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Research report

Brief dynamic therapy combined with pharmacotherapy in the treatment of major depressive disorder: Long-term results

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Abstract

Background: There is a paucity of controlled trials examining the efficacy of brief dynamic psychotherapy (BDT) in the treatment of major depressive disorder, especially in a long-term perspective. The aim of the present study is to evaluate recurrence rates in unipolar major depressed patients who are responsive to acute phase combined treatment with BDT plus pharmacotherapy in comparison with patients initially treated with pharmacotherapy alone.

Methods: Subjects for this study were 92 patients who met criteria for remission at the end of a 6-month acute treatment phase for major depressive disorder, single episode, with combined therapy (BDT plus pharmacotherapy) versus pharmacotherapy alone. 41 (64.1%) subjects were remitters to combined treatment and 51 (61.4%) were remitters to antidepressants alone. The study included a 6-month continuation treatment trial with pharmacotherapy and a following perspective, naturalistic 48-month follow-up (without any treatment).

Results: Patients who received combined treatment, in comparison with those who were treated with pharmacotherapy alone, show a significant lower rate of recurrences of depressive episodes at 48-months naturalistic follow up (27.5% in comparison with 46.9%: $\chi^2=3.525$; $df=1$; $p=.048$).

Limitations: Inclusion and exclusion criteria may limit the generalizability of the results. Furthermore it may be unclear whether the effect is attributable to BDT per se as opposed to extra time with a therapist.

Conclusions: The significant lower recurrence rates in a 48-month follow-up in the group of patients treated with the addition of BDT to medication in the acute phase support the view of the advantage in the long-term outcome of adding psychotherapeutic intervention to pharmacotherapy in the acute therapy of unipolar major depression.

Keywords: Brief dynamic therapy; Psychotherapy; Pharmacotherapy; Major depressive disorder; Combined treatment

1. Introduction

According to many clinicians' opinion, the combination of antidepressants and psychotherapy should be the treatment of choice in outpatients with major depression. Although the American Psychiatric Association's Practice Guideline remarks the effectiveness of combined treatment in the treatment of major depressive disorder, relatively few studies have investigated the benefits of adding psychotherapy to medication in depression, and study results are conflicting (Friedman et al., 2004; Fochtmann and Gelenberg, 2005).

Brief dynamic therapy (BDT) has been shown to be effective in the treatment of depression in monotherapy (Thompson et al., 1987; Gallagher and Thompson, 1983; Steuer et al., 1984; Arean et al., 1993; Gallagher-Thompson and Steffen, 1994; Cooper et al., 2003; Leichsenring, 2001; Leichsenring et al., 2004; Maina et al., 2005; Fonagy et al., 2005). In the acute treatment of major depression, the provision of supplemental

BDT to pharmacotherapy has been shown to be significantly more acceptable from patients (de Jonghe et al., 2001) and cost-effective (Burnand et al., 2002). Regarding the efficacy of the combination of BDT with pharmacotherapy, we recently compared the efficacy of BDT versus brief supportive psychotherapy added to medication in the treatment of major depressive disorder: although at the end of the combined therapies (acute treatment phase), no differences emerged between the two treatment approaches, the group of patients treated with BDT showed a further clinical improvement at the end of the following 6-month continuation phase (Maina et al., 2007). This finding is consistent with the results of a study of depressed inpatients that showed improved efficacy for adding cognitive treatment to pharmacotherapy at long-term

follow-up (Bowers, 1990). The long-term advantage of some combined treatments of depression suggests that the risk of recurrence despite a good therapeutic response to medication may be reduced by some specific psychotherapeutic interventions. BDT underlines and sustains the patient's problems not only during the treatment sessions because it enhances the patient's insight about repetitive conflicts (intrapsychic and interpersonal) and trauma: we would contend that BDT consists mainly of the systematic and theory-guided use of specific therapeutic factors (interpretation and clarification through the time limitation and the focal exploration).

Our study examines the hypotheses that depressed patients who are responsive to acute phase combined treatment with BDT plus pharmacotherapy would have lower recurrence rates in comparison with patients initially treated with pharmacotherapy alone. Furthermore, we hypothesized a better symptomatic and psychosocial long-term outcome especially for patients treated with BDT and pharmacotherapy at their first depressive episode.

