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Efficacy and tolerability of duloxetine in the treatment of patients with borderline personality disorder: a pilot study

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Abstract

Guidelines of the American Psychiatric Association for borderline personality disorder (BPD) indicate selective serotonin reuptake inhibitors and the serotonin and noradrenaline reuptake inhibitor (SNRI) venlafaxine for treating affective dysregulation and impulsive behavioural dyscontrol symptoms. The SNRI duloxetine has been studied in patients with major depression, generalized anxiety disorder and fibromyalgia, showing particular efficacy on somatic complaints. This study investigates duloxetine in the treatment of patients with BPD. Eighteen outpatients with a DSM-IV-TR diagnosis of BPD were treated with open-label duloxetine, 60 mg/day, for 12 weeks. Patients were assessed at baseline, week 4 and 12 with the CGI Severity item, the BPRS, the HAM-D, the HAM-A, the SOFAS, the BPD Severity Index (BPDSI) and the HSCL-90-Somatization Subscale (HSCL-90 SOM). Adverse effects were evaluated using the Dosage Record Treatment Emergent Symptom Scale. Statistics were performed with the analysis of variance. Significant P values were ≤ 0.05. Fourteen patients completed the study. Four patients (22.2%) discontinued treatment in the first 4 weeks because of non-compliance. A significant change was found for: BPRS, HAM-D, SOFAS, BPDSI total score and items 'impulsivity', 'outbursts of anger' and 'affective instability' and HSCL-90 SOM. Adverse effects were mild headache and nausea. Initial results suggest that duloxetine is an effective and well-tolerated treatment for BPD, with positive effects on somatic symptoms.

Key words

adverse effects; antidepressants; borderline personality disorder; duloxetine; somatic symptoms

Introduction

Current guidelines of the American Psychiatric Association (APA) for the treatment of borderline personality disorder (BPD) (APA, 2001; Oldham, 2005) indicate selective serotonin reuptake inhibitors (SSRIs) fluoxetine, fluvoxamine and sertraline, and the serotonin and noradrenaline reuptake inhibitor (SNRI) venlafaxine as first-line treatments of affective dysregulation and impulsive behavioural dyscontrol symptoms. In particular, these agents have been found effective on depressed mood, anger and aggressive impulsiveness, including self-injurious behaviours. Other drugs have been tested in samples of patients with BPD and are recommended by APA treatment guidelines: monoamine oxidase inhibitors, low doses antipsychotics and mood stabilizers as second choice or augmenting agents for affective dysregulation and impulsive behavioural dyscontrol; low doses antipsychotics as first choice drugs for cognitive-perceptual symptoms.

Several open label and placebo-controlled studies have supported the efficacy of SSRIs in the treatment of patients with BPD (Norden, 1989; Markovitz, 1990; Teicher, *et al*., 1990; Cornelius, *et al*., 1990; Kavoussi, *et al*., 1994; Salzman, *et al*., 1995; Markovitz, 1995; Coccaro and Kavoussi, 1997; Rinne, *et al*., 2002), whereas only one open label trial has been published on the efficacy of the SNRI venlafaxine in this disorder (Markovitz and Wagner, 1995). This study included 45 patients with a diagnosis of BPD, who were treated with venlafaxine (average daily dosage of 315.2 ± 95.8 mg/day,

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range 200–400 mg/day) over a 12-week period. The results on the 39 patients (86.7%) completing the trial were encouraging, showing an improvement in scores of all Hopkins Symptom Checklist-90 (HSCL-90) subscales, including somatic symptoms of HSCL-90 somatization subscale. Self-injurious behaviour was eliminated in five of the seven patients who presented this symptom. Concerning tolerability, side effects were minimal. Among these, sexual dysfunction occurred rarely (3 of the 39 patients, 8%).

