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EMPIRICAL PAPER

The efficacy of long-term psychodynamic psychotherapy, fluoxetine and their combination in the outpatient treatment of depression

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Abstract
Objective: There are few randomized controlled trials examining the efficacy of long-term psychodynamic psychotherapy (LTPP) in depression treatment. LTPP was compared with fluoxetine treatment and their combination; **Methods:** 272 depressed patients (aged 26–34, 72% with a first episode of depression) were randomized to receive LTPP (one session/week), fluoxetine treatment (20–60 mg/day) or their combination for 24 months. Beck Depression Inventory (BDI) was the outcome measure. The psychotherapy was not manualized and the treatment took place under real-life conditions in an outpatient psychiatric clinic. **Results:** Intention-to-treat analyses indicated that all the treatments were associated with significant reductions in the BDI scores (mean reduction of 18.88 BDI points). Furthermore, LTPP and combination therapy were more effective in reducing BDI scores than fluoxetine alone (22.08 and 22.04 vs. 12.53 BDI points). **Conclusions:** LTPP, pharmacological treatment with fluoxetine and their combination are effective in reducing symptoms of patients with moderate depression. LTPP and combined treatment were more effective compared to fluoxetine alone. These findings have implications for patients with depression who may benefit from long-term psychotherapy or combined treatment, or for depressed patients who do not wish to take medications such as fluoxetine.

Keywords: long-term psychodynamic psychotherapy; fluoxetine; depression

Introduction

Depressive disorders are among the most common mental disorders (World Health Organization [WHO], 2009). They are associated with functional disability and personal suffering for patients (Bastos & Trentini, 2013), as well as with a tremendous financial burden to society (WHO, 2009). There are evidence-based treatments for depression, such as medications and psychotherapies (Greenberg & Goldman, 2009). Among them, long-term psychodynamic psychotherapy (LTPP) may have a role to play in depression treatment (Luyten & Blatt, 2012).

However, there are not many prior studies comparing LTPP, medication or their combination in depression treatment. A meta-analysis showed that LTPP treatment resulted in large effect sizes (Cohen's *d* 0.80) for symptom reduction and improvement of social functioning (Leichsenring & Rabung, 2008). These results were based on seven studies, and only four of which were randomized clinical trials. The small number of studies keeps actual efficacy of LTPP for depression treatment still under debate (Berger, Brakemeier, Klesse, & Schramm, 2009; Huber, Henrich, Gastner, & Klug, 2012).

Taylor (2008) pointed out that this debate does not occur with short-term psychodynamic psychotherapy (STPP), which has consistently demonstrated its efficacy in randomized controlled trials. Some studies have suggested that there are no significant differences between STPP and other short-term treatments, like cognitive psychotherapy (Barber, Muran, McCarthy, & Keefe, 2013). However, considering the LTPP-STPP comparison, there is a group of evidences that

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in the long run LTPP tends to be more efficient than STPP (Knekt, Lindfors, Harkanen, et al., 2008; Taylor, 2008). There is also accumulating evidence to suggest that treatments for depression would have to be longer in order to prevent relapse (e.g., Hollon & Ponniah, 2010). Cohort and observational researches also suggest that more durable benefits may relate with longer-term treatments (Beutel & Rasting, 2002; Knekt, Lindfors, Laaksonen et al., 2008; Leichsenring, Biskup, Kreische, & Staats, 2005; Leichsenring & Rabung, 2011; Sandell et al., 2000). These findings suggest rising evidence about LTPP clinical importance and effectiveness in depression treatment.

Huber et al. (2012) compared psychoanalytic, psychodynamic, and cognitive-behavioral therapies for depression treatment in a process-outcome study based on a prospective, quasi-experimental design with a 1-year, 2-year, and 3-year follow-up. The study concluded that the three treatments were all very effective in the treatment of depression. Huber et al. (2012) suggested that patients with depressive disorder could be treated with long-term psychotherapy, in order to prevent relapses and chronicity. Huber and Klug (2006) investigated the effects of long-term psychotherapies in depressed patients. In a prospective, quasi-experimental study, 100 patients were compared pre and post-treatment, followed by a three-year follow-up. They found significant outcome differences between psychodynamic therapy and cognitive-behavioral therapy, and results pointed that psychodynamic therapy showed significantly longer-lasting effects.

Knekt et al. (2013) performed an RCT comparing LTPP and two short-term therapies. They found out that patients suffering from mood and anxiety disorders recovered faster in short-term treatments, but in the long run LTPP achieved greater benefits for the patients (after a 5-year follow-up, patients in this group showed fewer anxiety and depression symptoms, and their work ability improvement rate was higher). Leichsenring et al. (2005), in other study, pointed out that LTPP demonstrated significant and large effect sizes (all > 0.80). In terms of depressive symptoms, at 1-year follow-up, the effect size was 1.38.

Luyten and Blatt (2012), in a literature review about psychodynamic treatment of depression, concluded that the treatment should be included in treatment guidelines for depression. Their argument is that LTPP appears to be more clinically effective and perhaps even more cost effective in the long run. However, they pointed out that, compared with other treatments, the evidence base for LTPP in depression remains relatively small, but that there exists promising growing evidence for its efficacy and effectiveness, and recommended that further studies comparing LTPP and other treatments for depression should be done. Gibbons, Crits-Christoph, and Hearon (2008), in a previous review, reached very similar conclusions.

