment. Logistic regression was used to investigate residual symptoms associated with functional impairment at endpoint. Our results suggest that in partial remitters, the only residual symptom associated with a reduction in the risk of having impaired function was the resolution of painful physical symptoms (PPS). In patients who remitted, the presence of residual core mood symptoms (CMS), particularly in patients without any anxiety, predicted impaired functioning. The resolution of PPS in the presence of residual CMS was associated with less risk of impaired functioning. Our results contribute to understand better the role of specific residual symptoms on functional impairment. To achieve normal functioning, intervention on specific residual symptoms is recommended.

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1. Introduction

Currently symptomatic remission is the primary goal of treatment of depressive episodes. In addition, the remission (and, longer term recovery) of functioning to pre-morbid levels is increasingly identified as a significant objective (Papakostas, 2009). Functional recovery has been associated with a better long-term prognosis of depression (Solomon et al., 2004, 2008). In addition, functional recovery is also a clinical goal expressed by the patient with depression (Zimmerman et al., 2006). Nevertheless, the presence of residual symptoms is one of the factors hindering patients' functional recovery (Papakostas, 2009).

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A considerable number of patients respond to treatment despite not reaching a state of remission, and their main residual symptoms are insomnia, decreased concentration, and sadness among others (Kennedy et al., 2007; McClintock et al., 2011). Residual symptoms have been studied even in patients who achieve remission, where different results regarding the risk of relapse have been reported (Nierenberg et al., 2009; Iovieno et al., 2011). The presence of these residual symptoms has been found to be associated with significant changes in several areas of patient's functionality (Miller et al., 1998; Simon et al., 2000; Trivedi et al., 2009). Miller et al. (1998) found that only patients who achieved remission had levels of psychosocial functioning that approached to, or matched, a control sample without depression. The overall functionality, work and social functionality and other relevant areas were significantly altered in patients who responded but did not remit (Miller et al., 1998). In a more recent study, patients who achieved complete symptomatic remission had greater functional improvements than those who responded but did not achieve

remission (Trivedi et al., 2009). But even in patients who are in remission significant differences in functioning were found, depending on the degree of remission (Zimmerman et al., 2005, 2012; Romera et al., 2011). Several studies have shown higher levels of functionality in patients with lower scores on the Hamilton Rating Scale for Depression (HAM-D-17) in comparison with patients with higher scores (Zimmerman et al., 2005, 2012; Romera et al., 2011).

Although it is known that the presence of residual symptoms is associated with an alteration of the overall, social and occupational functioning (Miller et al., 1998; Simon et al., 2000; Trivedi et al., 2009; Romera et al., 2010, 2011), the contribution of the different residual symptoms (core depressive, anxious, insomnia, etc.) on functional impairment has not been well studied. The few studies that have evaluated the impact of residual symptoms on the patient's functionality (Miller et al., 1998; Zimmerman et al., 2007) have not looked at the specific role of each individual residual symptom.

The purpose of this exploratory analysis was to evaluate the association between several residual symptoms (core depression, anxiety, sleep, and painful physical symptoms) and functional impairment in patients with major depressive disorder (MDD) who responded to acute duloxetine treatment but did not reach remission. A further analysis was also conducted in patients who achieved remission.

2. Methods

This analysis includes patient level data from the initial open-label acute-therapy phase of two duloxetine studies in MDD, F1J-MC-HMBC (Perahia et al., 2006) and F1J-MC-HMDI (Perahia et al., 2009). Both studies contained open-label duloxetine treatment at a dose of 60 mg daily relapse prevention study (HMBC) or 60–120 mg daily recurrence prevention study (HMDI) with a similar design and both studies used the same instrument measuring functioning. All patients responding to treatment at the end of the open-label treatment period were included ($n=636$). Response was defined as having 50% or greater reduction in the HAM-D-17 total score between baseline and the end of the open-label phase (HMBC, Week 12; HMDI between Week 4 and Week 10 depending on how early patients responded).

2.1. Patients

Patients enrolled in the two studies met the DSM-IV (American Psychiatric Association, 2000) criteria for MDD without psychotic features assessed by the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). Baseline severity was assessed using the 17-item Hamilton Rating Scale for Depression (HAM-D-17; Hamilton, 1960) and the Clinical Global Impression-Severity (CGI-S) scale (Guy, 1976). At both the screening and second study visits, all study participants were required to meet the entry criteria of HAM-D-17 total score ≥ 18 and CGI-S score ≥ 4 , indicating at least moderate depression. In addition, participants must have had at least one (HMBC) or two (HMDI) other major depressive episodes before the current episode.

Reasons for exclusion from the study included having a current and primary Axis I disorder other than MDD; any anxiety disorder as a primary diagnosis within 1 year of entry to the study; a previous diagnosis of bipolar diagnosis, schizophrenia or other psychotic disorder, and treatment-resistant depression; serious suicidal risk; and serious medical illness.