Duloxetine is a recent dual reuptake inhibitor of serotonin and norepinephrine (SNRI) that has been widely tested in the treatment of major depressive disorder (Detke, *et al*., 2002; Nemeroff, *et al*., 2002; Goldstein, *et al*., 2004; Hirshfeld, *et al*., 2005; Brannan, *et al*., 2005; Perahia, *et al*., 2006; Brecht, *et al*., 2007; Hudson, *et al*., 2007; Wohlreich, *et al*., 2007; Dunner, *et al*., 2008; Raskin, *et al*., 2008), generalized anxiety disorder (Allgulander, *et al*., 2007; Endicott, *et al*., 2007; Hartford, *et al*., 2007; Koponen, *et al*., 2007; Russell, *et al*., 2007; Davidson, *et al*., 2008; Nicolini, *et al*., 2008; Rynn, *et al*., 2008) and fibromyalgia (Arnold, 2007; Arnold, *et al*., 2005, 2007; Rooks, 2007; Russell, *et al*., 2008). In studies of major depressive disorder, duloxetine was given 60 mg once daily, except for the trial performed by Dunner, *et al*. (2008), who administered the drug up to 120 mg a day. Samples with generalized anxiety disorder and fibromyalgia usually received a variable dose of duloxetine from 60 to 120 mg/day. Reported side effects were low and rarely lead to discontinuation (approximately 10% of patients according to Hudson, *et al*., 2007). The most frequent adverse events were nausea and dry mouth (Nemeroff, *et al*., 2002; Brecht, *et al*., 2007; Dunner, *et al*., 2008; Hudson, *et al*., 2007; Raskin, *et al*., 2008), followed by headache, somnolence, insomnia, dizziness (Nemeroff, *et al*., 2002; Hudson, *et al*., 2007), hyperhydrosis (Brecht, *et al*., 2007), diarrhoea (Raskin, *et al*., 2008) and weight gain (Dunner, *et al*., 2008).

Studies concerning duloxetine in the treatment of major depression and generalized anxiety disorders indicated that this drug is effective on patients' somatic complaints (Detke, *et al*., 2002; Nemeroff, *et al*., 2002; Goldstein, *et al*., 2004; Hirshfeld, *et al*., 2005; Brannan, *et al*., 2005; Perahia, *et al*., 2006; Brecht, *et al*., 2007; Hudson, *et al*., 2007; Wohlreich, *et al*., 2007; Dunner, *et al*., 2008; Nicolini, *et al*., 2008; Raskin, *et al*., 2008), such as overall pain, back pain, shoulder pain and time in pain, whereas awake as measured by visual analogue scales (Detke, *et al*., 2002; Nemeroff, *et al*., 2002).

No data concerning the efficacy of duloxetine in the treatment of patients with BPD is available at the present time. The rationale to test this dual action antidepressant is based on neurobiological studies indicating that BPD and aggressive impulsivity are associated with abnormalities in both serotonergic and noradrenergic systems (Oquendo and Mann, 2000; Coccaro, *et al*., 2003; Paris, *et al*., 2004; Gollan, *et al*., 2005; Soloff, *et al*., 2007). Moreover, data on genetic correlates suggest that both serotonin transporter gene and monoamine oxidase A gene play a role in the aetiological development of BPD (Ni, *et al*., 2006, 2007; Lyons-Ruth, *et al*., 2007; Pascual, *et al*., 2007). The interest in studying efficacy of duloxetine in patients with BPD is increased by encouraging results obtained with the SNRI venlafaxine and by literature data supporting the association of BPD and somatic symptoms (Sansone, *et al*., 2006).

The aim of this pilot study is to provide data on the efficacy and tolerability of duloxetine in the treatment of a group of patients with BPD, including the assessment of effects on somatic complaints.

Methods and materials

Eighteen consecutive outpatients aged between 18 and 50 years and receiving a DSM-IV-TR (APA, 2000) diagnosis of BPD were recruited. Patients attended the Service for Personality Disorders of the Unit of Psychiatry, Department of Neurosciences, University of Turin.

Exclusion criteria included: 1) diagnosis of dementia or other cognitive disorders, schizophrenia or other psychotic disorders and/or bipolar disorders; 2) a co-occurring major depressive episode and/or substance abuse disorder and 3) administration of psychotropic medications and/or psychotherapy in the 3 months before recruitment.

Psychiatric diagnoses were made by an expert clinician (S.B.) and were confirmed with the Structured Clinical Interview for DSM-IV Axis I and II Disorders (First, *et al*., 1997a,b).

Female patients in childbearing age were excluded if they were not using adequate birth control methods (according to the judgment of the clinician).

Each patient participated voluntarily in the study after providing a written informed consent. Declaration of Helsinki guidelines was followed.

Patients were treated with open-label duloxetine, 60 mg/day, for 12 weeks. No other psychotropic drug or psychological intervention was allowed during the trial.

