IMPACT OF AXIS I COMORBIDITY INTERACTION ON DULOXETINE OUTCOME IN MAJOR DEPRESSION

Alberto Chiesa, Elena Di Nasso, Claudio Mencacci, Diana De Ronchi, Alessandro Serretti

Abstract

Objective: In the last decades a substantial advance in the understanding of the influence of different variables on response to antidepressants has been achieved. However, little effort has been paid so far to investigating how such factors interact with each other to predict clinical improvement. Accordingly, the present study aimed to explore whether and how concurrent or lifetime psychiatric comorbidities could influence clinical outcome in a sample of patients with major depressive disorder (MDD) treated with duloxetine.

Method: One-hundred-one outpatients suffering from MDD were treated with duloxetine. They were assessed at baseline and at weeks 2, 4 and 8 by means of the 21 item Hamilton rating scale for depression (HAMD). Concurrent and lifetime comorbidities with other axis I psychiatric disorders were recorded by MINI-international Neuropsychiatric interview (M.I.N.I.) and the impact of the interactions of such comorbidities on clinical outcome was assessed.

Results: We observed a significant effect of the interactions between current obsessive compulsive disorder (OCD) and lifetime generalized anxiety disorder (GAD), as well as between lifetime panic disorder (PD) and lifetime GAD, current premenstrual dysphoric disorder (PDD) and current or lifetime PD, and current PDD and lifetime GAD on improvements of HAM-D during the study period.

Conclusions: Our results provide preliminary evidence to suggest that 5 different clinical variables including current OCD X lifetime PD or GAD, as well as current PDD X lifetime PD or GAD could interact with each other to predict clinical improvement in MDD patients treated with duloxetine. However, on account of several limitations, including the focus on a limited number of predictors and the relatively small sample size of our study, further research is needed to draw more definitive conclusions.

Key Words: duloxetine, major depression, anxiety, response, predictors

Declaration of interest: none

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Background

The importance of the search for predictors of response to antidepressants (ADs) in major depressive disorder (MDD) has long been recognized (e.g. (Downing and Rickels 1972, 1973, Ranelli and Miller 1981). MDD is indeed one of the most common mental disorder with a lifetime incidence as high as 12% in men and 20% in women in the U.S.A. (Kessler et al. 2003) and as high as 7.2% in men and 14.9% in women in Italy (e.g. (De Girolamo et al. 2006). In addition, approximately 30-40% of patients do not respond to current AD treatments (Cipriani et al. 2009, Rush et al. 2006). As a consequence there is a strong clinical need to predict which subject could benefit most from AD treatments in order to target specific strategies at early stages of treatment and enhance treatment outcome.

Unfortunately, however, there have been inconsistent results in clarifying which comorbidities modify AD response (Bagby et al. 2008). The large maiority of studies focusing on demographic characteristics, such as gender (Grigoriadis and Robinson 2007), age (Bagby et al. 2002, Grigoriadis and Robinson 2007, Mandelli, et al. 2007), ethnicity (Bagby et al. 2002), marital status (Bagby et al. 2002, Meyers et al. 2002) and educational level (Hirschfeld et al. 1998, Spillmann et al. 1997) have provided inconsistent results so far. Also, despite the fact that a large number of clinical variables, such as substance and alcohol abuse or dependence (Bagby et al. 2002, Kemp et al. 2008), personality disorders (Newton-Howes et al. 2006), higher severity of illness (Bagby et al. 2002, Souery et al. 2007), early onset (Bagby et al. 2002) and menopause (Pae et al. 2009) have been

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associated with non response to ADs, contrasting results have been reported as well and the predictive power of each single predictor separately analyzed is usually modest (Bagby et al. 2002, Kemp et al. 2008, Serretti et al. 2009). Additionally, discrepant results have also been reported with respect to the influence of other axis I psychiatric disorders comorbidity, particularly anxiety disorders, which frequently occur in comorbidity with MDD (Zimmerman et al. 2002). In particular, while early findings, mainly based on tricyclic antidepressants (TCAs), suggested a detrimental effect related to the comorbidity with anxiety disorders (Bagby et al. 2002), more recent studies have shown that for drugs with a main serotonergic action, such as selective serotonin reuptake inhibitors (SSRIs) or with a dual serotonergic/noradrenergic action, such as venlafaxine and duloxetine (Fava et al. 2007, Krishnan 2003), the comorbidity with anxiety disorders could be a positive rather than a negative prognostic factor. Also, a recent study focusing on the improvement of social adaptation in patients with MDD treated with serotonin and norepinephrine reuptake inhibitors found that patients treated with the noradrenergic AD reboxetine showed higher improvement in social adaptation in comparison with patients treated with the serotonergic AD fluoxetine (Briley and Moret 2010). As a consequence, the authors speculated that serotonin and norepinephrine reuptake inhibitors, such as venlafaxine, duloxetine and milnacipran, could be particularly helpful in improving social functioning.

