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**Combined treatment of borderline personality disorder with interpersonal psychotherapy and pharmacotherapy: predictors of response**

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## **Highlights**

Predictors of response to combination of fluoxetine and interpersonal therapy in BPD.

Severity of BPD and specific core symptoms are predictors of response.

Clinical response is not related to general psychopathology.

Response is not associated with symptoms of depression and anxiety.

## **Abstract**

**Objective:** borderline personality disorder (BPD) is characterized by affective instability, impulsive behaviors, and disturbed interpersonal relationships. A previous study of our group found that combined therapy with interpersonal psychotherapy adapted to BPD (IPT-BPD) and fluoxetine was superior than single pharmacotherapy in BPD patients. The aim of the present study was to examine what clinical factors predicted response to combined therapy in patients evaluated in the previous efficacy study.

**Method:** The subgroup of twenty-seven patients allocated to combined therapy was analysed. Patients were treated for 32 weeks with fluoxetine 20 to 40 mg/day plus IPT-BPD. Patients were assessed at baseline and week 32 with an interview for demographic and clinical variables, CGI-S, HDRS, HARS, SOFAS, BPDSI, and SAT-P. Statistical analysis was performed with multiple regression. The difference of CGI-S score between baseline and week 32 ( $\Delta$  CGI-S) was the dependent variable.

**Results:** Factors significantly and independently related to  $\Delta$  CGI-S were the BPDSI total score and the items abandonment, affective instability, and identity.

**Conclusions:** Patients with more severe BPD psychopathology and with a higher degree of core symptoms such as fear of abandonment, affective instability, and identity disturbance have a better chance to improve with combined therapy with fluoxetine and IPT-BPD.

**Keywords:** interpersonal psychotherapy, fluoxetine, combined therapy, borderline personality disorder, outcome, predictors.

## **1. Introduction**

Borderline personality disorder is a complex and severe mental disorder that is characterized by a pervasive pattern of instability of interpersonal relationships, self-image and emotions, and impulsive behaviors. It affects approximately 1% to 5% of the general population and as many as 25% of psychiatric outpatients (Gunderson and Ridolfi, 2001; Torgersen et al., 2001; Grant et al., 2008; Perroud et al., 2010). The long-standing impairment in functioning and personal distress are extensively documented in BPD. Patients affected by this disorder often require high treatment costs through broad use of psychiatric services (NIMHE, 2003, Ansell et al., 2007), stemming in part from their instability in affect and interpersonal relationships.

In the last two decades a growing number of studies about psychotherapy of BPD have been performed and several treatment models have shown some evidence of efficacy, including mentalization-based therapy (Bateman and Fonagy, 1999; 2008), dialectical behavior therapy (Linehan, 1993; Linehan et al., 1999; 2006; Verheul et al., 2003), cognitive therapy (Davidson et al., 2006), schema-focused therapy (Kellogg and Young, 2006; Giesen-Bloo et al., 2006), and systems training for emotional predictability and problem solving (STEPPS) (Blum et al., 2002). As for transference focused therapy (Clarkin et al., 2007; Yeomans et al., 2007), efficacy in BPD patients can be questioned as results of two controlled trials lead to divergent conclusions (Doering et al., 2010; Giesen-Bloo, 2006). A recent addition to these proposals is represented by interpersonal psychotherapy adapted to BPD (IPT-BPD), an intervention specifically designed for BPD patients to deal with problems in interpersonal contexts (Markowitz, 2005; Markowitz et al., 2006; Bellino et al., 2010).

The standard model of IPT for major depression was modified by Markowitz and colleagues (2005) to address the peculiar characteristics and the complex psychopathology of patients

with BPD. Authors conceptualized BPD as a mood-inflected chronic illness with recurrent outbursts of anger requiring prolonged duration of treatment up to 34 sessions over 8 months, and provided a more flexible setting to handle crises and improve compliance.

This modified version of IPT (IPT-BPD) shows some relevant similarities with other effective psychotherapies, such as a clear treatment framework, attention to affect, focus on treatment relationship, active role of therapist, change-oriented interventions (Weinberg et al., 2011).

