A PRELIMINARY INVESTIGATION OF CLINICAL AND DEMOGRAPHIC PREDICTORS OF IMPROVEMENT TO DULOXETINE TREATMENT IN PATIENTS WITH PREMENSTRUAL DYSPHORIC DISORDER AND COMORBID MAJOR DEPRESSION

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Abstract

Objective: Premenstrual dysphoric disorder (PMDD) is a common disorder which affects 2-8% of women in western countries, often occurs in comorbidity with other disorders such as major depression and is often non responsive to current medications. The aim of the present study is to investigate predictors of symptoms' improvement, particularly depressive symptoms, in a sample of women with comorbid PMDD and major depression treated with duloxetine.

Method: Forty-one women with PMDD and concurrent major depression were treated with duloxetine and assessed at baseline and at weeks 2, 4 and 8 by means of the 21 item Hamilton rating scale for depression (HAMD) and Clinical global severity scale (CGI-S). Clinical and demographical predictors of response were explored by means of univariate and multivariate analyses.

Results: None of the clinical and socio-demographical variables under investigation significantly predicted improvements of depressive symptoms over time. However younger age, a lower number of prior depressive episodes, a comorbidity with panic disorder and obsessive compulsive disorder, receiving treatment at baseline and the lack of adverse events before index depressive episode positively predict improvements on CGI-S scores.

Conclusions: Our results provide preliminary evidence to suggest that a number of variables could predict global clinical improvement but not depressive improvement in women with PMDD and concurrent major depression treated with duloxetine. However, on account of several limitations, including, among the others, the lack of a comparison group and the small sample size of our study, further research is needed to replicate and extend current findings.

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

Declaration of interest: none

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Background

Premenstrual dysphoric disorder (PMDD) is a disorder characterized by cyclic recurring mood, behavioural and somatic symptoms that usually begin 5–7 days before the onset of menses, although in some cases they can start as early as 12–14 days before menses, and begin to remit within a few days of the onset of menses (Yonkers et al. 2008). According to the DSM IV (American Psychiatric Association 1994) which includes PMDD in an appendix pending further research, main features of such disorder include depressed mood or dysphoria, anxiety or tension, irritability and decreased interest in usual activities that are associated to a significant impairment of work, school as well as social activities and relationships and that cannot be solely attributed to an exacerbation of another disorder .

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PMDD affects about 2-8% of women in Western countries (Rivera-Tovar & Frank 1990; Soares et al. 2001) and about 1.2-5.3% of women in Asian countries (Takeda et al. 2006), although the percentage of subthreshold symptoms could be as high as 18.6% (Wittchen et al. 2002). If one considers that a high number of patients with PMDD reports feelings that life is not worth living (Campbell et al. 1997) and that for approximately 15% of symptomatic women such feelings result in suicide attempts (Chaturvedi et al. 1995, Wittchen et al. 2002), the importance of an early diagnosis and treatment becomes evident.

The treatment of choice for PMDD are selective serotonin reuptake inhibitors (SSRIs) (Rapkin & Winer 2006) which are supposed to modulate sex steroid–driven behaviour which have been found to be disrupted in PMDD (Eriksson et al. 2002). Additionally, a possible mechanism of action of SSRIs in PMDD could be

related to the close association between PMDD and major depression, which often occurs in comorbidity or can be triggered by PMDD in susceptible individuals (Breaux et al. 2000).

Although SSRIs are usually well tolerated and can improve the quality of life of women suffering from PMDD (Freeman 2005, Rapkin et al. 2006), however, not all subjects benefit from treatment and a relatively high proportion of subjects taking SSRIs experiences unwanted side effects such as sexual dysfunction (Macdougall & Steiner 2003, Olah 2002) and prematurely discontinues the treatment (Sundstrom-Poromaa et al. 2000). Accordingly, the search for newer treatment options for PMDD has recently gained increasing attention and has led to the investigation of the potential efficacy of a number of drugs including dual action antidepressants such as venlafaxine (Cohen et al. 2004, Freeman et al. 2001) and, more recently, duloxetine (Mazza et al. 2008, Ramos et al. 2009), finding preliminary positive results. Duloxetine, in particular, is different from the majority of drugs studied so far because it is a potent dual reuptake inhibitor of both serotonin and noradrenaline with about an equal affinity for binding to the serotonin and noradrenaline reuptake transporters (Gupta et al. 2007) which has shown efficacy for several disorders such as major depression (Girardi et al., 2009) and is related to a lower likelihood of inducing sexual dysfunction as compared to SSRIs and venlafaxine (Serretti & Chiesa 2009a).