Two patient populations were used for the analyses, one included only partial remitters ($n=200$), defined as patients who had responded with $\geq 50\%$ reduction on the HAM-D-17 total score between baseline and the end of the open-label phase (HMBC: Week 12; HMDI: between Week 4 and Week 10) but still had an endpoint HAM-D-17 total score > 7 . The other population included only remitters, defined as patients who had responded with an endpoint HAM-D-17 total score ≤ 7 , ($n=436$).

To aid with the interpretation of the results, patients with no symptoms (that is, with a score of zero) at baseline for any of core mood, insomnia, anxiety, or somatic symptoms were excluded from the analysis.

2.2. Measurements

Residual symptoms were defined according to Dombrovski et al. (2008) for each of the subscales of the HAM-D-17 as having a score of ≥ 1 at baseline and endpoint, the subscales being: core mood symptoms (CMS), including items 1

(depressed mood), 2 (guilt), 3 (suicide) and 7 (work/activities); persistent insomnia including items 4 (early), 5 (middle), and 6 (late insomnia); persistent anxiety including items 9 (agitation), 10 (psychic anxiety), 11 (somatic anxiety), and 15 (hypochondriasis); somatic symptoms including item 13.

Painful physical symptoms (PPS) were assessed by the Visual Analog Scale (VAS). Residual PPS was defined as having a VAS score for overall pain of > 30 mm at both baseline and endpoint. Emergent PPS was defined as having a VAS score for overall pain of ≤ 30 mm at baseline and > 30 mm at endpoint. No PPS was defined as having a VAS score for overall pain of ≤ 30 mm at both baseline and endpoint, and resolved PPS was defined as having a VAS score for overall pain of > 30 mm at baseline and ≤ 30 mm at endpoint. A cut-off point of 30 on the VAS includes patients with at least moderate pain (Collins et al., 1997).

Functioning was assessed by the Sheehan Disability Scale (SDS) which is an unweighted composite of three self-rated items regarding family, work, and social impairment. The total score is the sum of the three domain scores ranging from 0 (unimpaired) to 30 (highly impaired) (Leon et al., 1997). A SDS total score > 6 is indicative of functional impairment (Sheehan and Sheehan, 2008).

2.3. Statistical analysis

Logistic regression was used to investigate factors, specifically residual symptoms, associated with having functional impairment (SDS total score of > 6) at endpoint. Independent variables are as follows: study, age, gender, baseline total SDS score, baseline total HAM-D-17 score, presence of comorbidity (somatic, psychiatric, both, neither), number of previous episodes of depression, duration of the current episode of depression ($<$ or ≥ 24 weeks), presence of residual core mood symptoms, presence of residual insomnia, presence of residual anxiety symptoms, presence of residual somatic symptoms, PPS (none, emergent, residual or resolved with residual PPS as the reference), and study week (based on visit number) at which the patient completed the acute phase of the study (always Week 12 for HMBC patients, but varies for those from HMDI).

The initial model included all variables which were removed one by one starting with the variable with the greatest p -value. To check that each of these variables did not contribute significantly to the model, the likelihood ratio test ($-2\log L$, intercept and covariates) with and without the variable was tested for significance (at the 5% level), and if it proved to be significant, the variable was re-introduced into the model. This process was repeated until only variables with p -values of less than 0.2 remained in the model.

To this model was added all two-way interactions between the variables measured at endpoint and still in the model, that is, all measures of residual symptoms, giving a maximum of 10 interaction terms. The likelihood ratio test with and without all these interactions was compared to see whether the interaction terms add significantly to the model. If they do (at the 5% level of significance), the interaction terms were removed one by one as described above until only those with $p < 0.1$ remain. This was done in both the partial remitters and the remitters patient populations. Given the exploratory nature of this analysis, no corrections were made for multiple comparisons. Statistical analysis was done using SAS version 9.2.

3. Results

3.1. Clinical and demographic characteristics

A total of 200 patients who reached partial remission and 436 patients who attained remission were analyzed in this post-hoc analyses from studies HMBC and HMDI. Baseline clinical and demographic characteristics of partial remitters (patients who responded but did not reach remission) and remitters are summarized in Table 1. Data were indicative of a population with moderate to severe, recurrent depression.

At the end of the acute phase, partial remitters had a mean (S.D.) HAM-D-17 total score of 8.6 (0.84) and a mean (S.D.) SDS total score of 11.4 (6.99), and the remitters population had a mean (S.D.) HAM-D-17 total score of 4.6 (1.87) and a mean (S.D.) SDS total score of 7.6 (6.57). At the end of acute phase, 31.5% of partial remitters and 53.2% of remitters achieved normal levels of functioning (SDS ≤ 6).

3.2. Prevalence of residual symptoms

In partial remitters, population residual symptoms were a common feature. More frequent symptoms were residual core mood symptoms ($n=192$; 96.0%) and residual anxiety symptoms ($n=188$;

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