Combination of a specific psychotherapy for BPD patients with drug therapy, i.e. serotonergic antidepressants, is common in clinical practice and was recommended as first choice for patients with affective dysregulation and impulsive-behavioral dyscontrol by the American Psychiatric Association treatment guidelines (APA, 2001, 2005). Moreover, there is some evidence that psychotherapy may enhance pharmacotherapy effects (WFSBP, 2007; Lieb 2010; Stoffers 2010).

In a randomized controlled study (Bellino et al., 2010) we compared single pharmacotherapy with fluoxetine 20-40 mg/day and combined therapy with IPT-BPD plus fluoxetine at the same dose in a sample of BPD outpatients with no psychiatric comorbidity. Results highlighted that combined therapy with IPT-BPD was superior than fluoxetine monotherapy with respect to three of the core symptoms of BPD (interpersonal relationships, affective instability, and impulsivity), anxiety symptoms and subjective quality of life (subjective perception of psychological and social functioning). According to these initial results, combination of antidepressants and adapted IPT can be considered as a potentially useful intervention in this clinical population. Nevertheless, the combined approach requires a large investment of clinical and economical resources and it should be targeted on selected patients. The need to provide clear indications for combined therapy can be addressed by investigating clinical predictors of response to this treatment modality.

The aim of the present study was to examine what demographical and clinical characteristics predicted response to combined therapy with IPT-BPD in the sample of BPD patients assessed in our previous study of efficacy (Bellino et al., 2010). Our hypothesis is that the association of the two treatments has more chances to induce a clinical response in patients with specific BPD symptoms, independently of general psychopathology and symptoms of anxiety and depression.

## **2. Methods**

The present study is a further evaluation of the same BPD patients already included in our previous investigation (Bellino et al., 2010). The subgroup of twenty-seven patients randomly allocated to combined therapy with fluoxetine 20 to 40 mg/day plus IPT adapted to BPD was analyzed. Methods concerning trial design, selection and randomization of patients, and assessment instruments were the same.

Participants were enrolled from outpatients attending the Centre for Personality Disorder of Psychiatric Clinic, Department of Neuroscience, University of Turin, Italy, from January to December 2007. Consecutive outpatients who received a DSM-IV-TR diagnosis of BPD were included. Exclusion criteria were: a lifetime diagnosis of delirium, dementia, amnesic disorder, or other cognitive disorders; schizophrenia or other psychotic disorders; bipolar disorder; a concomitant diagnosis of any Axis I or II disorder. Diagnoses were made by an expert clinician and were confirmed using the Structured Clinical Interview for DSM-IV Axis I or II disorders (First et al., 1997a, 1997b). Patients of childbearing age were excluded if they were not using an adequate method of birth control according to the judgment of the clinician. Patients were also excluded if receiving psychotropic drugs in the last 2 months and (or) psychotherapy in the last 6 months. The study was approved by the Ethical Committee of our

University Hospital. Written informed consent was obtained from all patients prior to their participation. Declaration of Helsinki guidelines were followed.

Patients analysed in the present study were those treated with fluoxetine 20 to 40 mg per day associated with IPT-BPD. Psychotherapy was provided by a therapist who was not the psychiatrist prescribing medication and who had at least 5 years of experience practicing IPT. Sessions of psychotherapy were steadily supervised by a senior psychotherapist (S.B.) with particular attention to check for fidelity to the manual. Pharmacotherapy and psychotherapy were started at the same time and lasted 32 weeks. Thirty-four sessions of IPT-BPD were provided.

Patients were assessed at baseline and week 32 with the following instruments: a semi-structured interview for clinical and demographical characteristics; the severity item of the Clinical Global Impression scale (CGI-S) (Guy, 1976); the Hamilton scales for depressive and anxious symptoms (HDRS, HARS) (Hamilton, 1959, 1960); the Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992); the Satisfaction Profile (SAT-P) (Majani and Callegari, 1998); the Borderline Personality Disorder Severity Index (BPDSI) (Arntz et al., 2003).

The CGI is a clinician-rated instrument to make global assessment of illness and consists of three different measures: severity of illness, global improvement, and efficacy index (comparison between patient's baseline condition and a ratio of current therapeutic benefit and severity of side effects). In this study, we considered the first scale: severity of illness. It is a 7-point scale that requires the clinician to rate the severity of illness at the time of assessment: (1) normal, (2), borderline mentally ill, (3) mildly ill, (4) moderately ill, (5) markedly ill, (6) severely ill, (7) extremely ill.

