Combined therapy with interpersonal psychotherapy adapted for borderline personality disorder: A two-years follow-up

Combined therapy with interpersonal psychotherapy adapted for borderline personality disorder: a two-years follow-up

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Highlights

- IPT- BPD plus drug was superior to single drug after 32 weeks trial.
- Difference persisted at 24 months follow-up for impulsivity and relationships.
- It also persisted for perception of psychological and social functioning.
- Differences concerning anxiety and affective instability were lost after 6 months.
- The most of benefits of combining IPT-BPD endured two years after termination.

Abstract

Few investigations evaluated the long-term effects of psychotherapies in borderline personality disorder (BPD). In a previous study, we compared efficacy of combination of fluoxetine and interpersonal psychotherapy adapted to BPD (IPT-BPD) versus single fluoxetine administered for 32 weeks. This study is aimed to investigate whether the results obtained with the addition of IPT-BPD persist during a follow-up period. Forty-four patients who completed the 32 weeks trial underwent 24 months of follow-up receiving fluoxetine 20-40 mg/day. Clinical Global Impression Severity (CGI-S), Hamilton Rating Scales for Depression and Anxiety (HDRS, HARS), Social and Occupational Functioning Assessment Scale (SOFAS), Satisfaction Profile (SAT-P), and Borderline Personality Disorder Severity Index (BPDSI) were repeated at 6, 12, and 24 months. Statistical analysis was performed with the general linear model. Results showed that most of the differences between combined therapy and single pharmacotherapy at the end of the 32 weeks trial were maintained after 24 months follow-up. The addition of IPT-BPD to medication produced greater effects on BPD symptoms (impulsivity and interpersonal relationships) and quality of life (perception of psychological and social functioning) that endured after termination of psychotherapy. On the contrary, different effects on anxiety symptoms and affective instability were lost after 6 months.

Key words

Interpersonal psychotherapy, combined therapy, borderline personality disorder, efficacy, long-term treatment, follow-up

1. Introduction

Borderline personality disorder (BPD) is a severe and complex mental disorder that encompasses pervasive dysfunctional patterns of experience and behavior. Patients with BPD are characterized by instability in affects and interpersonal relationships, impulsive behavioral dyscontrol, transient stress-related cognitive-perceptual symptoms and low level of identity integration (Gunderson, 2001; Skodol, 2005; Gabbard, 2014). A common feature of BPD subjects is the tendency to be poorly adherent to treatments and to discontinue the therapeutic programme in early phases. Difficulties in obtaining patients' compliance and relatively high rates of drop-out may partially explain the paucity of studies that investigate long-term efficacy of therapeutic interventions in this mental disorder (Gunderson, 2001; Gunderson et al., 2005; Bender, 2005; Gabbard, 2014).

In accordance with the results of systematic reviews and treatment guidelines for the management of BPD, options to treat this disorder include both pharmacotherapy and psychotherapy (American Psychiatric Association, 2001; Oldham, 2005; NICE, 2009; NHMRC, 2012; Stoffers et al, 2012) and combination of them can be considered a valid approach in treating this clinical population (American Psychiatric Association, 2001; Oldham, 2005). Some authors suggested that psychotherapy may enhance pharmacotherapy effects, although it remains unclear how this treatments actually interact (Lieb et al, 2010). To date, psychotherapy models more extensively studied in BPD as single or combined treatment are: dialectical behavioral therapy (Linehan, 1993; Linehan et al., 1999, 2006; Verheul et al, 2003), followed by mentalisation-based treatment (Bateman and Fonagy, 1999, 2008), transference-focused psychotherapy (Clarkin et al., 2006), cognitive therapy (Davidson et al.,2006), schema-focused therapy (Kellogg and Young, 2006; Giensen-Bloo et al., 2006), and system training for emotional predictability and problem solving (STEPPS) (Blum et al., 2002). In recent years, interpersonal psychotherapy modified for BPD patients (IPT-BPD) was added to the other specific models of psychotherapy. IPT adapted for BPD was derived from the standard model of IPT for major depression initially developed by Klerman and colleagues (1984) and was designed by Markowitz (2005) to address the peculiar features of BPD and to deal with difficulties in interpersonal relationships experienced by these patients. The adaptation included noticeable changes in methods and techniques of IPT: a different conceptualization of the disorder was proposed (BPD was defined as a mood-inflected chronic illness similar to dysthymic disorder, but with sporadic outbursts of anger); length of treatment was prolonged (up to 34 IPT sessions over 8 months, with an acute phase of 18 IPT