2. Methods

2.1. Study design

Subjects for this study were 92 patients who met criteria for remission (defined as a 17-item Hamilton Rating Scale for Depression-17 Item total score ≤ 7) at the end of a 6-month acute treatment phase for major depressive disorder, single episode, with two different treatment strategies: combined therapy (BDT plus medication) versus medication alone. Those experiencing a clinical remission were then enrolled into the study: 6 months of continuation treatment with medication (same drug and same dose) and a following perspective, naturalistic 48-month follow-up period (without any treatment). At the end of the acute phase 41 (64.1%) subjects were remitters to combined treatment and 51 (61.4%) were remitters to antidepressants alone.

2.2. Study population

Eligible patients for the acute phase had been recruited from all outpatients with a principal diagnosis of major depressive disorder, single episode, consecutively referred to the Mood and Anxiety Disorders Unit, Department of Neuroscience, University of Turin (Italy) over a period of 3 years (January 1999–February 2002). The question of the relative long-term efficacy of the 2 acute treatments (combined versus medication) was addressed in a randomized parallel-group design. Patients were allocated randomly to combined treatment (antidepressants plus BDT) or to antidepressants alone by the study recruiter, who drew one of two colored balls from a bag, the assignment of each therapy to a different colored ball having been defined at the start of the study and maintained until the end of the recruitment period. The brief dynamic therapy started within 2 weeks after the initiation of pharmacotherapy. The trial was preceded by a 2-week period in which the diagnosis was assessed by means of the Structured Clinical interview for DSM-IV axis I and II disorders (First et al., 1997a,b), the inclusion and exclusion criteria were checked, and the

baseline assessments were made. If necessary, this period was used as a drug washout period (without placebo). The criteria used for being included in the study were: (a) main diagnosis of major depressive disorder, single episode, according to DSM-IV-TR; (b) a baseline score on the 17-item Hamilton Rating Scale for Depression (HAM-D)b15; (c) the presence of a focal problem and/or of a recent precipitant life event (as suggested by Malan (Malan, 1963; Malan, 1976) and Horowitz (Horowitz et al., 1997) for the inclusion in a brief dynamic therapy); (d) males or females 18–65 years old; (e) written informed consent. The exclusion criteria from the investigation were: (a) evidence of mental retardation, lifetime history of organic mental disorders, psychotic disorders or bipolar disorders, (b) severe axis II psychopathology (cluster A personality disorders, antisocial personality disorder and borderline personality disorder according to DSM-IVTR), (c) concomitant severe or unstable or active neurological or physical diseases, (d) substance and drug abuse, (e) any contraindication for one of the antidepressants prescribed by the pharmacotherapy protocol, (f) before the possible start of the trial, the patient had been already treated adequately by antidepressants during the present depressive episode, (g) the patient used psychotropic medication other than the one prescribed by the pharmacotherapy protocol, (h) pregnancy or risk of pregnancy during the medication treatment phase of the study, (i) suicidal risk that contraindicated the participation in a clinical trial (e.g. hospitalization was recommended). The protocol was approved by the local Ethical Committee. The sampling selection through each stage of the inclusion/exclusion criteria is shown in Fig. 1.