Recently, increasing attention has been given to the predictors of response to duloxetine, a potent dual reuptake inhibitor of both serotonin and noradrenaline which lacks significant affinity for histamine H1, α-adrenergic, dopamine D2, serotonin and opioid receptors and has about the same affinity for binding compared to the serotonin and noradrenaline reuptake inhibitors (Gupta et al. 2007). In an early study, several factors including total HAM-D score at baseline, anxiety related comorbid conditions, pain and elevated anxiety/somatization scores, probably related to a more severe and persistent levels of depression, predicted a poorer outcome to duloxetine treatment (Howland et al. 2008). However, in an independent study, MD patients with elevated anxiety/somatization symptoms treated with duloxetine achieved a faster onset of response as compared with non anxious MD patients, although no significant difference in response rates was observed at endpoint (Fava et al. 2007).

Additionally, further studies focusing on long term outcomes, reported that early improvement in total depressive symptoms, as well as in specific items including psychological anxiety, motor retardation and suicidality, positively predicted sustained remission to duloxetine (Katz et al. 2009) and that higher persisting levels of pain severity and depressive symptoms after an acute 12-weeks treatment with duloxetine were consistent predictors of future relapses (Fava et al. 2009).

Overall, such findings show how current evidence about this topic is limited so far. Most common explanations for the discrepancies observed across the studies include systematic differences in study design and duration, as well as different definitions of response and different types and doses of ADs under investigation (Bagby et al. 2002, Kemp et al. 2008, Serretti et al. 2009). Alternatively, it is possible that single predictors could interact with each other. Indeed, the hypothesis that the interaction of more variables could be a more reliable predictor of response as compared with the influence of single predictors has recently gained increasing attention and provided preliminary positive results both in clinical and genetic research [e.g. (Serretti and Smeraldi 2004, Serretti et al. 2007)].

Accordingly, building on our previous observations suggesting a different response to duloxetine in patients suffering from MDD with or without current or lifetime axis I comorbidities, particularly anxiety disorders (Di Nasso et al. 2010), the present study was aimed at exploring whether and how the interactions of such factors could influence clinical improvements on depressive, anxiety and retardation scores in the same sample of patients treated with duloxetine.

Methods

Sample description

One hundred ninety-seven outpatients were consecutively recruited at the Neuroscience department, depression unit, belonging to Fatebenefratelli Hospital, Milan, Italy, and screened by two expert psychiatrists. Inclusion criteria were: a) a diagnosis of major depressive episode, both single and recurrent, according to the DSM criteria as assessed by MINI-international Neuropsychiatric interview (M.I.N.I.) (Sheehan et al. 1998), b) a baseline score ≥ 17 as assessed by the Hamilton rating scale for depression (HAM-D) (M. Hamilton 1960), c) age 18 and ≤ 65 and d) whether patients were using other ADs at study entry, the willingness to switch to duloxetine because of lack of efficacy and/or tolerability problems. Exclusion criteria were: a) a comorbidity with a personality disorder, as assessed with the Structured Clinical Interview for Axis II personality disorders (First et al. 1990), b) a comorbidity with alcohol and/or substance abuse/dependence, c) a diagnosis of bipolar disorder, d) current or lifetime psychotic symptoms, e) severe unstable medical and neurological comorbidities, f) prior treatment with duloxetine and g) the unwillingness or the impossibility according to the clinician's opinion to stop concomitant psychotropic medications including ADs, mood stabilizers, antipsychotics and anxiolytics. Following the application of inclusion and exclusion criteria, 101 patients could be included in the present study.

Past and present comorbidities with further axis 1 disorders, as well as premenstrual dysphoric disorder (PDD) were assessed by the M.I.N.I. As only a few patients had suffered from lifetime psychiatric disorders other than panic disorder (PD) or generalized anxiety disorders (GAD), such patients were labelled as suffering from "miscellaneous lifetime conditions". Further clinical and socio-demographical features including gender, age, educational level, occupational status, marital status, familial history of psychiatric disorders, medical illnesses, life events before current depressive episode, onset, duration of illness and, for female patients, menopausal status were also recorded.