Unfortunately, however, a few authors have investigated possible predictors of response to drugs currently used to treat PMDD so far, finding a limited number of variables such as higher levels of post-menstrual and premenstrual scores at baseline that could significantly predict higher symptoms persistence at endpoint in patients treated with sertraline (Freeman et al. 2000) and no study has yet focused on predictors of response to newer drugs such as venlafaxine and duloxetine. On the other hand, a higher evidence-based knowledge about possible predictors of response to such drugs in women suffering from PMDD could allow to identify subjects who could benefit most from antidepressant treatment and to target specific strategies at early stages of treatment so as to enhance treatment outcome.

As a consequence, on account of the paucity of studies aimed at investigating predictors of antidepressant treatment outcome in women suffering from PMDD and of the high comorbidity between PMDD and major depression, the present study is aimed at exploring predictors of symptoms' improvement, particularly depressive symptoms, in a sample of women with PMDD and comorbid major depression treated with duloxetine.

Methods

Sample description

The present study is based on a subset of a larger sample of patients suffering from major depression and treated with duloxetine for 8 weeks. A detailed description of the whole sample can be found in such study (Di Nasso et al. 2010). Briefly, one hundred ninety seven outpatients were consecutively recruited at the Neuroscience department, depressive unit, belonging to Fatabenefratelli 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 IV criteria as assessed by MINI-international Neuropsychiatric interview (Sheehan et al. 1998), b) a baseline score ≥ 17 as assessed by the Hamilton rating scale for depression, c) age ≥ 18 and ≤ 65 and d) whether the patients were using other antidepressants at study entry, the willingness to switch to duloxetine because of lack of efficacy and/or tolerability issues. Exclusion criteria were: a) a comorbidity with a personality disorder, b) a comorbidity with alcohol and/or substance abuse/dependence (both of which are not treated in our centre), c) current or lifetime psychotic symptoms, d) severe unstable medical and neurological comorbidities, e) prior treatment with duloxetine and e) the unwillingness or the impossibility according to the clinician's opinion to stop concomitant psychotropic medications including antidepressants, mood stabilizers, antipsychotics and anxiolytics. Past and present comorbidities with other axis I disorders as well as further clinical and socio-demographical features including gender, age, educational level, occupational status, marital status, familial history of psychiatric disorders, medical illnesses, number of previous depressive episodes, life events before current depressive episode, onset and duration of illness were also recorded.

Patients were initially treated with 30 mg duloxetine for 1 week. During the same time frame, antidepressants other than duloxetine were stopped. 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. In the original study, out of 197 patients, 101 patients could be included. In the present study we focused on 41 out of 101 patients included in the original study who fulfilled DSM IV criteria for PMDD. 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/somatization 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. In addition, clinical global impression severity scale (CGI-S) (Guy 1976) was assessed at 4 and 8 weeks. Response was defined as a reduction ≥ 50% on HAM-D scores from baseline. Remission was defined as an HAM-D score ≤ 7. There was good reliability among the interviewers (k>0.8). Dosages of duloxetine were recorded at the 8th week as well.

Outcome measures

Our primary outcome measure was the influence of predictors under investigation on depressive symptoms as measured by the percentage reduction of HAM-D total scores during the study period. Our secondary outcome measures included the effects of the same predictors on CGI and anxiety/somatization improvements as well as on response and remission rates at 8 weeks.

Statistical analysis

All data collected during the study were analysed using Statistica software. Predictors of clinical improvement on total HAM-D scores as well as on anxiety/somatization scores and CGI-S scores were analysed by the repeated measures ANOVA and the multivariate analysis of variance/covariance (MANOVA/MANCOVA) when controlling for potential confounders (see below). Improvements on all such variants were calculated according to the following formula (considering as an example HAM-D scores): [(HAM-Dtime X - HAM-Dbaseline)/ HAM-Dbaseline]*100. Influence of included predictors on response and remission rates at 8 weeks were analysed by χ^2 statistics. Continuous outcomes were categorized according to the median. Following the univariate analysis, we performed a correlation analysis between all predictors under investigation so as to investigate possible stratification effects and analysed the influence of each variable correlated to predictors significantly associated to clinical outcomes in univariate analysis.