The growing evidences reported in previous studies about LTPP's efficacy motivate more research. Main benefits of LTPP pointed by literature include, but are not limited to, clinical recovering from mood and anxiety disorders (Knekt et al., 2013), longer-lasting treatment effects (Huber & Klug, 2006), and consequent prevention of relapse and chronicity (Hollon & Ponniah, 2010). Furthermore, there are also some evidences that LTPP can induce neurocognitive gain in depressed patients (e.g., Bastos, Guimarães, & Trentini, 2013).

The aim of the present study was to compare LTPP to antidepressant medication (fluoxetine) and their combination in terms of efficacy in the remission of depressive symptoms. The main hypothesis of the study is that LTPP's efficacy for depression treatment is as good as a well-known medication (in this case, fluoxetine), and possibly not as good as combined treatment in reducing depressive symptoms.

Materials and Methods

Design

The study is a randomized controlled trial investigating changes in symptoms of depressed patients and comparing LTPP, fluoxetine, and combined treatment. A nonintervention control group was not included because of ethical considerations. It would not be possible for depressed patients to stay without any treatment for 24 months. Brazilian ethical guidelines for research with humans prohibit inclusion of control group is such a situation. The investigation was carried out in accordance with the Declaration of Helsinki, and the informed consent of the participants was obtained. The local Ethics Committee approved the study design.

Participants

The participants were adult patients treated in a mental health clinic in the urban area of Porto Alegre, Brazil. Inclusion criteria were: presence of major depressive disorder or depressive disorder not otherwise specified, according to the SCID I and II criteria of the DSM-IV-TR, moderate depressive symptoms (Beck Depression Inventory [BDI] scores between 20 and 35), age between 26 and 34, and to have signed informed consent to participate in the research.

Exclusion criteria were DSM-IV-TR Axis I and II comorbidities, risk of suicide, use of other medications

that may influence the mental functioning, severe somatic diseases and contraindication to treatment with fluoxetine. Patients were also excluded if pregnant.

Procedure

A clinical psychologist initially interviewed all patients who underwent screening. In case of diagnosis hypothesis of depressive disorder and absence of clear exclusion criteria, the patients were invited for baseline assessment a week later.

During baseline diagnostic assessment, for diagnosis purpose, it was administered the Structured Clinical Interview for the DSM, SCID-I and SCID-II (Del-Ben, Rodrigues, & Zuardi, 1996; Del-Ben, Zuardi, & Rodrigues, 1998; Del-Ben et al., 2001). Subsequently, the BDI was used for measuring the severity of the depressive symptoms. The inclusion and exclusion criteria were checked again, the objectives of the research were explained, and all the information about the participation in the project was provided. Informed written consent was obtained from each patient before randomization. Patients that met the inclusion and exclusion criteria were then randomized to one of the treatments. The treatments started in the following week. BDI assessments were conducted at baseline and at 6, 12, 18 and 24 months after baseline. All treatments lasted 24 months. Patients who were absent for more than three consecutive sessions during the period of psychotherapy or absent from a psychiatric consultation were withdrawn from the study.

Interventions

Long-term psychodynamic psychotherapy. The psychodynamic psychotherapy was conducted individually and in weekly sessions. This model of psychotherapy acts in a supportive-interpretive *continuum*, depending on the therapeutic needs of the patient (Gabbard, 2004; Gunderson & Gabbard, 1999). The construction of the relationship between patient and therapist is emphasized.

Shedler (2010) points out that the distinctive techniques of the long-term psychodynamic psychotherapy include the focus on the affect and expression of emotion; exploration of attempts to avoid distressing thoughts and feelings; identification of patterns and recurring themes; discussions of past experiences; focus on interpersonal relationships; focus on the therapy relationship; and exploration of desires, dreams, and fantasies. The LTPP variant used in this study was similar to the one proposed by Gabbard (2004, 2010). The psychotherapy was not manualized and the treatment took place under real-life conditions.

Psychotherapeutic technique adherence was verified in order to control if the therapists were really using psychodynamic and psychoanalytical techniques during sessions with their patients. Independent specialized judges reviewed transcribed psychotherapy sessions. Preliminary results showed high judge's agreement (as calculated by Prevalence-Adjusted and Bias-Adjusted Kappa—as proposed by Byrt, Bishop, & Carlin, 1993) and the technique used was considered psychoanalytic oriented. Further information about technique adherence may be included and published in a future report.

Fluoxetine. For the present study, fluoxetine was chosen for its excellent cost-effectiveness comparing to the costs of depression treatment (Salminen et al., 2008). In Brazil, fluoxetine is one of the most inexpensive antidepressants available. More important, the efficacy of fluoxetine in the clinical teatment of depression has been shown (e.g., Hashemi et al., 2012). Salminen et al. (2008) stressed that fluoxetine is effective in the reduction of symptoms and functional improvement of patients who suffer from depression.

Fluoxetine was prescribed according to the official guidelines of the Brazilian Ministry of Health (http://www4.anvisa.gov.br/base/visadoc/BM/BM[34652-1-0].PDF). Patients received fluoxetine, starting at 20 mg/day during 2 weeks. Then, if necessary, a gradual increase was determined, reaching up to 60 mg/day.