Table 1. *Baseline characteristics of the sample*

Sample size	101
Sex	
-Men	14
-Women	87
Age (mean±sd)	46.67±12.35
Current comorbidities	
-PD	24
-OCD	19
-none	0
Lifetime comorbidities	
-PD	49
-GAD	35
-Miscellaneous axis I disorders	20
PDD (premen. females only)	
-Yes	24
-No	41
Anxious depression (mean±sd)	8.27±4.31
Retardation (mean±sd)	1.18±0.68
Baseline HAM-D severity (mean±sd)	22.34±4.92

PD=panic disorder; OCD=obsessive compulsive disorder; GAD=generalized anxiety disorder; PDD=premenstrual dysphoric disorder; premen=premenopausal; HAM-D=Hamilton Rating Scale for Depression; sd=standard deviation

Relevant baseline characteristic of included patients are shown in **table 1**.

Patients were initially treated with 30 mg duloxetine for 1 week. During the same time frame, anxiolytics and antidepressants other than duloxetine were gradually tapered so as to reduce the risk of discontinuation-associated neuropsychiatric symptoms. Type and dosages of antidepressants and anxiolytics at study entry was not recorded. None of the screened patients was assuming mood stabilizers or antipsychotics at baseline. Following this period, doses of duloxetine could be flexibly increased up to 120 mg, with increases not higher than 30 mg for week, according to clinician's opinion. Concomitant psychotropic treatments other than duloxetine were not allowed during the study. Patients were then followed for 8 weeks in order to assess clinical improvement after switch to or initiation of duloxetine. Only two patients dropped out during the study period. The study protocol was approved by the local ethical committee. All participants signed informed consent before entering into the study.

Efficacy assessment

Efficacy measures were assessed at baseline and at weeks 2, 4 and 8. Depression severity was assessed by means of the 21 items HAM-D. As operationally defined in previous studies, e.g., Tollefson et al. 1994, clinically significant concurrent anxiety was defined as a score ≥ 7 on the six item HAM-D anxiety-somatization factor which includes HAM-D items numbered 10-13, 15 and 17. Single values from item 8 (retardation) were also recorded. Response was defined as a reduction ≥50% on HAM-D scores from baseline. Remission was defined as a HAM-D score ≤ 7. There was good reliability among the interviewers (k>0.8).

Outcome measures

Our primary outcome measure was the effect of the interactions among all current and lifetime comorbidities under investigation on clinical improvement as measured by the percentage reduction of HAM-D total scores during the study period. Our secondary outcome measures included the effects of such interactions on anxiety levels (extrapolated by items 10-13, 15 and 17 of the HAM-D), on retardation scores and on response and remission rates at 8 weeks.

Statistical analysis

All data collected during the study were analysed using Statistica software (StatSoft 1995). In **table 2**, HAM-D, anxiety/somatization and retardation scores at different time points, as well as clinical response and remission rates at 8 weeks displayed according to clinical predictors are shown. When the interaction of two predictors produced groups of 5 or less subjects, such subjects were systematically excluded from the analysis so as to reduce the likelihood of false positive findings. Predictors of clinical improvement on total HAM-D scores, as well as on anxiety/somatization and retardation scores were analysed by the repeated measures ANOVA. Improvements on all such variants were calculated according to the following formula (consider as an example HAM-D scores): $((\text{HAM-D}_{\text{time}_X} - \text{HAM-D}_{\text{baseline}})/ \text{HAM-D}_{\text{baseline}})*100$. Influence of predictors on response and remission rates at 2 months were analysed by χ^2 statistics. All the analysis were performed on the whole sample. The only exception was characterized by the analysis of the interaction between PDD and other comorbidities which focused on the subsample of premenopausal women. Statistical significance was conservatively set at 0.003, approximately corresponding to the Bonferroni's correction for multiple testing (15 predictors), two tailed. With these parameter we had a sufficient power (0.80) to detect a medium-large effect size of 0.34 corresponding, for instance to a difference at week 8 of 3.2 points in HAM-D scores between patients with comorbid PD and obsessive compulsive disorder (OCD) and patients without any of such comorbidities.