Statistical significance was conservatively set at 0.003, approximately corresponding to the Bonferroni's correction for multiple testing (17 predictors). With these parameter we had a sufficient power (0.80) to detect a large effect size of 0.8 corresponding, for instance, to a difference at week 8 of 2.75 points in HAM-D scores between patients with and without comorbid panic disorder.

Results

Demographic and clinical characteristics

Demographic and clinical characteristics of the subjects included into the analyses are listed in table 1. Overall, HAMD scores, anxiety/somatization scores and CGI-S scores significantly decreased from baseline to endpoint (F=158.5, d.f.=2,80, p<0.000001; F=28.4, d.f.=2,78, p<0.000001; F=46.16, d.f.=1,40, p<0.000001 respectively). Thirty-nine subjects achieved response and 10 subjects achieved remission at 8 weeks. No drop outs were observed during the study period.

Influence of clinical and demographical characteristics on HAM-D improvement

None of the clinical or demographic predictors under investigation was found to be significantly associated to HAM-D improvements over the 8 week period (all p-values > 0.003).

Influence of clinical and demographic characteristics on CGI-S scores

A significant time x age interaction was observed on CGI-S improvement over time, such that older subjects were less likely to improve as compared to younger subjects (F=73.28, d.f.= 1,39, p<0.00001, for detailed data see table 2). Similarly, subjects with 3 or more prior depressive episodes were less likely to improve on CGI-S scores as compared with subjects with two or less prior depressive episodes (F=41.83, d.f.=1,39, p<0.00001). Also, subjects with comorbid panic disorder (PD), comorbid obsessive compulsive disorder (OCD), subjects treated at baseline with another antidepressant and subjects who did not report adverse life events before current depressive episode showed significantly higher improvements on CGI-S scores as compared with subjects without comorbid PD, comorbid OCD, subjects untreated at baseline and subjects reporting no adverse life events before current depressive episodes respectively (F=32.48, d.f.=1,39, p<0.00001; F=44.04, d.f.=1,39, p<0.00001; F=19.21, d.f.=1,39, p<0.0001, F=28.61, d.f.=1,39, p<0.0001 respectively). No other clinical and demographical predictors under investigation were significantly associated to CGI-S improvements over time.

Influence of clinical and demographic characteristics on anxiety/somatization improvement

A significant time x age interaction was observed on improvements of anxiety/somatisation scores, such that older subjects showed a higher improvement during the first weeks of treatment whereas younger subjects showed higher improvements at 8 weeks (F=10.87, d.f.=2,76, p<0.0001). In addition, subjects with comorbid PD and OCD showed higher levels of improvements as compared to subjects without comorbid PD and OCD respectively (F=6.35, d.f.=2,76, p=0.002; F=6.96, d.f.=2,76, p=0.001 respectively).

Influence of clinical and demographic characteristics on response and remission rates

As only two subjects did not respond at 8 weeks, predictors of response were systematically excluded from the analyses. On the other hand, four predictors of remission were identified. More in detail, older subjects, subjects with lifetime PD or GAD as well as subjects with a familial history of psychiatric disorders were less likely to achieve remission as compared to younger subjects as well as subjects without lifetime PD, GAD or a familial history of psychiatric disorders respectively (χ^2 =13.88, d.f=1, p=0.0001; χ^2 =11.17, d.f=1, p=0.0008; χ^2 =9.55, d.f=1, p=0.002; χ^2 =11.16, d.f=1, p=0.0008 respectively).

Analysis of confounders

In order to exclude possible confounding effects related to masked correlations between different predictors, we then performed a correlation analysis among all predictors under investigation and we assessed the impact of each variable correlated with predictors significantly associated to clinical improvement on all significant associations.

None of the variables under investigation influenced repeated measures ANOVA on CGI-S and anxiety/somatisation improvements over time. On the other hand, when the association between lifetime PD and remission was controlled for age, the association was no more significant ($p<0.003$), probably because of an association between higher age and a higher likelihood of developing PD over the life span. Also, when the association between lifetime GAD and remission was controlled for age, medical comorbidities and familial history of psychiatric disorders, such association was no more significant. Similarly, when the association between familial history of psychiatric disorders and remission was controlled for lifetime GAD, such association was no more significant.

Discussion

Our study was aimed at exploring clinical and demographical predictors of improvement in a sample of patients suffering from PMDD and concurrent MD treated with duloxetine. The results of our study suggested that none of the predictors under investigation was associated with improvement of depressive symptoms over time. Of note, such results are similar to an early study focusing on sertraline which did not found any evidence to suggest that a number of socio-demographical or clinical predictors including, among the others, age, educational level, comorbidities with other disorders as well as pre and post menstrual HAMD scores could predict clinical improvement in 62 women with PMDD (Freeman et al., 2000).