At the first consultation, patients received detailed explanation about the delayed onset of therapeutic effects and potential drug side effects. The second visit to psychiatrist occurred 2 weeks later. Twice a month visits to psychiatric consultations were kept up until the dosage regulation had finished. After, the patients were appointed to monthly visits, where they received the medication and the psychiatrists verified the treatment adherence.

Combination therapy. The combination therapy consisted of both of the above-mentioned interventions concurrently.

Psychotherapists and psychiatrists. The 24 psychotherapists (16 female and 8 male) were clinical psychologists specialized in long-term psychodynamic psychotherapy. The mean duration of clinical experience was 11 years, and mean age was 35 years. The psychotherapists were divided into two groups of 90-minute collective supervision conducted by the same supervisor (twice a month basis), where reports of the consultations were debated during the study.

Biological therapists were six expert physician–psychiatrists (3 female and 3 male). The mean duration of clinical experience was 6 years, and the mean age was 31 years. There were no significant statistical differences for variables involving the psychotherapists, psychiatrists, and supervision groups in the tests of variables between conditions.

Outcome Instruments

The primary outcome measure was the Beck Depression Inventory (BDI—Beck & Steer, 1993). The BDI is adapted and validated in Portuguese (Cunha, 2001). The BDI is a self-report questionnaire to assess depression severity, and it is widely used by clinicians and researchers (Dunn, Sham, & Hand, 1993; Kendall & Sheldrick, 2000). It has excellent psychometric characteristics (Beck, Steer, & Brown, 1996). The Brazilian BDI consists of 21 items, including symptoms and attitudes, with intensity ranging from zero to three. The items refer to different symptoms of depression (e.g., sadness, fatigue, and loss of appetite). The final add up results in a total score that can be classified as follows: *minimum* (score 0–11), *mild* (score 12–19), *moderate* (score 20–35) and *severe* (score 36–63). It is important to notice that Brazilian BDI version has different score range classifications compared to Beck and Steer (1993) original BDI. Brazilian BDI cutting points tend to be higher (Cunha, 2001). Furthermore, the cut-off for clinical significance in the Brazilian BDI is <11 points (Cunha, 2001), while in the American BDI, the cut-off is usually set in <9 points (Elkin et al., 1989).

Statistical Methods

BDI scores of the three groups were compared at pre-treatment, and every six months during treatment (at four times: 6, 12, 18 and 24 months). For this comparison, a mixed model analysis was used, an extension of the model of repeated measures analysis of variance that allows the simultaneous comparison of two factors: the inter-subject factor (groups) and the intra-subject factor (time of the treatment) on the dependent variables (Gueorguieva & Krystal, 2004). Interaction effects between these two factors on the dependent variables were also investigated. The mixed model was also used to evaluate possible differences between groups at the different moments. The level of significance adopted was $p < .05$.

Intragroup (within treatment) and between groups (between treatment) effect sizes were calculated. The within treatment effect sizes were corrected for dependence between treatment means using Morris and DeShon's (2002) Equation 8. Between-treatment effect sizes were calculated according to Cohen's original instructions (Cohen, 1988). The statistical analyses were conducted with the software SPSS v.18 (IBM Corporation).

Results

Patient Flow

Subjects were selected among 417 individuals who were initially recruited and assessed. Subjects who met inclusion criteria and agreed to participate in the study ($N = 272$ [65.2%]) were randomized to treatments: LTPP ($n = 90$), FLU ($n = 91$), and COM ($n = 91$). Figure 1 shows the participants' flow.

After the randomization, 11 individuals of the psychotherapy group, 7 of the fluoxetine group and 15 of the combination treatment group refused to continue in the study. During the treatment, the mental state of three individuals became worst, and the psychotherapy needed to be replaced by other method of therapy. Three other individuals left the study after two visits without justification.

In the fluoxetine group, the mental state of four patients became worst and they needed to be hospitalized. Eleven individuals missed psychiatric appointments and were withdrawn from the study.

In the combination therapy group, nine individuals gave up after the first month and five quit in the second month. Two hundred and two patients concluded the study: 67 in the fluoxetine group, 73 in the psychotherapy group, and 62 in the combination therapy group.

Patient Characteristics

The basic characteristics of the three groups are in Table I. There were no significant differences in relation to age, proportion of men and women, level of education, marital status, family income, number of previous depressive episodes, and BDI initial score between the three groups.

Treatment Outcomes

The results of the mixed analysis of all groups are shown in the Table II. The analysis of the mixed models of the BDI scores revealed that the patients, in general, presented a significant decrease in the intensity of the depressive symptoms ($F8;479 = 45,96$, $p < .001$).

The patients initiated treatment with moderate depressive symptoms and concluded treatment with significantly fewer symptoms in BDI. Figure 2 lines represent BDI means of each group along time.