Results

Demographic and clinical characteristics

Relevant clinical characteristics of the subjects included into the analyses are listed in table 1. Overall, HAMD scores, anxiety/somatization scores and retardation scores significantly decreased from baseline to endpoint ($F=348.8$, d.f.=3,297, $p<0.000001$; $F=16,52$, d.f.=3,291, $p<0.000001$; $F=100,57$,

d.f.=2,200, p<0.000001 respectively). Eight-one subjects achieved response and 26 subjects achieved remission at 8 weeks.

Influence of the interaction of comorbid axis I disorders on clinical improvement

We observed a significant effect of the interaction between current OCD and lifetime GAD on total HAM-D scores (**figure 1** and **table 2)**. In particular, patients with current OCD, but without lifetime GAD (n=19) showed a reduced improvement during the first 2 weeks of treatments followed by slightly higher improvements at 8 weeks, as compared with patients with lifetime GAD and no current OCD (n=35) and patients without both lifetime GAD and current OCD (n=47). Patients with lifetime GAD and no current OCD showed higher levels of improvement during the first two weeks of treatment followed by smaller improvements in the following weeks, whereas patients without neither lifetime GAD nor current OCD showed higher improvements as compared with other two groups at 4 weeks (F=4.19, d.f.=4,194, p=0.002). Also, a concurrent lifetime comorbidity with PD and GAD (n=7) predicted higher levels of improvements at 8 weeks, as compared with other combinations of such comorbidities, whereas subjects with neither lifetime GAD nor lifetime PD (n=24) showed the smallest improvements at endpoint (F=3.54, d.f.=4,192, p=0.002, see figure 1).

Pertaining to the influence of the interactions with PDD, women without PDD (n=20) showed more improvement at 4 weeks, but less at 8 weeks as compared with subjects with current PDD with (n=20) or without (n=21) current PD (F=4.16, d.f.=4,116, p=0.003). Also, women with no current PDD and without a history of PD (n=10) showed the lowest improvements at 8 weeks as compared with other possible combinations whereas subjects with both current PDD and lifetime PD (n=33) showed lower improvements during the first weeks of treatment, although they do not significantly differ from other groups at endpoint (F=4.46, d.f.=6,122, p=0.0004). Finally, although patients with current PDD and lifetime GAD (n=7) showed lower improvements in the first weeks of treatment, they reached similar outcomes at endpoint (F=10.06, d.f.= 4, 114, p=0.000001). No other interaction was significant (all p-values>0.0033).

Influence of the interaction of comorbid axis I disorders on anxiety/somatization scores

Patients with current PD, but not lifetime GAD (n=24) showed higher improvements at 8 weeks, as compared with patients without current PD with (n=35) or without (n=42) GAD (F=6.64, d.f.=4,1881, p=0.00005). Also, patients with current OCD and lifetime PD (n=18) showed lower improvements over time, that were particularly evident at week 4, in comparison with other possible interactions of conditions, whereas patients without neither current OCD nor lifetime PD (n=51) showed higher improvements at 4 and 8 weeks (F=7.13, d.f.=4,186, p=0.00002). In addition, patients with current OCD, but not lifetime GAD (n=19) showed higher improvements at 2 weeks followed by lower improvements at following time points, whereas patients without current OCD (n=82) showed higher improvements at 4 weeks. However, only subjects without lifetime GAD (n=47) showed marked improvements at 8 weeks (F=7.04, d.f.=4,188, p=0.00002). Finally, subjects with concurrent lifetime PD and GAD (n=42) were more likely to improve over time as compared with other possible interactions (F=5.62, d.f.=6,186, p=0.00002).

Influence of clinical and demographic characteristics on retardation scores

Both subjects with current PD or OCD, but not lifetime GAD (n=24 and n=19 respectively) showed higher improvements on retardation scores as compared with subjects without current PD or OCD with (n=35 or both conditions) or without (n=42 and n=47 respectively) a comorbidity with lifetime GAD. However, subjects without neither current PD or OCD nor lifetime GAD (n=42 and n=47) showed smaller improvements at week 2 than subjects without current PD or OCD, but with lifetime GAD (n=35 for both conditions, F=6.64, d.f.=2,82, p=0.002 and F=7.24, d.f.=2,82, p=0.001 respectively). No other interaction was significant.