However, our results suggested that higher CGI-S improvements over time were predicted by lower age, a comorbidity with PD or OCD, a lower number of prior depressive episodes, receiving no treatment before the switch to duloxetine and absence of life events before index depressive episode. A possible explanation of the observed discrepancy suggesting alternatively no advantages on HAM-D scores but significantly higher improvements on CGI-S scores could be explained if one considers that the latter scale, which is not specific for depressive symptoms, could have captured other dimensions that the HAM-D could miss.

Interestingly the notion that lower age and the absence of life events before current depressive episode could be positive predictors of response to antidepressants in major depression has long been recognised, even though discrepant findings, possibly related to differences in study design, different types and doses of antidepressants and different definitions of response, have been reported as well (Serretti et al. 2009b). On the other hand, a possible explanation as to why a comorbidity with anxiety disorders such as PD or OCD, which have been usually associated to a lower outcome in major depression (Serretti et al. 2009b), have been associated to a higher improvement of CGI-S scores over time could be imputed to the specific mechanism of duloxetine characterized by a reuptake inhibition of both serotonin and noredrenaline (Gupta et al. 2007). Indeed, a handful of studies provides preliminary evidence suggesting that dual action antidepressants such as duloxetine and venlafaxine could show some advantage over drugs that solely inhibit the reuptake of serotonin for the reduction of anxiety symptoms (Bakish 1999, Davidson et al. 2002, Fava et al. 2007). Interestingly, such explanation is also consistent with our findings suggesting that anxiety/somatisation scores improved to a higher extent in patients with comorbid PD or OCD as compared to

Table 1. *Baseline characteristics of the sample*

Sample size	41
Age	40.22±9.21
School	
- Primary school	10 (24%)
- Secondary school	27 (66%)
- Graduate	4 (10%)
Occupational status	
- unemployed	15 (37%)
- employed	26 (63%)
Marital status	
-Single	15 (37%)
-Married	25 (60%)
-Divorced/widowed	1 (3%)
Mean number of DE	3.41±2.58
Concomitant comorbidities	
-PD	20 (49%)
-OCD	19 (46%)
Lifetime comorbidities	
-PD	32 (78%)
-GAD	5 (12%)
-Other axis I disorders	6 (15%)
Anxious depression	
-Yes	35 (85%)
-No	6 (15%)
Familial history of psychiatric disorders	
-Yes	37 (90%)
-No	3 (10%)
Medical comorbidities	
-Yes	7 (17%)
-No	34 (83%)
Life events before current depressive episodes	
-Yes	30 (73%)
-No	11 (27%)
Drug status at baseline	
-Yes	26 (63%)
-No	15 (17%)
Age at onset of illness	25.1±9.12
Mean duration of illness	15.14±6.79

Table 2. *Clinical global impression severity (CGI-S) scores, anxiety/somatisation scores at different time points and clinical remission at 8 weeks according to clinical and demographical predictors. Only significant associations are shown*

		Anxiety/somatization scores					*CGI-S scores*				*Remission at 8 weeks*		
		Baseline	2 weeks	4 weeks	8 weeks	P*	Baseline	4 weeks	8 weeks	p*	Yes	No	p
Age	Younger Older	13.23±1.64 7.20±2.39	8.47±1.47 4.45±1.90	7.33±1.27 3.26±2.07	5.28±1.14 3.40±2.32	0.00007	4.95±0.21 4.40±0.68	3.90±0.30 3.55±1.35	1.95±0.38 3.35±1.53	<0.000001	10 0	10 21	0.0002
MD episodes	1 or 2 ≥3	-	-	-	-		4.81±0.49 4.46±0.63	3.73±0.53 3.73±1.48	2.07±0.68 3.60±1.54	<0.000001	-	-	
Comorbid PD	Yes No	13.05±1.90 7.66±2.92	8.05±2.16 5.04±2.20	6.95±2.08 3.85±2.25	5.05±1.57 3.71±2.23	0.003	4.95±0.22 4.42±0.67	3.75±0.71 3.71±1.18	1.90±.0.44 3.33±1.46	0.00001	-	-	
Comorbid OCD	Yes No	13.26±1.69 7.27±2.86	8.31±1.85 4.95±2.19	7.15±1.92 3.81±2.20	5.15±1.53 3.68±2.19	0.001	4.94±0.22 4.45±0.67	3.78±0.71 3.68±1.17	1.84±0.37 3.31±1.42	<0.000001	-	-	
Lifetime PD	Yes No	-	-	-	-		-	-	-		4 6	28 3	0.0008
Lifetime GAD	Yes No	-	-	-	-		-	-	-		4 6	1 31	0.002
Therapy at baseline	Yes No	-	-	-	-		4.65±0.62 4.73±0.45	3.61±0.63 3.93±1.38	2.07±0.56 3.60±1.68	0.00008	-	-	
Life events	Yes No	-	-	-	-		4.70±0.59 4.63±0.50	3.63±0.61 4.00±1.61	2.13±0.68 4.00±1.61	0.00004	-	-	
Familial history	Yes No	-	-	-	-		-	-	-		6 3	32 0	0.0008