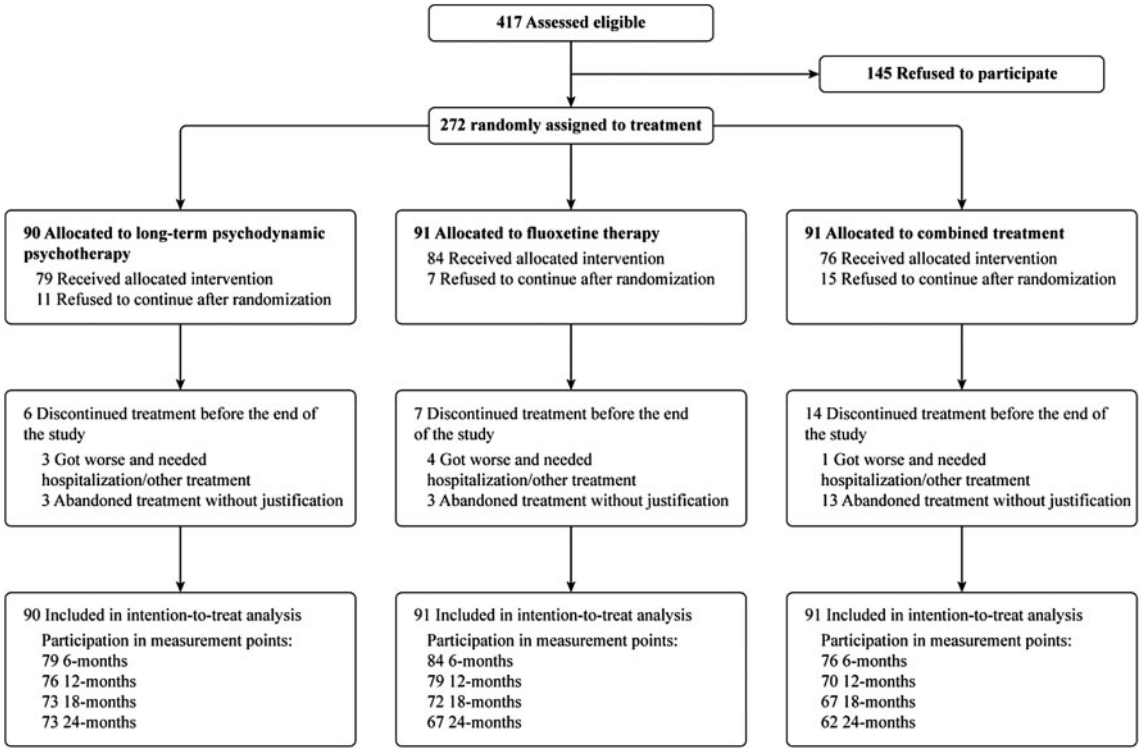

Figure 1. Participants flow diagram.

Results of investigating the percentage of clinical cases (above clinical cut-off point) for each point of evaluation separately showed some differences between groups. At treatment termination, the intention-to-treat remission rates showed different results.

The LTPP group started treatment with BDI mean score of 27.36, and ended with a mean score of 5.28, achieving a 22.08 mean reduction in BDI points. This group reached the cut-off point for clinical significance in 18 months of treatment (in mean). The FLU group initiated the treatment mean score of 26.69, and ended with a 14.16 mean. Participants of FLU group achieved a 12.53 total mean reduction in BDI points. This group did not reach the cut-off point for clinical significance (in mean). The COM group, in its turn, started treatment with a mean of 26.20 points, and in the last measurement, the mean point of BDI was 4.16. This group achieved a 22.04 total mean reduction in BDI points. COM group reached the cut-off point mean for clinical significance in 18 months of treatment. It is important to notice, however, that COM group had a BDI mean of 11.64 points at the 12th month of treatment. This can be considered an overlap in classification score (i.e., a score which would place a given participant at the boundary between mild and minimum depressed level of functioning, because the pooled standard deviation for this group was 2.78).

In the LTPP group, 74% of patients achieved cut-off point, compared to 65% of COM group and 22% of FLU group. These differences are statistically significant ($p < .001$). Another noteworthy finding was that the number of patients below cut-off point in the COM group was significantly lower than LTPP and FLU by the sixth month of treatment,

Table I. Sociodemographic, clinical and cognitive characteristics of participants in the three treatment groups at baseline ($n = 272$).

	Total	LTPP	FLU	COM	*df*	*F*	χ^2	*p*⋆
Gender (% male/female)	38/62	39/61	37/63	40/60	2		2.08	0.35
Marital status (% single/cohabiting)	65/35	62/38	66/34	68/32	2		1.42	0.55
Level of education (% until high school/upper)	32/68	31/69	35/65	30/70	2		1.06	0.61
No previous episodes (%)	72	72	73	70	2		0.37	0.59
Age (*SD*)	29.61 (2.31)	29.82 (2.43)	29.47 (2.17)	29.55 (2.33)		540		0.57
BDI mean score at baseline (*SD*)	26.87 (3.77)	27.31 (4.16)	26.71 (3.28)	26.60 (3.87)		912		0.40

⋆Between-group sociodemographic and clinical characteristics of participants' differences were determined by ANOVA (if the variable was continuous) or Chi-square (if the variable was dichotomous).

Table II. Basic intention-to-treat model with mean scores and standard errors of the BDI in different times in the three treatments, attrition rates and within treatment effect sizes.