sessions to establish a therapeutic alliance and a continuation phase of 16 sessions to develop more adaptive interpersonal relationships); flexibility of setting was enhanced (a 10-minute telephone contact once a week was provided) to handle crises and minimize the risk of therapeutic ruptures.

Although several studies have established the efficacy of different psychotherapies of BPD at the end of short-term trials, only few investigations have evaluated the long-term effects of these treatments (Bateman and Fonagy, 2001, 2008; Fassbinder et al., 2007; McMain et al, 2012). In the majority of these studies the duration of follow-up has been shorter than one year (Linehan et al, 1993, 1999, 2002, 2006; van den Bosh et al, 2005).

In the case of IPT adapted to BPD no trials are available considering long-term follow-up either of single psychotherapy or combined therapy. Favourable data supporting the long-term efficacy of IPT derived from follow-up studies of IPT or therapy combining IPT and pharmacotherapy that were performed in other mental disorders, such as major depression of adolescents (Young et al, 2006,2010; Jacobsen et al, 2012; Zhou et al, 2015) and adults (Schramm et al, 2008; Zobel et al., 2011; Toth et al., 2013; Lemmens et al, 2015), perinatal depression (Brandon et al., 2012; Reay et al., 2012), dysthymia (Browne et al., 2002), and eating disorders (Wilfley et al., 2002; Carter et al., 2011; Hilbert et al., 2012).

In a randomized controlled study (Bellino et al., 2010, 2015) we compared efficacy of combined therapy with IPT-BPD and fluoxetine (20-40 mg/day) versus single fluoxetine (20-40 mg/day) for 32 weeks in a group of BPD patients without concomitant psychiatric comorbidity and we analysed clinical predictors of response to combined therapy. At the end of the trial, combined therapy was found significantly superior to single fluoxetine in decreasing severity of three symptoms of BPD (disturbance of interpersonal relationships - P=0.009, affective instability - P=0.02, and impulsivity - P=0.01), anxiety (HARS - P=0.006), and two factors of subjective quality of life (subjective perception of psychological functioning - P=0.003 - and social functioning - P=0.008).

In the present study we prospectively investigate whether the differences of efficacy of combined therapy with IPT-BPD and fluoxetine versus single fluoxetine registered at 32 weeks were maintained during a follow-up period of 2 years.

2. Methods

2.1. Procedure

The present study is the follow-up of a 32 weeks controlled trial, that was published in 2010 (Bellino et al., 2010). Methods concerning design, procedures, selection and randomization of patients, and evaluation tools in the short-term trial were described in detail in our previous article.

In the original study, 55 consecutive outpatients meeting DSM-IV-TR criteria for BPD were enrolled from subjects attending the Center for Personality Disorder of the Psychiatric Clinic, Department of Neurosciences, University of Turin, Italy, from January to December 2007. People with a lifetime diagnosis of delirium, dementia, amnestic disorder, or other cognitive disorders; schizophrenia or other psychotic disorders; bipolar disorder; and patients with a concomitant diagnoses of Axis I or II disorders were excluded. Patients of childbearing age were excluded if they were not using an adequate method of birth control, in accordance with the judgment of the clinician. Patients that received psychotropic drugs in the last 2 months and (or) psychotherapy in the last 6 months were also excluded. Diagnoses were made by an expert clinician and were confirmed using the Structured Clinical Interview for DSM-IV Axis I and II disorders (First et al., 1997a, 1997b).Written Informed consent was acquired from all subjects before their participation. Declaration of Helsinki guidelines were followed and the Ethical Committee approval was obtained.