The HDRS is a clinician-rated scale that scores severity of 21 depressive symptoms in the last week. Items are variably scored 0-2, 0-3, or 0-4, with a total score ranging from 0 to 64. Higher scores indicate more severe symptoms of depression.

The HARS is a clinician-rated scale scoring severity of 14 symptoms of anxiety in the last week. Item are all scored 0-4, with a total score ranging from 0 to 56. Higher scores indicate more severe anxiety symptoms.

The SOFAS is a clinician-rated scale to measure a patient's impairment in social and occupational areas. It is independent of the psychiatric diagnosis and the severity of the patient's symptoms. The score is ranged between 0 and 100. Higher scores indicate a better functioning.

The SAT- P is a self-administered questionnaire consisting of 32 scales which provides a satisfaction profile in daily life and can be considered as an indicator of subjective quality of life. The SAT-P considers five different factors: "psychological functioning"; "physical functioning"; "work"; "sleep, food, and free time"; "social functioning". The SAT-P asks the patient to evaluate his satisfaction in the last month for each of the 32 life aspects on a 10 centimeter analogical scale ranging from "extremely dissatisfied" to "extremely satisfied".

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 behavior', 'affective instability', 'emptiness', 'outbursts of anger', 'dissociation and paranoid ideation', and one item scored on a 4-point severity scale, concerning 'identity'.

Response was measured as the change of CGI-S score during the trial period. A comprehensive review of literature was used to identify potential predictors of response. In our study the putative predictors were the following: demographic characteristics (age,

gender, marital status), clinical features (family psychiatric history, baseline global severity of symptoms – CGI-S, baseline severity of depressive and anxious symptoms – HDRS, HARS, baseline severity of BPD symptoms – BPDSI total score and single items), and measures of social functioning (SOFAS) and subjective quality of life (SAT-P five factors).

Statistical analysis was performed with analysis of variance for categorical variables (gender, marital status, previous hospitalization, employment), with linear regression for continuous variables (age, education, baseline CGI-S, HDRS, HARS, SOFAS, BPDSI total score and single items, SAT-P factors). Dependent variable was the difference of CGI-S score between baseline and week 32 ( $\Delta$  CGI-S). All variables that were found significant were included in a multiple regression analysis (stepwise backward). Significance level was  $P \leq 0.05$ .

### **3. Results**

We analyzed data concerning the twenty-seven patients allocated to the arm of combined therapy in our previous study (Bellino et al., 2010). Five drop-outs (18.5% of the initial sample) were due to non-compliance. Twenty-two patients completed the trial (81.5%).

The mean age of the sample was  $26.23 \pm 6.4$  years; the male to female ratio was 8 to 19. Twelve of the 27 patients (44.4%) were married; 16 subjects (59.26%) had a previous hospitalization; 13 patients (48.15%) were employed.

Table 1 reports other demographic and clinical characteristics of the participants.

The statistical analysis of outcome measures was performed on the 22 patients who completed the 32 weeks of treatment. Results of ANOVA calculated for categorical variables did not show any significant differences of mean  $\Delta$  CGI-S between groups. Continuous variables significantly related to  $\Delta$  CGI-S at the linear regression were: SOFAS ( $P=0.043$ ); BPDSI total score ( $P=0.001$ ) and BPDSI domains abandonment ( $P=0,001$ ), affective instability ( $P=0.030$ ),

identity ( $P=0.001$ ), and paranoid ideation/dissociative symptoms ( $P=0.008$ ). At the multiple regression analysis, the following clinical variables were found significantly and independently related to  $\Delta$  CGI-S score: BPD Severity Index total score ( $P=0.028$ ) and BPDSI domains abandonment ( $P=0.001$ ), affective instability ( $P=0.023$ ), and identity ( $P=0.003$ ).

Table 2 and 3 display results of linear regression and multiple regression analysis.

#### **4. Discussion**

The aim of our study was to identify which demographic and clinical factors are predictors of response to combined treatment with the serotonergic antidepressant fluoxetine and IPT adapted to BPD. Our findings indicated that response to combined treatment with fluoxetine and IPT adapted to BPD had a positive relation with the global severity of BPD and the degree of a few core symptoms: fear of abandonment, affective instability and identity disturbance. These results are not easily comparable with those from previous investigations, because predictive factors of response in BPD patients were studied for some models of psychotherapy, but neither for IPT, nor for combined therapy with drugs.