Patients were repeatedly tested (at baseline, week 4 and week 12) using the following assessment instruments:

1) the Clinical Global Impression Scale – Severity item (CGI-S) (Guy, 1976a);
2) the Brief Psychiatric Rating Scale (BPRS) (Ventura, *et al*., 1993);
3) the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1959);
4) the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1960);
5) the Social Occupational Functioning Assessment Scale (SOFAS) (Goldman, *et al*., 1992);
6) the BPD Severity Index (BPDSI) (Arntz, *et al*., 2003);
7) the Hopkins Symptom Checklist-90 Somatization Subscale (HSCL-90 SOM) (Derogatis, *et al*., 1973) for somatic symptoms.

The BPDSI is a semi-structured clinical interview assessing frequency and severity of BPD-related symptoms. The interview consists of eight items scored on 10-point frequency scales (0 = never; 10 = daily), including 'abandonment', 'interpersonal relationships', 'impulsivity', 'parasuicidal behaviour', 'affective instability', 'emptiness', 'outbursts of anger', 'dissociation and paranoid ideation', and one item scored on a 4-point severity scale, concerning 'identity'. The BPDSI showed excellent reliability coefficients and good validity indices in two studies performed by Arntz, *et al*. (2003).

The HSCL-90 SOM is a subscale of HSCL-90 composed by 12 items assessing somatic symptoms of patients, such as 'headaches', 'faintness or dizziness', 'pains in heart or chest', 'pains in lower back', 'nausea or upset stomach', 'soreness of muscles', 'trouble getting your breath', 'hot or cold spells', 'numbness or tingling in body parts', 'lump in the throat', 'weakness or heavy feelings in body parts'. Each item is scored on a 5-point frequency scale (0 = not at all; 4 = extremely).

The Dosage Record Treatment Emergent Symptom Scale (DOTES) (Guy, 1976b) was used to collect adverse effects.

Statistics were performed on each rating scale by using the analysis of variance (ANOVA) for repeated measures (software system SPSS, version 13.0; SPSS Inc., Chicago, Illinois, USA). *P* values were considered significant when ≤0.05.

Results

Fourteen of the 18 patients (77.8%) completed all 12 weeks of the trial. Four patients (22.2%) discontinued treatment in the first 4 weeks because of non-compliance. The final sample of 14 patients had a mean age of 29.6 ± 2.33 years; they were nine women (64.3%) and five men (35.7%). Seven subjects (50%) were married; six (42.9%) had an employment. Years of education were 13.1 ± 7.6. Mean duration of illness was 8.53 ± 5.43. Eight patients (57.1%) had been admitted at least once at the psychiatric unit of a general hospital.

Mean scores ± SD of single items of the HSCL-90 Somatization Subscale are reported in Table 1. Somatic symptoms with highest mean scores were: 'pain in lower back' (3.67 ± 0.58), 'lump in the throat' (3.29 ± 0.76), 'headaches' (3.2 ± 1.3) and 'trouble getting your breath (3.17 ± 0.75). Results of ANOVA applied to rating scales scores are reported in Tables 2 and 3.

A statistically significant improvement was observed in CGI-S mean score ($P = 0.002$), BPRS mean score ($P = 0.001$), HAM-D mean score ($P = 0.035$), SOFAS mean score ($P = 0.0005$), BPDSI total score ($P = 0.001$), three BPDSI items, 'impulsivity' ($P = 0.028$), 'outbursts of anger' ($P = 0.0005$), 'affective instability' ($P = 0.001$) and HSCL-90 Somatization Subscale mean score ($P = 0.0005$).

On the contrary, there were no significant changes of HAM-A mean score, and BPDSI items of 'abandonment', 'interpersonal relationships', 'parasuicidal behaviour', 'emptiness', 'dissociation and paranoid ideation' and 'identity'.

Table 1 Mean ± SD scores of the single items of the HSCL-90 Somatization Subscale calculated in the initial group of 18 patients

Symptoms	Mean	SD
Pain in lower back	3.67	0.58
Lump in the throat	3.29	0.76
Headaches	3.2	1.3
Trouble getting your breath	3.17	0.75
Faintness or dizziness	3.0	1.41
Nausea or upset stomach	2.83	0.75
Feeling weak in body parts	2.5	0.71
Pains in heart or chest	2.4	0.55
Soreness of muscles	2.0	0.82
Heavy feelings in arms or legs	2.0	1.41
Hot or cold spells	2.0	0
Numbness or tingling in body parts	0	0

SD, standard deviation.