		Month								
Time treatment	Basal BDI	6	12	18	24 (final)	Δ	Attrition rate	Pooled *SD*	*d*	Corrected *d*⋆
LTPP (*SE*)	27.36 (0.44)	19.74† (0.51)	15.04† (0.38)	10.43† (0.49)	5.28† (0.42)	22.08		3.69		
Effect sizes (95% CI)		1.85 (±0.36)	3.46 (±0.48)	4.26 (±0.56)					5.97 (±0.72)	4.50 (±0.54)
N	90	79	76	73	73	17	19%			
Patients with scores above the clinical cut-off⋆⋆ (*n*)	100% (90)	96% (76)	86%† (65)	34%† (25)	8%† (6)					
FLU (*SE*)	26.69 (0.32)	18.34† (0.64)	17.23 (0.39)	15.76 (0.33)	14.16† (0.31)	12.53		2.65		
Effect sizes (95% CI)		1.97 (±0.36)	3.13 (±0.45)	3.96 (±0.53)					4.72 (±0.61)	3.91 (±0.50)
N	91	84	79	72	67	24	26%			
Patients with scores above the clinical cut-off (*n*)	100% (91)	95% (80)	88% † (69)	71%† (51)	68%† (47)					
COM (*SE*)	26.20 (0.49)	16.46† (0.63)	11.64† (0.44)	7.93† (0.33)	4.16† (0.32)	22.04		2.78		
Effect sizes (95% CI)		2.24 (±0.38)	4.09 (±0.54)	5.54 (±0.69)					6.76 (±0.83)	5.70 (±0.67)
N	91	76†	70	67	62	29	32%			
Patients with scores above the clinical cut-off (*n*)	100% (91)	85%† (65)	46%† (32)	12%† (8)	3%† (2)					

Note. Underlined entries mean significant differences between treatments ($p < .05$).
†Denotes a significant difference within treatment ($p < .05$).
⋆*d* was corrected for dependence between means within treatment, using Morris and DeShon's (2002) equation 8, i.e., *d* uses variants of *M*1–*M*2 (in this case, Basal BDI – Final BDI of a given treatment) as the numerator. It scales a simple difference between means in *SD* units. In other words, $d = 1$ represents a 1 *SD* difference in the means.
⋆⋆The cut-off for clinical significance in the Brazilian BDI is <11 points.

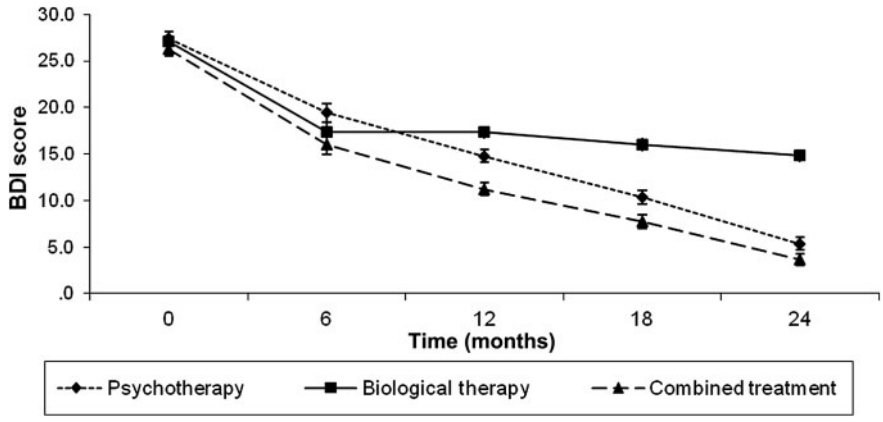

Figure 2. Mean scores on the Beck Depression Inventory in the three treatment groups along 24 months.
Note: Bars represent standard errors.

and these numbers remained significantly lower until the end of the study. It is also important to point out that the LTPP group had significantly more patients below cut-off point than the FLU group by the 18th month of treatment, and this significant difference remained until the end.

Regarding the attrition rates (dropouts) observed in the groups it is important to note that there are significant differences between then ($p < .05$). LTPP (19%, $n = 17$) had the lower attrition rate, followed by FLU (26%, $n = 24$) and COM (32%, $n = 29$).

The within treatment effect sizes were considered very large in the three treatment groups (corrected *d*s ranging from 3.91 to 5.70). On the other hand, between treatments effect sizes varied. Table III displays between treatments effect sizes at different times of treatment.

In the LTPP-FLU comparison, effect sizes ranged from 0.28 to 2.84, all favoring LTPP. The mean effect size was 1.32. BDI mean scores difference ranged from 1.40 to −8.88 BDI points in the LTPP group. In the LTPP-COM comparison, effect sizes ranged from 0.36 to 1.00, all favoring COM. The mean effect size was 0.69. Finally, COM-FLU comparison effect sizes ranged from 0.36 to 3.92, all favoring COM. The mean effect size was 2.21.

Discussion

Several clinical studies about the treatment of depression have been conducted to establish therapeutic efficacy in a series of populations (Roth & Fonagy, 2005). In the present study, the efficacy and clinical significance of three different treatments were investigated. Results demonstrated significant decrease in BDI scores. Within treatment BDI scores and effect sizes varied in each treatment. There were also several differences between treatments. The following subheadings address these issues point-by-point.

Within Treatment Effect Sizes

Within treatment, effect sizes were very large (corrected *d*s were 4.50 for LTPP, 3.91 for FLU, and 5.70 for COM). These effect sizes are surprisingly enormous, if compared to what other studies report (e.g., Lambert & Ogles, 2004; Taylor, 2008). Still, the "inflated appearance" of within treatment effect sizes reported here does not mean that the effects encountered are not real for this group of participants. However, they are indeed much larger than what previous researches about psychotherapy outcome used to report. The at first glance unusual treatment effects have to be addressed critically and interpreted with prudence.