Influence of clinical and demographic characteristics on response and remission rates

There was a significant interaction between current and lifetime PD on response rates, such that subjects with both current PD and lifetime PD (n=22) had the highest rates of response whereas subjects with neither PD nor lifetime PD (n=50) showed the lowest rates of response (χ^2=11,99, d.f.=2, p=0.002). Similarly, women with both PDD and lifetime PD (n=33) had the highest likelihood of response whereas those with neither PDD nor lifetime PD (n=10) had the lowest likelihood of response and further combinations had an intermediate likelihood of response (χ^2=20.46, d.f.=3, p=0.0001). On the other hand, none of the clinical variables under investigation significantly predicted remission at 8 weeks.

Discussion

The main finding of our study was that 5 different clinical variables including current OCD X lifetime PD or GAD, as well as current PDD X current PD, lifetime PD or GAD could interact with each other to predict clinical improvement in a sample of MDD patients treated with duloxetine at different dosages.

Such observations raise at least two important issues. First of all, since anxiety disorders and symptoms frequently occur in comorbidity with MDD (e.g. (Zimmerman et al. 2002) and are generally considered

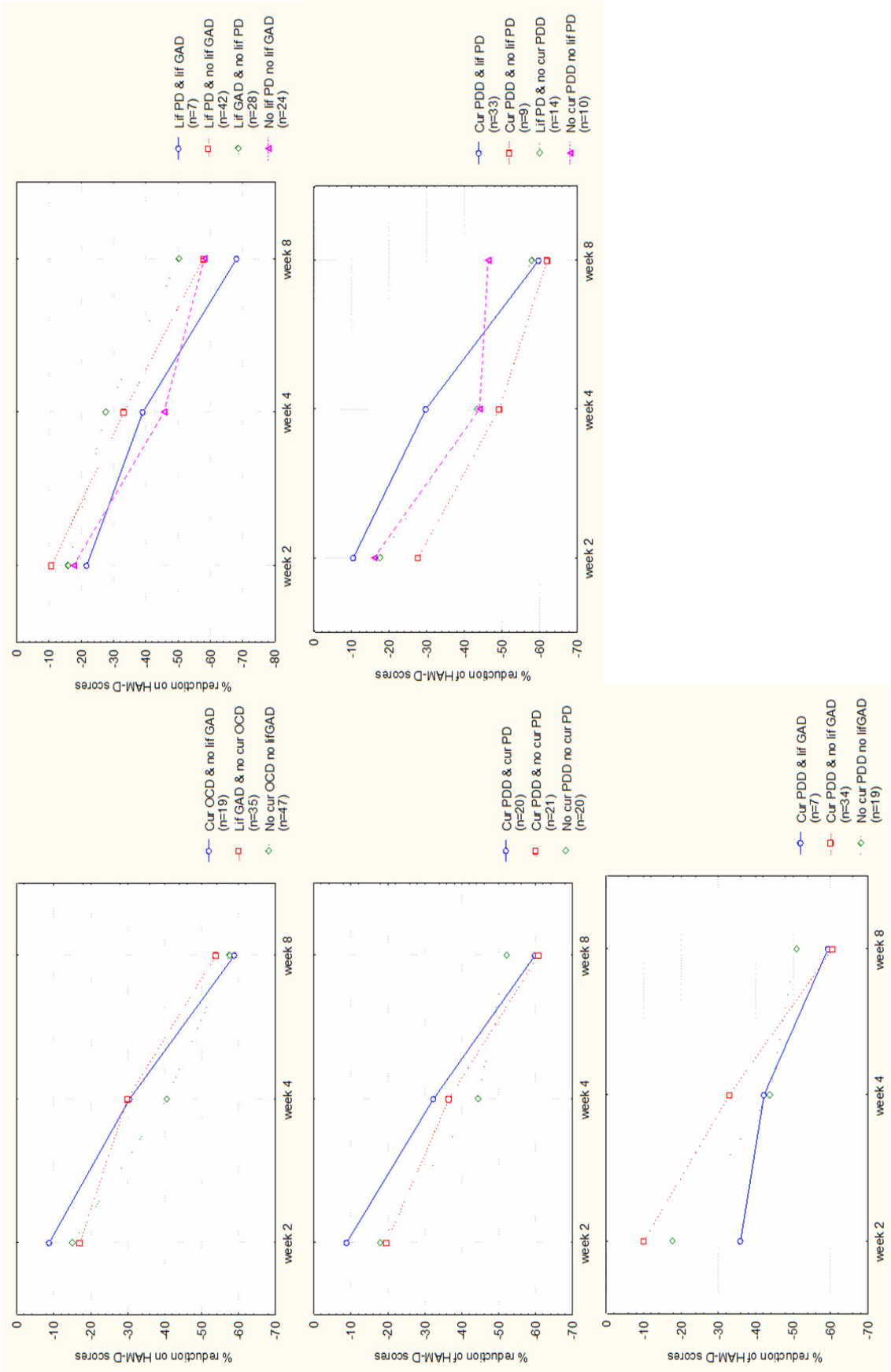

Figure 1. *Percentages of improvement on HAM-D scores displayed according to the interactions of comorbid axis I psuchiatric disorders. Cur=current; lif=lifetime; PD=panic disorder; OCD=obsessive compulsive disorder; GAD=generalized anxiety disorder; PDD=premenstrual dysphoric disorder*

Table 2. *Hamilton rating scale for depression (HAM-D) scores, anxiety/somatization and retardation scores at different time points and clinical response and remission at 8 weeks displayed according to clinical predictors. Only significant associations are shown.*

		Total HAM-D scores					Anxiety/somatization scores					Retardation scores				Response at 8 weeks		
		Baseline	2 weeks	4 weeks	8 weeks	P*	Baseline	2 weeks	4 weeks	8 weeks	P*	Baseline	4 weeks	8 weeks	p*	Yes	No	P
Cur PD X lif PD	Cur PD and life PD					-	13.36±2.08	8.59±1.99	7.13±1.64	5.31±1.28					-	22	0	0.002
	Llife PD, no cur PD						9.76±3.36	5.92±2.16	4.29±1.99	3.92±1.69	0.00002					24	3	
	No cur PD, no life PD						5.26±2.80	3.81±2.14	2.06±1.90	1.58±1.69						33	16	