The most common adverse effects reported in the final sample of 14 patients were nausea and headache (three patients both, 21.4%). Other adverse effects included gastrointestinal disturbances (two patients, 14.3%), dizziness and insomnia (one patient each, 7.2%). Four patients (28.6%) had no adverse effects. The four drop-outs were not because of adverse effects.

Discussion

Results of duloxetine treatment of a group of patients with BPD indicate the efficacy of this SNRI on a broad spectrum of symptoms, as shown by significant changes of CGI severity item score, BPRS mean score, HAM-D mean score, BPDSI total score, three BPDSI items scores ('impulsivity', 'outbursts of anger' and 'affective instability') and HSCL-90 Somatization subscale score. Because of the lack of previous studies of duloxetine in patients with BPD, these data can only be compared with findings concerning SSRIs and the SNRI venlafaxine.

As far as symptoms dimensions of BPD are concerned, duloxetine appears to be selectively effective on impulsiveness, as indicated by BPDSI 'impulsivity' item, and on affective dysregulation, as shown by BPDSI 'outbursts of anger' and 'affective instability' items. These data are in accordance with previous findings of SSRIs trials in patients with BPD (Norden, 1989; Markovitz, 1990; Teicher, *et al*., 1990; Cornelius, *et al*., 1991; Kavoussi, *et al*., 1994; Salzman, *et al*., 1995; Markovitz, 1995; Markovitz and Wagner, 1995; Coccaro and Kavoussi, 1997; Rinne, *et al*., 2002) and with the study performed by Markovitz and Wagner (1995) on venlafaxine. In particular, venlafaxine was related to a marked reduction of self injurious behaviours, a symptom of impulsivity. It should be noticed that previous studies did not assess BPD-related symptoms with the BPDSI.

The efficacy of duloxetine on somatic complaints has already been reported in several studies of patients with major

Table 2 Results of the analysis of variance for repeated measures performed with the Borderline Personality Disorder Severity Index (BPDSI) total and factor scores and with the HSCL-90 Somatization Subscale (HSCL-90 SOM) score in 14 patients who completed 12 weeks of treatment with duloxetine

Measure		Mean score	SD	SE	*P*
BPDSI total score	T0	45.24	5.59	1.864	0.001
	T1	39.60	4.89	1.630	
	T2	32.64	6.99	2.330	
Abandonment	T0	6.66	1.62	0.540	NS
	T1	6.23	1.63	0.543	
	T2	6.20	1.60	0.533	
Interpersonal relationships	T0	7.33	1.24	0.113	NS
	T1	6.86	1.28	0.428	
	T2	6.71	1.36	0.454	
Identity	T0	4.53	2.55	0.316	NS
	T1	4.51	2.60	0.302	
	T2	4.11	2.28	0.302	
Impulsivity	T0	6.9	1	0.334	0.028
	T1	5.78	1.17	0.388	
	T2	5.46	1.16	0.388	
Parasuicidal behaviour	T0	2.12	2.15	0.717	NS
	T1	2.03	1.98	0.660	
	T2	1.99	1.90	0.632	
Affective instability	T0	7.67	1.06	0.28	0.001
	T1	6.18	1.01	0.27	
	T2	5.3	0.95	0.25	
Emptiness	T0	7.43	0.47	0.158	NS
	T1	7.14	0.39	0.129	
	T2	7.14	0.45	0.150	
Outbursts of anger	T0	7.10	0.8	0.268	0.0005
	T1	6.02	0.57	0.190	
	T2	5.22	0.71	0.236	
Dissociation and paranoid ideation	T0	4.53	2.55	0.849	NS
	T1	4.51	2.60	0.868	
	T2	4.11	2.28	0.760	
HSCL-90 SOM	T0	2.90	0.56	0.150	0.0005
	T1	2.04	0.33	0.887	
	T2	1.33	0.42	0.113	

SD, standard deviation; SE, standard error; T0, baseline; T1, 4 weeks of treatment; T2, 12 weeks of treatment; NS, not significant.

depression (Detke, *et al*., 2002; Nemeroff, *et al*., 2002; Goldstein, *et al*., 2004; Hirshfeld, *et al*., 2005; Brannan, *et al*., 2005; Perahia, *et al*., 2006; Brecht, *et al*., 2007; Dunner, *et al*., 2008; Hudson, *et al*., 2007; Wohlreich, *et al*., 2007; Raskin, *et al*., 2008). Although data concerning duloxetine in BPD treatment are not available, the other SNRI venlafaxine was found to be effective on somatic complaints of patients with BPD rated with HSCL-90 (Markovitz and Wagner, 1995).