A closer look at BDI standard deviations reported in three previous studies already mentioned is important, because standard deviations are the key to understand the huge and unusual within treatment effect sizes found in the present research. Cohen's *d* is in units of standard deviation, and this may explain the idiosyncrasy of the within treatment effect sizes. Variability of response within group (as reflected by standard deviation) is relatively low, when compared to previous studies. For instance, Knekt, Lindfors, Laaksonen et al. (2008), Huber et al. (2012) and Buchheim et al. (2012) researches all had very large standard deviations in BDI mean results (ranging from 8.2 to 9.9 BDI points) compared to BDI mean scores standard deviations of the present study (3.69 in LTPP, 2.65 in FLU, and 2.79 in COM). This minimal BDI variability dilated the within treatment effect sizes, and may have occurred because of the clinic homogeneity of the sample. Taking the LTPP within treatment effect size as an example, the effect size arithmetically indicates that the average treated patient in this particular group decreased 4.50 standard deviations from basal to final assessment. COM and FLU within treatment effect sizes followed the same logic.

Table III. Between treatments effect sizes and BDI mean scores differences in different times.

Comparison	Month				Mean effect size	Mean BDI difference	β
	6	12	18	24			
LTPP–FLU (95% CI)	0.28 (±0.26)	0.66 (±0.32)	1.51 (±0.37)	2.84 (±0.82)	1.32 (±0.44)		5.89
BDI difference	1.40	−2.19	−5.33	−8.88		−3.75	
LTPP–COM (95% CI)	0.70 (±0.32)	1.00 (±0.35)	0.73 (±0.34)	0.36 (±0.34)	0.69 (±0.33)		1.82
BDI difference	3.28	3.40	2.50	1.12		2.57	
COM–FLU (95% CI)	0.36 (±0.31)	1.65 (±0.37)	2.92 (±0.48)	3.91 (±0.59)	2.21 (±0.43)		11.21
BDI difference	−1.88	−5.59	−15.69	−10.00		8.29	

Note. Underlined entries mean significant differences between treatments ($p < 0.05$). Effect sizes are in Cohen's *d*, and followed Cohen's instructions for calculation (Cohen, 1988).

Restricting discussion to research related to BDI as outcome measure for psychodynamic psychotherapy in general, some studies do report very large within treatment effect sizes. In a review about the empirical status of psychodynamic therapies, Gibbons et al. (2008) found at least two studies reporting "extra large" effect sizes using BDI as outcome measurement: Hersen, Bellack, Himmelhoch, and Thase (1984), in a study comparing short-term psychodynamic psychotherapy to medication found a 3.41 within treatment effect size in STPP. Moreover, Kornblith, Rehm, O'Hara, and Lamparski (1983) found a 3.57 within treatment effect size in STPP.

Large effect sizes were also found in two similar longitudinal RCTs comparing LTPP to shorter-term therapies. Knekt, Lindfors, Laaksonen, et al. (2008) randomized 367 patients with anxiety or mood disorders to three different treatments (STPP, LTPP, or psychoanalysis), and assessed participants several times with a set of instruments. LTPP group with mood disorders (n = 113) had a basal BDI mean of 19.8 points, and finished the study with a mean of 7.5 points. The pooled standard deviation was 8.51. Thus, within treatment effect size was 1.44. Huber et al. (2012) compared psychoanalytic therapy, LTPP, and cognitive-behavioral therapy in the treatment of depression. LTPP group (n = 31) initiated treatment with a BDI mean of 25.1 (SD = 8.7) and ended with 8.3 (SD = 9.9). Effect size was 2.10.

On the other side, meta-analyses have reported very different effect sizes compared to what was found here. Leichsenring and Rabung (2008, 2009, 2011) reported large within treatment effect sizes (range: 0.97–1.94) in the treatment of "complex depressive disorders" with LTPP. De Maat, de Jonghe, Schoevers, and Dekker (2009) examined the efficacy of LTPP for patients suffering from what the authors called "mixed/moderate pathology" and had a pre to post-treatment effect size of 0.78 for "general symptom improvement."

FLU treatment group, in its turn, presented different within treatment patterns of response. The average treated patient in this particular group decreased 3.71 standard deviations from basal to final assessment. Considering effect size, this is a very high antidepressant response in comparison to previous trials, but it is important to consider that treatment outcome studies with fluoxetine usually show different results. Shedler (2010) analyzed the US Food and Drug Administration databases, and reported a 0.26 within treatment effect size for fluoxetine. This is a small effect size. Salminen et al. (2008) compared the efficacy of STPP and fluoxetine in major depressive disorder of mild to moderate intensity. Fluoxetine patients (n = 25) basal BDI was 24.8, and final BDI mean after four months was 11.3. The within treatment effect size was a large 1.62. Hashemi et al. (2012) used the BDI in a clinical trial. Participants were 120 depressed patients taking nortriptyline or fluoxetine. Before intervention, the mean BDI score was 33.12 in the fluoxetine group. Six months later the BDI score was 16.96. Effect size was 2.79, considered very large. In the present study, participants of FLU group had a basal BDI of 26.69, and in the sixth month assessment, BDI was 18.34, with a 0.64 effect size.