The first clinical implication of our findings is that clinical improvement of our patients did not depend on baseline severity of general symptoms, but was more specifically related to BPD psychopathology. This finding is basically in accordance with several studies in literature (Meares et al., 1999; Giesen-Bloo et al., 2006; Black et al., 2009), indicating that higher pre-treatment severity of BPD predicted greater symptom change with different models of psychotherapies (IPP-Integrative Psychotherapy Practice, Schema-focused therapy, Transference-focused psychotherapy, STEPPS). Some Authors interpreted this result as “a meaningful indication that patients with high symptom severity actually have a great potential

for change and are more likely than others to experience improvement” (Black et al., 2009; Barnicot et al., 2012).

With regard to specific domains of BPD symptoms, a relation with response to combined therapy was found for fear of abandonment.

The intolerance to aloneness in patients affected by BPD is probably linked to the fearful insecure attachment style derived by precocious separation experiences (Masterson, 1976; Gunderson, 1996; Fossati, 2012). Patients with this clinical feature can benefit from combined therapy with IPT, a psychotherapy that provides a well-defined setting, a predictable duration and clear treatment expectations, with a good potential to accommodate their need for safety (Richard-Jodoin, 1989). In addition, IPT adapted to BPD included the opportunity of intersession contacts with therapist (one phone call/week), while combination with antidepressants required the presence of a second clinician who prescribed pharmacotherapy. Both these characteristics of our intervention can contribute to relief abandonment feelings.

In our analysis, another core BPD symptom predicting a better response to combined treatment was identity diffusion. Some Authors in efficacy-studies observed that short-term psychotherapy (in particular dialectical behavioral psychotherapy) can improve identity disturbance in patients affected by BPD enhancing the patient’s sense of self and coherence in their feelings and thoughts (Swann et al., 2003; Lynch et al., 2007; Rowpke et al., 2011). Nevertheless, in contrast with our finding, some therapy-studies showed that BPD patients with severe identity diffusion responded less favourably to psychotherapy than do patients without identity disturbance (Hull et al., 1993; Yen et al., 2009). A possible explanation for this discordance is that our patients were actually treated with a combination of IPT and drugs. We can presume that clinical improvement in patients with more refractory symptoms depends on the mutual reinforcement of the two treatments. BPD patients who were unable to

develop a stable and cohesive sense of self are burdened by a precarious e troubled worldview in the context of interpersonal interactions. So, a model of psychotherapy focused on interpersonal problems, like IPT, encourages the person to establish more balanced, realistic, and intimate relationships, resulting in a more coherent sense of self.

We also found that affective dysregulation was associated with a good response to combined therapy. A few previous studies investigated affective instability among predictors of treatment outcome in BPD obtaining mixed and controversial findings (Lieb et al., 2004; Robins and Chapman, 2004). Bohus and colleagues (2004) and Meehan (2008) showed that higher level of pre-treatment affective instability, particularly expressed by outbursts of anger, predicted greater symptom change after treatment. On the contrary, Yen and colleagues (2009) in their predictor analysis did not find significant association between affective dysregulation at baseline and treatment outcome. According to the American Psychiatric Association guidelines, pharmacotherapy combined to psychotherapy has an important adjunctive role for diminution of affective instability (APA, 2005).

It is interesting to notice that no demographic variables (age, gender, marital status) had significant effects on clinical improvement in our patients. This data confirm previous findings summarized in a recent review by Barnicot et al. (2012).

The present study suffered from some limitations. The small sample size precluded fine-grained evaluation of various factors. Another limit was that potentially important variables were not evaluated: e.g. childhood trauma, therapeutic alliance, treatment process in psychotherapy. The exclusion of patients with Axis I and II psychiatric comorbidity implies that clinical characteristics of our BPD patients can be partly different from clinical practice and affects generalizability of our findings. On the other hand, the inclusion of BPD patients with concomitant psychiatric disorders could affect clinical characteristics and response to

treatment. So, this is a key issue in selection of patients for clinical trials. The fourth limit was that assessment instruments did not include a scale designed to evaluate the specific mechanisms of action of IPT-BPD. In addition, as more than twenty variables were examined as potential predictors, type I statistical errors can occur. However, only six variables that were found significant at the linear regression were include in the multiple regression model. At last, intention-to-treat analysis was not considered neither in the efficacy trial (Bellino et al, 2010), nor in the present study.