2.2. Treatment

In the initial 32 weeks trial, patients were randomly allocated to two treatments: (1) 28 patients received fluoxetine (20-40 mg/day) plus clinical management; (2) 27 patients received fluoxetine (20-40 mg/day) plus IPT-BPD. Randomization was performed using the web program Research Randomizer version 3.0 (Urbaniak and Plous, Social Psychology Network, Wesleyan University, Middletown, CT). Pharmacotherapy and psychotherapy started at the same time. Psychotherapy was provided by two therapists who were not the psychiatrist prescribing medication and who had at least 5 years of experience practicing IPT. The two psychotherapists treated respectively 14 and 13 subjects. Therapists in both treatment arms were well experienced in the management of borderline personality disorder. Sessions of psychotherapy were supervised twice per month by a senior psychotherapist (S.B.) checking for the fidelity to manual. Thirty-four sessions of IPT-BPD were provided.

Forty-four patients who completed the 32 weeks trial (22 who received combined therapy and 22 who received single antidepressant) underwent 24 months of follow-up. All subjects received single pharmacotherapy with fluoxetine (20-40 mg/day) during the follow-up period.

2.3 Measurement

Clinical assessment was repeated at 6, 12, and 24 months of follow-up. This study used the same evaluation instruments as the original investigation: 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). Some of these instruments (CGI-S, HDRS, HARS, SOFAS, and BPDSI) were administered by a single clinician with a long experience in rating scales, who was not the same clinician who made the diagnosis and was not involved in the treatment procedures. All these characteristics of the assessor were required in order to obtain a higher reliability and to avoid any interference between assessment and treatment.

The CGI is a clinician-rated scale for the 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 that consist of 32 scales providing 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 symptoms. This instrument 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’.

2.4 Statistical analysis

Statistical analysis was performed with the univariate general linear model to calculate the effects of two factors, (1) duration of follow-up and (2) type of treatment administered in the 32 weeks trial, on each evaluation scale that had shown a significantly better improvement with combined therapy compared with single pharmacotherapy after 32 weeks. Analysis was performed on data collected at 24 months of follow-up. If at 24 months the effect of treatment type was no longer significant, analysis was repeated for data obtained at 6 and 12 months, in order to establish when the difference of effects between treatments was lost. Significance level was $P \leq 0.05$.

3. Results

During the follow-up study, the group of 22 patients who had previously been treated with combined therapy received a mean ± SD dose of fluoxetine of 32.2 ± 5.3 mg/day , the group of 22 patients who had previously been treated with single fluoxetine received a mean ± SD dose of fluoxetine of 33.1 ± 6.1 mg/day. Fourteen patients of the initial group of 44 BPD subjects (31.8%) dropped out, 8 (18.2%) in the first 6 months of follow-up, 2 (4.6%) in the following 6 months, and 4 (9.1%) in the last 12 months. Of the 30 patients who completed all the three follow-up assessments, 14 (46.6%) subjects had received single pharmacotherapy in the 32 weeks original study, while 16 (53.4%) subjects had been treated with combined therapy. No significant difference of drop-out rate was found between the two treatment groups during follow-up and participants attended an average of 2.60 of three evaluations (SD=0.78). Forty-four patients who entered follow-up were 13 (29.5%) males and 31 (70.5%) females, with a mean age of 26.9±5.1. Demographic and clinical characteristics of the two

groups of patients at the beginning of follow-up are reported in Table 1. No significant differences of baseline characteristics were found between the two groups with t-test and chi-square test.