Finally, within treatment effect size found in COM group indicated that the average treated patient decreased 5.70 standard deviations from basal to final assessment. De Maat, Dekker, Schoevers, van Aalst, et al. (2007) performed a mega-analysis comparing the efficacy of STPP, antidepressants and their combination in the treatment of depression. Combination therapy yielded an effect size of 1.59, what is different from what was found in the present research.

Remission Rates

A large reduction in the number of patients with clinically elevated BDI scores occurred. Reduction in LTPP group reached 74% of total cases. Previous studies using percentage as measurement of efficacy

have reached similar results. Berghout and Zevalkink (2009) evaluated the clinical significance of LTPP in four groups of about 60 patients in different phases of treatment. Compared to basal assessment, they found significant decrease in the percentage of clinical cases after treatment (87%). Leichsenring et al. (2005) reported that around 80% of the patients receiving psychoanalytic treatments reached clinically significant reduction of symptom by the end of treatment.

In FLU group, 22% of the participants reached the BDI cut-off point for clinical significance. Results indicated that 78% still had elevated BDI scores by the end of the study. Taylor (2008) affirms that drug treatments for depression are capable of producing around 12–13 score improvement in the BDI. This magnitude of improvement is very similar to the values found here (12.53 points). It is important to point out that a complete remission of depressive symptoms with fluoxetine may not be realistic for outpatient treatments of moderate depression. It could be that some patients achieved significant symptom change, but at the end of treatment, they had not completely recovered. These particular cases are often referred to as "improved," instead of "recovered" (Jacobsen & Truax, 1991).

In COM group, 65% of the participants reached the BDI cut-off point for clinical significance. De Jonghe et al. (2004) examined whether associating antidepressants to STPP would improve in the outcome of mild to moderate depression treatment. Two-hundred patients were treated, and remission rate was 81%. De Maat, Dekker, Schovers, and de Jonghe (2007) conducted a meta-analysis comparing the efficacy of short-term psychotherapies and combination therapy in the treatment of depression. Results regarding moderate depression showed a 47% remission rate for combined treatment. Combined treatment outperformed STPP in moderate chronic depression. These results are in line with the ones found by Friedman et al. (2004), who reported that associating psychotherapy and antidepressants was most clinically relevant among chronic or severely depressed patients.

Comparison between Treatments

Remission rates based on BDI were significantly better for LTPP and COM, compared to FLU, and represent different mean effect sizes between treatments. LTPP-FLU mean effect size was large (1.32). There are no previous studies comparing directly the efficacy of LTPP and medication for moderate depressed patients. Salminen et al. (2008) found a STPP-fluoxetine small effect size of 0.12. Small effect sizes are normally found comparing STPP with pharmacotherapy alone in the treatment of depression (de Maat, Dekker, Schoevers, van Aalst, et al., 2007).

There were significant differences between LTPP and COM. Mean effect size was moderate, favoring COM (0.69). Remission rates were significantly different (66% in COM and 74% in LTPP). These numbers might suggest that COM tends to promote more intense therapeutic effects, while LTPP effects tend to reach a wider number of patients. Studies comparing psychodynamic psychotherapy combined with medication and psychodynamic psychotherapy alone usually report that both seem to be equally efficacious (de Maat, Dekker, Schoevers, van Aalst, et al., 2007). This also suggests similar clinical significance between LTPP and COM. However, in COM group BDI mean achieved the cut-off for clinical significance faster than LTPP group (12 and 18 months, respectively). This result is in line with what was found by de Maat, Dekker, Schoevers, van Aalst, et al. (2007). They reported that patients declared they felt combined treatment superior to psychodynamic therapy alone (STPP) for faster symptom reduction. De Maat, Schoevers, et al. (2007) in a mega-analysis comparing STPP, medication, and combination therapy, found a small to moderate effect size favoring combination therapy over STPP.

COM-FLU comparison resulted in differences favoring COM. Mean effect size was very large (2.21). Remission rates were significantly different (66% in COM and 22% in FLU). BDI mean scores at final were different either (COM = 4.16; FLU = 14.16). All these findings are supported by previous studies. De Jonghe et al. (2001) found significantly larger remission rates for STPP combined with medication (37.3%), compared to medication alone (15.5%), with a moderate effect size (0.57). Burnand, Andreoli, Kolatte, Venturini, and Rosset (2002) demonstrated that combination therapy was superior to medication alone in terms of clinical significance, but with a small effect size (0.36). Mostly, comparisons between medication and combined treatment for depression report more pronounced differences in remission rates, instead of differences in effect size. According to Greenberg and Goldman (2009), around 33% of depressed patients achieve remission after treatment with antidepressants, while combined treatments reach higher remission rates (50–90%).

Finally, the number needed to treat (NNT) methodology also helps to compare the treatments for discussion. Using FLU as control (because fluoxetine has been considered an efficacious treatment for depression for more than 30 years) changes the results. When LTPP is compared to control

(FLU), 51% of FLU subjects have the adverse outcome; 7% of LTPP subjects have the adverse outcome; the difference indicating the absolute risk reduction is 45% ± 11% (95% CI); the NNT is 3, and the 95% confidence interval for this NNT ranges from 1.8 to 3.0. This means that, about one in every three moderately depressed patients will benefit from LTPP. When COM is compared to control (FLU), the scenario shows that 52% of FLU subjects have the adverse outcome; 2% of COM subjects have the adverse outcome; the difference indicating the absolute risk reduction is 49% ± 11% (95% CI); and NNT is 3 (ranging from 1.8 to 3.0 [95% CI]). NNT indicates that about one in every three patients moderately depressed patients will benefit from COM. The 95% confidence interval for the COM group NNT ranges from 1.7 to 2.6. Thus, LTPP and COM showed very similar levels of effects when compared to a notorious treatment used as control (FLU).