Cur PD X life GAD	Cur PD and life GAD					-	13.36±2.08	8.59±1.99	7.13±1.64	5.31±1.28		0.91±0.28	0.16±0.38	0.08±0.28				-
	Llife GAD, no cur PD						6.68±2.51	4.74±1.50	2.48±1.97	1.94±1.74	0.00005	1.48±0.70	1.28±0.92	0.48±0.56	0.002			
	No cur PD, no life GAD						6.90±4.47	4.41±2.92	3.20±2.36	2.82±2.18		1.07±0.74	0.66±0.92	0.35±0.48				
Cur OCD X life PD	Cur OCD and life PD					-	13.61±0.77	8.61±1.37	7.55±0.85	5.44±0.92					-			-
	Life PD, no cur OCD						10.10±3.61	6.25±2.55	4.41±2.10	4.03±1.79	0.00002							
	No cur OCD, no life PD						5.26±2.80	3.81±2.14	2.06±1.90	1.58±1.69								
Cur OCD X life GAD	Cur OCD, no life GAD	27.36±1.42	24.94±3.02	19.21±4.75	11.36±2.75	0.002	13.23±1.69	8.31±1.85	7.15±1.92	5.15±1.53		1.00±0.00	0.10±0.31	0.05±0.22				-
	Life GAD, no cur OCD	20.68±4.10	17.31±4.79	14.77±5.37	9.65±4.02		6.68±2.51	4.74±1.50	2.48±1.97	1.94±1.74	0.00002	1.48±0.70	1.28±0.92	0.48±0.56	0.001			
	No cur OCD, no life GAD	21.55±5.13	18.31±5.25	12.71±5.62	8.69±3.81		7.41±4.66	4.73±3.18	3.37±2.43	3.00±2.23		1.02±0.73	0.63±0.89	0.34±0.47				
Life PD X life GAD	Life PD and life GAD	23.57±5.96	18.14±4.52	14.42±5.06	7.71±4.78	0.002	9.00±1.73	5.14±0.89	3.28±1.49	2.57±1.13					-			-
	Life PD, no life GAD	25.69±3.71	22.92±4.51	17.28±5.44	10.69±2.82		11.82±3.39	7.45±2.49	5.95±2.21	4.90±1.49	0.00002							
	Life GAD, no life PD	19.96±3.26	17.10±4.92	14.85±5.35	10.14±3.74		6.10±2.36	4.64±1.61	2.28±2.05	1.78±1.85								
	No life PD, no life GAD	18.91±4.38	15.50±3.90	9.73±3.92	7.26±4.18		4.50±3.08	2.73±2.19	1.72±1.66	1.31±1.46								
Cur PDD X cur PD	Cur PDD and cur PD	27.40±1.39	24.95±2.94	18.70±5.16	11.10±2.93	0.003					-				-			-
	Cur PD, no cur PDD	22.57±5.46	18.71±7.13	14.80±7.46	8.47±4.10													
	No cur PD, no cur PDD	21.10±5.67	17.00±4.80	11.50±4.97	9.75±4.68													
Cur PDD X life PD	Cur PDD and life PD	26.30±3.56	23.54±4.43	18.66±5.17	10.51±2.90	0.000 4					-				-	32	1	0.0001
	Curr PDD, no life PD	19.25±4.55	14.27±7.67	8.62±6.20	6.62±5.39											6	2	
	Life PD, no cur PDD	24.58±3.65	20.00±3.88	12.91±2.74	10.25±2.92											13	1	
	No cur PDD, no life PD	18.28±5.25	14.42±2.81	10.42±4.92	10.14±5.14											4	6	
Cur PDD X life GAD	Curr PDD and life GAD	21.28±6.61	13.42±7.16	12.00±6.19	8.00±4.79	0.000 01					-				-			-
	Cur PDD, no life GAD	25.67±3.89	23.47±4.56	17.67±6.41	10.11±3.51													
	No cur PDD, no life GAD	22.26±5.20	17.94±4.41	12.00±3.77	10.21±3.75													