patients without such comorbidities. Finally, the observation that a higher number of prior depressive episodes was associated to lower improvements on CGI-S scale is consistent with a number of previous observations reporting the detrimental effect of a higher number of prior depressive episodes on the response to antidepressants in major depression, (e.g., Ezquiaga et al. 1998, Gorwood et al. 2010).

On the other hand, we also observed that a lifetime history of PD or GAD negatively predict remission defined as a HAM-D score ≤ 7 at endpoint. A possible explanation for these findings could be imputed to the notion that patients with a history of such disorders could be characterized by a higher global severity as well as a longer duration of illness and could be therefore less responsive to pharmacological treatment. Also, higher age as well as a familial history of psychiatric disorders negatively predicted remission. It should be noted however that strong correlations were observed among such predictors, such that the negative influence of higher age on treatment outcome could be simply due to the higher likelihood of having suffered from PD or GAD during the life span, whereas the detrimental effect related to a familial history of psychiatric disorder could be simply due to the strong correlation between such predictor and a lifetime history of GAD. Note however that such speculative explanations deserve further empirical investigations.

Several limitations should be taken into account into the interpretation of the results of the present study. The major limitation is that we did not investigate the improvement of PMDD symptoms by means of a scale specifically designed for such purpose. However, as reported above, the present study was based on a subset of a larger study which primary aim was the investigation of the predictors of depressive symptoms' improvement in patients with major depression treated with duloxetine. A second concerning limitation is that side effects were not recorded. As a consequence it is not possible to rule out that the apparent worsening of symptoms in some patients could be more properly attributed to the appearance of unwanted side effects rather than to a specific worsening of depressive symptoms. Note however that no serious adverse events (including as an example hospitalisations or suicidal attempts were recorded during the study duration), partially dampening concerns about this critical issue. Additionally, clinically significant concurrent anxiety was defined as a score ≥ 7 on the six item HAM-D anxiety-somatization factor, however other scales specifically designed to assess anxiety symptoms such as the Hamilton rating scale for anxiety (Hamilton 1959) could be more specific for the assessment of baseline and follow-up anxiety levels. A further limitation could be related to the inclusion of both drug naïve patients and patients who were taking other medications at the beginning of the study and to the fact that dosages of previous drugs at study entry was not recorded. It should be noted however the almost complete lack of effects of taking or not drugs at baseline on outcome measures and it is therefore unlikely that this variable could have influenced the results. Also, we did not include patients with personality disorders as well as with comorbid substance and alcohol abuse, both of which could influence treatment outcome (Bagby et al. 2002, Newton-Howes et al. 2006) and we included women with both PMDD and major depression so that our results cannot be generalized to women with PMDD and no further comorbidities. It is noteworthy, however, the large majority of women with PMDD suffers from concomitant affective or anxiety disorders (Breaux et al. 2000). A further limitation is characterized by the flexible dose design of the present study, even though no significant difference was observed between patients treated with lower or higher doses of duloxetine (data not shown). Additionally, the lack of a placebo control group does not allow to understand to what extent the influence of observed predictors could be properly attributed to duloxetine rather than to other non specific effects. Finally, an important limitation of the present study concerns the small sample size of our sample that could have obscured more subtle differences between different sub-groups of patients.

In conclusion, our results preliminary suggest that several variables could predict clinical outcomes in women with PMDD and concurrent MD treated with duloxetine. However, on account of several limitations stated above, further research is needed to replicate and extend our results in larger samples using a randomized controlled design and investigating the effects of drugs other than duloxetine.

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