In conclusion, our study is an initial investigation aimed to identify what clinical characteristics of patients with BPD predicted response to a combined treatment with adapted IPT and fluoxetine. Patients with more severe global BPD symptoms and with higher degree of fear of abandonment, affective instability and disturbance of personal identity were found to present a better response. These results represent a preliminary confirm of our hypothesis. Research in this field has major clinical implications, contributing to design more specific treatment guidelines for homogeneous groups of BPD patients. Further investigations are required to replicate our results in larger samples.

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Table 1. Baseline demographical and clinical characteristics of the sample of 27 BPD patients allocated to combined therapy with fluoxetine 20 to 40 mg/day and IPT-BPD. Continuous variables.

Variable	Mean	SD
Age	26.23	6.4
Education, years	12.35	4.4
CGI-S	5.43	0.5
HARS	12.22	2.2
HDRS	13.12	1.9
SOFAS	33.87	7.5
BPDSI total score	45.14	5.6
BPDSI interpersonal relationships	7.87	0.64
BPDSI impulsivity	7.17	0.87
BPDSI affective instability	7.4	1.14
BPDSI abandonment	6.56	1.61
BPDSI parasuicidal behavior	2.17	2.18
BPDSI paranoid ideation	5.00	2.14
BPDSI outburst of anger	7.2	0.756
BPDSI emptiness	7.46	0.44
BPDSI identity	2.48	0.92
SAT-P psychological functioning	41.13	5.07
SAT-P social functioning	49.97	8.81
SAT-P physical functioning	29.69	4.2

SAT-P work	34.69	6.83
SAT-P sleep, food, and free time	41.56	6.65

Table 2. Results of linear regression in the sample of 22 BPD patients who completed the combined therapy with fluoxetine 20 to 40 mg/day and IPT-BPD. The difference of CGI-S score between baseline and week 32 ( $\Delta$  CGI-S) was the dependent variable. Significant level was  $P \leq 0.05$ .

Variable	Coefficient	SE	t	<i>P</i>
Age	- 0.207	0.062	- 1.160	0.255
CGI-S	- 0.273	0.353	- 1.553	0.131
HARS	0.057	0.085	0.310	0.758
HDRS	0.095	0.097	0.520	0.607
SOFAS	- 0.360	0.023	- 2.111	0.043
BPDSI total score	0.618	0.026	4.308	0.001
BPDSI interpersonal relationships	0.110	0.285	0.607	0.548
BPDSI impulsivity	- 0.285	0.200	- 1.630	0.114
BPDSI affective instability	0.384	0.150	2.280	0.030
BPDSI abandonment	0.547	0.096	3.583	0.001
BPDSI parasuicidal behavior	- 0.187	0.083	- 1.045	0.304
BPDSI paranoid ideation	- 0.458	0.077	- 2.823	0.008
BPDSI outburst of anger	0.008	0.244	0.046	0.963
BPDSI emptiness	- 0.203	0.413	- 1.134	0.266
BPDSI identity	0.614	0.158	4.261	0.001
SAT-P psychological functioning	0.198	0.036	1.104	0.279
SAT-P social functioning	0.023	0.021	0.127	0.900
SAT-P physical functioning	0.121	0.044	0.668	0.509

SAT-P work	0.066	0.027	0.360	0.721
SAT-P sleep, food, and free time	0.262	0.027	1.488	0.147

Table 3. Results of multiple regression analysis (stepwise backward) in the sample of 22 BPD patients who completed the combined therapy with fluoxetine 20 to 40 mg/day and IPT-BPD. The difference of CGI-S score between baseline and week 32 ( $\Delta$  CGI-S) was the dependent variable. Significant level was  $P \leq 0.05$ .

Variable	Coefficient	SE	t	<i>P</i>
BPDSI total score	0.222	0.017	2.334	0.028
Fear of abandonment	0.452	0.058	4.914	0.001
Affective instability	0.242	0.089	2.422	0.023
Identity	0.307	0.103	3.259	0.003