Cur=current; life=lifetime; PD=panic disorder; OCD=obsessive compulsive disorder; GAD=generalised anxiety disorder; PDD=premenstrual dysphoric disorder; family history=family history of psychiatric disorder; *=the p value for such analyses is referred to repeated measures ANOVA.

a negative prognostic factor (Krishnan 2003), our findings suggest that this could not be true for duloxetine. Indeed, current evidence suggests that the detrimental effect related to a comorbidity with anxiety disorders could be evident with TCAs and with drugs with a main noradrenergic action, as compared with drugs with a main serotonergic or a dual serotonergic/noradrenergic action (Bagby et al. 2002, Bakish 1999, Hoehn-Saric et al. 2000). Of interest is, moreover, the notion that our results provide preliminary evidence that a careful examination of the interactions between different clinical variables could provide a more reliable prediction of improvement, as compared with single predictors alone, at least in some cases, and underscore the importance of further research in this direction. However, in some cases, no interaction between different predictors was observed. This suggests the validity of investigating single predictors as well (Bagby et al. 2002, Kemp et al. 2008, Fava et al. 2007, 2009).

Our study suffers from some limitations that should be acknowledged. The major one is that that we focused on a limited combination of predictors (Bagby et al. 2002, Kemp et al. 2008). In addition, clinically significant concomitant anxiety was defined as a score ≥ 7 on the six-item HAM-D anxiety-somatization factor: it is, therefore, possible other scales could be more specific for this purpose. A further bias could be related to the inclusion of both drug naïve patients and patients who were taking other medications at the beginning of the study when they were switched to duloxetine. Further, previous drugs and their dosages at study entry were not recorded. As a consequence, this could have exposed some patients to a combination of antidepressant treatments for the first few days. It should be noted, however, that, in a previous study focusing on the impact of single predictors on clinical improvement (Di Nasso et al. in press), no effect of baseline drugs was observed on any outcome measures and it is therefore unlikely that this variable could have influenced the results. A further limitation is characterized by the flexible dose design of the present study. However, no significant difference was observed on clinical improvement, as well as on response and remission rates stratified for low vs. high doses of duloxetine (Di Nasso et al. in press). Additionally, the lack of a placebo control group does not allow to investigate to which extent the influence of observed predictors could be properly attributed to duloxetine rather than to other non specific effects. Also, patients were prospectively followed up to only 8 weeks. This time frame could be considered as insufficient to assess clinical improvements in anxious patients and in patients with comorbid anxiety disorders who usually take more time to respond to drugs. The lack of investigation of plasma levels should also be considered as a limitation of the present study. Finally, the inclusion of outpatients only and the relatively small sample size may not permit to generalize our results to inpatients.

In conclusion, our results provide preliminary evidence to suggest how a careful examination of the interactions between different clinical variables could provide a more reliable prediction of improvement as compared with single predictors alone, at least in some cases. However, on account of the several limitations stated above, further research is needed to replicate and extend our results.

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