Statistical analysis was performed in the 30 patients who completed the 24 months of follow-up with the univariate GLM to calculate the effects of the two factors "follow-up duration" and "treatment type in the 32 weeks trial". The object was to investigate which differences between combined therapy and single pharmacotherapy after 32-weeks were maintained during the two-years follow-up.

Similar findings were obtained with the univariate GLM for two scales: the HARS and the BPDSI item "affective instability". At the end of the 32 weeks trial both duration and treatment type showed a significant effect on the HARS score ($P<0.001$ and $P=0.006$) and on the item "affective instability" ($P<0.001$ and $P=0.02$). In both cases, no significant effect was found at the end of the 24 months follow-up. It means that the two scales did not have further changes during the follow-up period and the advantage of combined therapy was not maintained. In order to evaluate whether the advantage of combined therapy was still present for the two scales after 6 and 12 months of follow up, results of the ANOVA calculated for these two time intervals were analysed. The effect of both duration and treatment type were still significant at 6 months for the HARS ($P = 0.01$; $P = 0.03$) and for the item "affective instability" ($P = 0.01$; $P = 0.03$). Significant effects were lost for both duration and treatment type and for both HARS and "affective instability" at 12 months (HARS: $P = 0.09$; $P = 0.07$. "Affective instability": $P = 0.07$; $P = 0.08$) (Tables 2 and 4).

Different results were found with the univariate GLM for the two BPDSI items "impulsivity" and "interpersonal relationships" and for the two SAT-P factors "psychological functioning" and "social functioning". The significant effect of treatment duration observed after 32 weeks of treatment (in all cases $P=0.001$) was lost after follow-up for all the four scales. On the contrary, the effect of treatment type was significant in all cases both at the end of the 32 weeks treatment (impulsivity $P=0.01$, interpersonal relationships $P=0.009$, psychological functioning $P=0.003$, and social functioning $P=0.008$) and at the end of the 24 months follow-up (impulsivity $P<0.001$, interpersonal relationships $P=0.005$, psychological functioning $P=0.002$, and social functioning $P=0.001$). It means that the two BPDSI items and the two SAT-P factors did not present any further change during follow-up, but the better results produced by combined therapy persisted. (Table 3 and 4).

4. Discussion

As BPD is a chronic and lifelong disorder, one of the most important criteria for evaluating the efficacy of treatments is the long-term outcome. For this reason, our study is aimed to verify whether the benefits from the addition of interpersonal psychotherapy to pharmacotherapy after 32 weeks of treatment persist during a follow-up period of two years after termination of psychotherapy.

Unfortunately, it is not possible to compare the results of this study with previous follow-up studies of combined therapy with interpersonal psychotherapy plus pharmacotherapy in BPD patients. To our knowledge, this is the first trial addressing this topic.

In the original short-term study, after 32 weeks of treatment the two alternative treatments, fluoxetine plus IPT-BPD versus fluoxetine plus clinical management, were found both efficacious in BPD patients with some significant differences in favor of combined therapy. In particular, combination of IPT-BPD and pharmacotherapy was more efficacious than single pharmacotherapy in reducing severity of anxious symptoms, in improving subjective perception of psychological and social functioning, and in treating three BPD symptom domains: impulsive behavioral dyscontrol, affective instability, and interpersonal relationships.

The results of the follow-up evaluation indicated that patients initially treated with combined therapy maintained significant advantages over controls in some BPD core symptoms and domains of subjective quality of life during the 24 months follow-up. In particular, the superior results produced by combined therapy after 32 weeks on symptoms of impulsivity and interpersonal relationships, and on quality of psychological and social functioning were still measured two years after termination of psychotherapy. On the contrary, the advantage of combined therapy in terms of improvement of anxiety and affective instability was not replicated at follow-up. More exactly, it was still significant after 6 months of follow up, but it was lost at the 12 months assessment.