Attrition Rates

COM had larger attrition rate (32%) compared to LTPP (19%) and FLU (26%). This has been reported by previous studies (e.g., Greenberg & Goldman, 2009; Hawley, Ho, Zuroff, & Blatt, 2007). There are also evidences showing that if patients had opportunity to choose a treatment, more patients indicate that they would choose psychotherapy rather than drugs (Lin et al., 2005; van Schaik et al., 2004). Indeed, some researchers believe that if it there is any possibility to spare patients from the risks of taking drugs that should be done, because there are strong evidences that psychotherapy has less chances to lead to relapse when it is terminated and produces fewer side effects (e.g., Greenberg & Goldman, 2009).

Limitations

The present research, like many studies, has some limitations. Individuals assessed here do not represent all patients with depression that need treatment. Therefore, results cannot be generalized. The dilated effect sizes reported here may lead to an overestimation of treatment effect and were caused by group averages low variability. This also posts a question mark on the clinical significance utility of the interpretation criteria of within treatment effect sizes. In longitudinal research designs that aim to increase internal validity using a very specific profile of participants, within treatment effect sizes may not be as useful as it is in shorter-term treatments. The participants' homogeneity can also be interpreted as a limitation of the present study, because it may threaten external validity of the findings. Furthermore, participants were mostly young adult women, and with good socioeconomic conditions and high educational level. According to Houle et al. (2013), this profile of participants generally adapts more easily to psychotherapeutic context, and this characteristic may help to understand low attrition rates found in LTPP group, for example. Patients with other features might not have adapted to a long-term psychotherapy or to a longitudinal study.

An additional limitation was the use of a single endpoint measure, assessing only the perspective of the patients in relation to their symptoms. Future studies shall seek to approach different perspectives (such as the perspectives of the patients' relatives or friends), different areas of symptoms (such as cognition) and different areas of functioning (such as work and social life). Moreover, there has not been a follow-up after the conclusion of treatments. This could contribute to obtain deeper and more comprehensive notion of the changes in patients.

The LTPP applied in the study, although theoretically and technically well focused on collective supervisions, was not strictly guided by a proper practical manual. On the other hand, fluoxetine was given in accordance with government-manualized guidelines. This creates a validity problem interpreting results. However, the controversy between manualized versus non-manualized treatments constitutes a research dilemma. This occurs particularly in long-term treatments, where more general theoretical guidelines may be of preferred use (Knekt, Lindfors, Harkanen, et al., 2008; Piper, McCallum, Joyce, Azim, & Ogrodniczuk, 1999).

Other limitations include the lack of a non-intervention control group (which was not included in the research desing because of ethical questions), the intrinsic differences between treatments (biological vs. face-to-face, treatment amounts, and so on), and the expectancies of the providers and patients (which were not assessed and constitute an issue to be addressed in future researches). At any rate, the authors have made a decision, on the grounds of limitations of space, of not to itemizing all possible limitations of the present study except the ones, especially relevant. Instead, the authors rely on the overall discussion contained in this paper and entrust the readers' criticism.

Strengths and Potential Implications

Main findings of the present study underline the efficacy of LTPP and combination treatment. They were superior over the time in all aspects evaluated here when compared to the use of fluoxetine alone in the treatment of patients with moderate depression.

The results found here also support the idea that LTPP is an effective treatment for moderate depression. Hereupon, it is necessary to point out that it is beyond the scope of this study to provide definitive statements regarding the benefits of the treatments described here.

The strengths of this manuscript include some features. First, it has a sizable sample size in each treatment group and randomization of patients. Second, it monitored patients for a meaningful time and had multicriteria of analysis for representing outcome. Third, the clinical relevance of the main questions addressed (e.g., given the long-term time course, psychotherapy benefit more than biological treatment or not; what is the additive clinical value, if any, of combined treatment over a longitudinal course, and so forth).

All together, it seems that LTPP may be a viable clinical option for some patients, comparing to COM. Remission rates are quite similar and there is no strong between treatments effect size favoring COM, and there are no significant differences in BDI scores.

Finally, it is important to consider that there are relatively few randomized controlled trials (RCT) of LTPP for depression. The authors of the present research are unaware of the existence of other RCT in which LTPP was both compared with a legitimate psychopharmacological treatment and with combination therapy, and likewise treatment outcome was assessed in many meaningful intervals. The relative absence of RCTs with LTPP in the treatment of depression creates serious limitation in literature, which could lead to automatic exclusion of this therapy from clinical choices for depression treatment. The present research and its findings shall offer a partial, but quite infrequent contribution to psychiatric and psychological fields. It may provide a conceptual extension to what have been found by other researchers (e.g., Huber et al., 2012; Knekt, Lindfors, Harkanen et al., 2008) suggesting that long-term psychotherapy is clinically superior when provided over the same period of time as a known SSRI treatment.

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