The improvement of overall psychopathology is concordant with previous data concerning SSRIs and venlafaxine in the treatment of BPD (Norden, 1989; Markovitz, 1990; Teicher, *et al*., 1990; Cornelius, *et al*., 1991; Kavoussi, *et al*., 1994; Salzman, *et al*., 1995; Markovitz, 1995; Markovitz and Wagner, 1995; Coccaro and Kavoussi, 1997; Rinne, *et al*., 2002).

The mean change of little more than two points on the HAM-D score is statistically significant, but clinically meaningless. The mean increase of 13 points on the SOFAS, from 33 to 46, indicates a considerable improvement of social, occupational or school functioning, although a serious impairment in these areas is still present after treatment.

Results of our study were obtained by using a single dosage of 60 mg once daily. This is the dose of duloxetine administered in several studies of major depressive disorder. However, other studies have used higher doses up to 120 mg/day. Maybe higher doses of duloxetine have a better efficacy in patients with BPD.

Concerning tolerability, more common adverse effects in our patients were headache and nausea, followed by gastrointestinal disturbances, dizziness and insomnia. No drop-outs were due to side effects. These results on adverse effects replicate previous data concerning duloxetine in patients with major depressive disorder (Nemeroff, *et al*., 2002; Brecht, *et al*., 2007; Hudson, *et al*., 2007; Raskin, *et al*., 2008; Dunner, *et al*., 2008)

Table 3 Results of the analysis of variance for repeated measures performed with the rating scales for psychiatric symptoms and social functioning in 14 patients who completed 12 weeks of treatment with duloxetine

Measure		Mean score	SD	SE	*P*
CGI-Severity item	T0	4.44	0.52	0.176	0.002
	T1	4	0.71	0.236	
	T2	3.33	0.50	0.167	
BPRS	T0	42.55	4.88	1.163	0.001
	T1	37.89	4.28	1.429	
	T2	33.44	4.33	1.444	
HAM-A	T0	13	1.73	0.577	NS
	T1	11	1.12	0.373	
	T2	9.44	1.24	0.412	
HAM-D	T0	13.11	1.90	0.633	0.035
	T1	12.44	2.01	0.669	
	T2	10.78	1.56	0.521	
SOFAS	T0	33.11	6.29	2.098	0.0005
	T1	41.33	5.07	1.691	
	T2	46.11	3.79	1.263	

SD, standard deviation; SE, standard error; CGI, Clinical Global Impression; BPRS, Brief Psychiatric Rating Scale; HAM-A, Hamilton Rating Scale for Anxiety; HAM-D, Hamilton Rating Scale for Depression; SOFAS, Social and Occupational Functioning Assessment Scale; T0, baseline; T1, 4 weeks of treatment; T2, 12 weeks of treatment; NS, not significant.

and are similar to data on venlafaxine tolerability in BPD (Markovitz and Wagner, 1995). Findings of our study represent an initial indication that duloxetine is a safe and well-tolerated agent in patients with BPD, too.

The drop-out rate of about 22% is good for a 12 weeks trial in patients with BPD. For example, it is approximately the same than Van den Eynde, *et al.* (2008) found in a recent 12 weeks study of quetiapine in 41 patients with BPD. A good rate of drop-outs may represent an indicator of efficacy and tolerability of duloxetine treatment.

In conclusion, results of this pilot study in a small sample of patients can be considered an initial evidence that duloxetine is an effective treatment for BPD. In particular, it can play a significant role when patients exhibit high levels of impulsive behavioural symptoms, affective instability and/or somatic complaints. The favourable data on adverse effects emerging from our cases needs to be confirmed in larger populations. If replicated, the good tolerability profile could contribute to improve compliance in patients with BPD, who need long-term therapy and frequently show poor adherence to treatments. For the present, the lack of published investigations concerning duloxetine in the treatment of BPD does not allow a reliable comparison of data concerning either efficacy or tolerability.

Limitations of our study are the small sample size, the lack of a double-blind controlled design and the use of a single dosage of 60 mg/day of duloxetine. However, this pilot study is aimed to provide initial data on the use of duloxetine in patients with BPD and to encourage controlled investigations in larger clinical populations.

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