Considering these results, we can suggest that a psychotherapy specifically adapted for BPD patients, such as IPT-BPD, has a positive impact on core BPD symptoms and patients' functioning that endures for a long period after its termination. In fact, IPT-BPD is a model of psychotherapy that is aimed to improve BPD psychopathology by a modification of dysfunctional interpersonal patterns. In addition, better skills to organize interpersonal relationships obtained with this therapy are expected to promote a more stable social environment and consequently a more successful control of impulsive reactions. So,

impulsive behavioral dyscontrol and instability in interpersonal relationships can be significantly affected and persistently improved a long time after concluding the psychotherapeutic intervention.

Our BPD patients experienced also a long-lasting improvement of two key factors of quality of life, subjective perception of psychological and social functioning. This finding is consistent with a previous study of long-term effects of psychotherapy in patients with personality disorders (Antonsen et al., 2014).

Two significant effects of type of treatment after 32 weeks, concerning severity of anxiety and level of affective instability, were no longer present at two-years follow-up. Both results are not easy to explain due to the lack of previous comparable findings. A hypothesis that can only be suggested for further evaluation is that the additional effects of psychotherapy on anxiety and affective symptoms are transient products of non-specific factors, related to the supportive action of therapeutic relationship, and are lost with the end of this relationship. In order to test this hypothesis, it would be interesting to investigate whether once-per-month sessions of non-specific supportive intervention during the follow-up period could succeed in maintaining the superior effects of combined therapy on anxiety symptoms and affective instability.

The strengths of the present study are the randomized controlled design and the extended period of follow-up evaluation. We used both self-evaluated and clinician-rated instruments to obtain a more reliable assessment. Moreover, patients who completed the follow-up period were 68.2% of the initial sample, which can be considered an acceptable proportion.

On the other hand, our findings are affected by some limitations. The first limit concerns the relatively small size of the clinical sample. A second limitation is possibly due to the exclusion of psychiatric comorbidities. In fact, this choice allows to avoid the effects of coexisting disorders on treatment response, but has the consequence that clinical characteristics of our patients are partly different from those found in clinical practice and can limit generalizability of findings. Other limits were that session adherence to IPT-BPD and medication compliance were not assessed.

In conclusion, results of this study showed that a large part of the differences between combined therapy and single pharmacotherapy registered in BPD patients at the end of a 32 weeks trial were maintained after 24 months of follow-up. The addition of interpersonal psychotherapy to the antidepressant produced greater effects on some BPD core symptoms

and some factors of quality of life that endured for two years after that psychotherapy terminated and all patients continued to receive only medication.
Further investigations are needed to replicate these initial findings, considering the paucity of available data and the relevance of this topic for clinical practice.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Table 1. Demographic and baseline clinical characteristics of the sample of 44 BPD patients who entered the 24 months follow-up study.

Parameter	Pharmacotherapy (n=22)	Combined therapy (n=22)
Age (mean ± SD), years	26.7 ± 5.3	26.23 ± 6.4
Gender (female), n (%)	16 (72.7%)	15 (68.2%)
Marital status (married), n (%)	11 (50%)	14 (63.6%)
Employment (employed), n (%)	9 (40.9%)	8 (36.4%)
Education (mean ± SD), years	12.74 ± 4.8	12.32 ± 5.3
Previous hospitalization, n (%)	14 (63.6%)	16 (72.7%)

SD = standard deviation.

Table 2. Results of univariate GLM for anxiety symptoms measured with HARS.

Scale	Treatment	Baseline (end of 32 weeks trial, T0) Mean ± SD	Results of 32 weeks trial	6 months (T1) Mean ± SD	12 months (T2) Mean ± SD	24 months (T3) Mean ± SD	Results of 24 months follow-up
HARS	Fluoxetine + Clinical management	9.82±1.29	**T** F=60.66 df=2 *P*< 0.001	9.85±2.4	9.92 ± 2.7	10.02±3.2	**T** F=56.43 df=3 *P*=0.12
	Fluoxetine + IPT	9.03±1.67	**tr** F=7.86 df=1 *P*=0.006	9.68±2.8	9.79 ± 3.1	9.89±3.5	**tr** F=4.82 df=1 *P*=0.09
			Txtr F=0.14 df=2 *P*=0.87				**Txtr** F=0.17 df=3 *P*=0.82

(T): time; (tr): treatment.

Table 3. Results of univariate GLM for factors of subjective quality of life (SAT-P).

Factor	Treatment	Baseline (end of 32 weeks trial, T0) Mean ± SD	Results of 32 weeks trial	6 months (T1) Mean ± SD	12 months (T2) Mean ± SD	24 months (T3) Mean ± SD	Results of 24 months follow-up
Psychological functioning	Fluoxetine + Clinical management Fluoxetine + IPT	59.71±10.8 60.31±15	**T** F=60.59 df=2 *P*< 0.001 **tr** F=9.17 df=1 *P*=0.003 **Txtr** F=4.49 df=2 *P*=0.012	60.11±10.4 60.53±14.8	59.31 ±10.9 62.4 ± 13.7	59.69±10.9 62.81±13.5	**T** F=57.72 df=3 *P*=0.08 **tr** F=10.25 df=1 *P*=0.002 **Txtr** T=3.91 df=3 *P*= 0.03
Social functioning	Fluoxetine + Clinical management Fluoxetine + IPT	56.97±11.99 67.35±14.59	**T** F=11.76 df=2 *P*< 0.001 **tr** F=5.54 df=1 *P*=0.008 **Txtr** F=4.59 df=2 *P*=0.03	55.60±12.4 67.99±14.45	56.53±12.1 70.12±13.2	55.32±12 70±13.1	**T** F=8.93 df=3 *P*=0.1 **tr** F=7.32 df=1 *P*=0.001 **Txtr** F=5.22 df=3 *P*=0.01

(T): time; (tr): treatment.

Table 4. Results of univariate GLM for items of BPDSI.

Item	Treatment	Baseline (end of 32 weeks trial, T0) Mean ± SD	Results of 32 weeks trial *P*	6 months (T1) Mean ± SD	12 months (T2) Mean ± SD	24 months (T3) Mean ± SD	Results of 24 months follow-up *P*
Interpersonal relationships	Fluoxetine + Clinical management Fluoxetine + IPT	6.97±1.30 5.83±1.42	**T** F=21.17 df=2 *P*< 0.001 **tr** F=7.07 df=1 *P*=0.009 **Txtr** F=7.85 df=2 *P*=0.001	7.03±1.24 5.03±1.51	7.01 ±1.26 5.45 ± 1.99	7.20±1.15 5.72±2.01	**T** F=3.77 df=3 *P*=0.15 **tr** F=8.12 df=1 *P*=0.005 **Txtr** F=1.82 df=3 *P*= 0.42
Impulsivity	Fluoxetine + Clinical management Fluoxetine + IPT	6.26±1.12 5.23±1.11	**T** F=25.37 df=2 P< 0.001 **tr** F=6.78 df=1 *P*=0.01 **Txtr** F=10.33 df=2	6.20±1.16 5.10±1.21	6.05±1.22 4.95±1.45	5.98±1.26 4.89±1.52	**T** F=4.61 df=3 *P*=0.1 **tr** F=9.23 df=1 *P*<0.001 **Txtr** F=2.54 df=3

			P<0.001				*P*=0.31
Affective Instability	Fluoxetine + Clinical management	6.63±0.99	**T** F=16.70 df=2 *P*< 0.001	6.42±1.01	6.38±1.12	6.40±1.10	**T** F=14.75 df=3 *P*=0.09
	Fluoxetine + IPT	5.61±1.18	**tr** F=5.81 df=1 *P*=0.02	5.96±0.90	5.99±0.88	6.06±1.22	**tr** F=1.91 df=1 *P*=0.1
			Txtr F=5.07 df=2 *P*=0.007				**Txtr** F=1.09 df=3 *P*=0.2

(T): time; (tr): treatment.