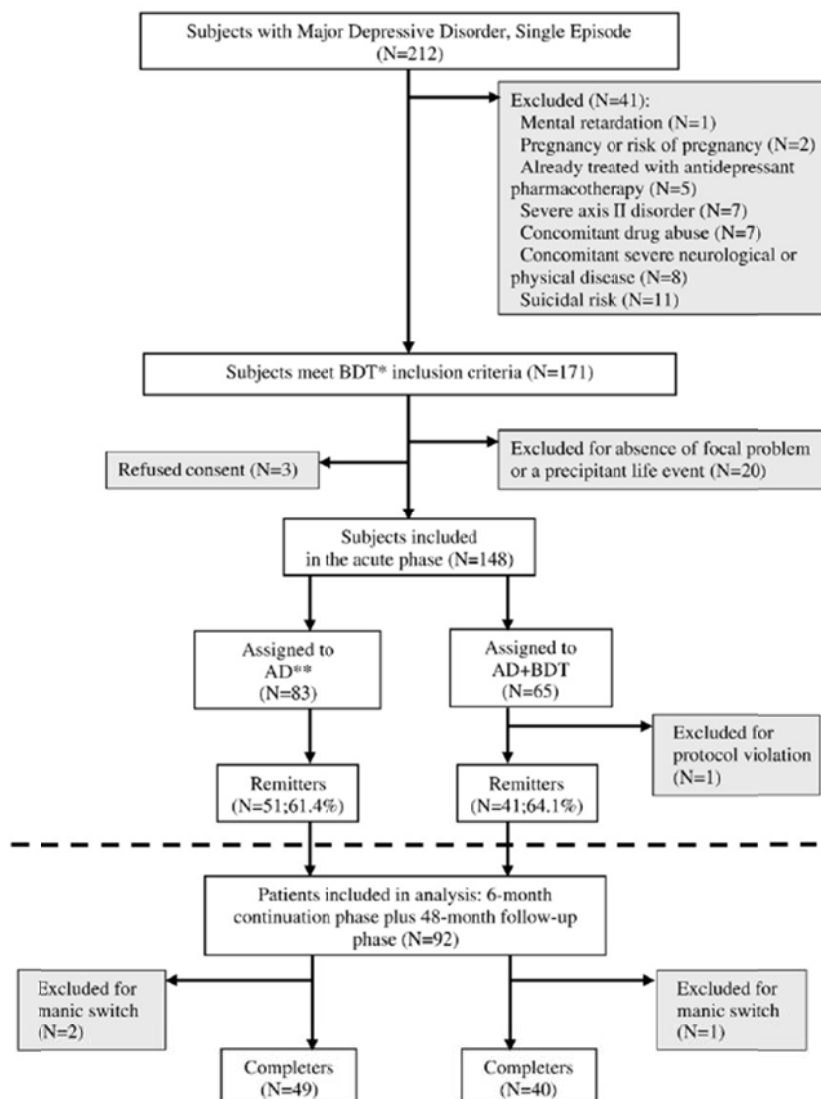


Fig. 1. Flow diagram. *: brief dynamic therapy; **: antidepressant pharmacotherapy.

2.3. Treatments

2.3.1. Pharmacotherapy

All patients were treated according to the following antidepressant protocol: a selective serotonin reuptake inhibitor, paroxetine or citalopram, was provided at the minimum daily dose of 20 mg/day. Dosage adjustments were made on the basis of individual responsiveness and tolerability; the daily dose could be increased up to 60 mg/day. Other psychiatric treatments were not permitted throughout the treatment period. The intended medication period was 12 months (acute and continuation phase). The psychiatrist makes 12 appointments of 20 min each with his patient, the first 4 weekly, the following 5 monthly, the last 3 every 2 months. The task of the psychiatrist was to provide pharmacotherapy and clinical management, the latter consisted of providing psychoeducation, discussing the effects and side effects of medication, and motivating the patient to comply with the medication regimen.

2.3.2. Brief dynamic therapy

All patients treated with BDT were also treated by a psychotherapist (who was not the psychiatrist providing medication). The primary objective of BDT is to enhance the patient's insight about repetitive conflicts (intrapsychic and interpersonal) and trauma that underlie and sustain the patient's problems. The principal instrument of BDT are interpretation and clarification: the therapist makes use of the actual relationship and attends to linkages with past significant relationships. The time limitation and the focal exploration of the patient's life and emotions distinguish the treatment from many current psychoanalytic psychotherapies. The psychotherapeutic technique we apply in our Department as BDT derives from Malan's focused, short-term psychoanalytic psychotherapy (Malan et al., 1976). In the initial phase of BDT, the clinical picture is assessed and, identified as part of a treatable disorder, as primary problem area is defined as a focus. Symptoms, conflicts or crisis may represent primary problem areas. In the middle phase, the identified focus is addressed. In the terminal phase, the end of the treatment is explicitly discussed, progress is reviewed and gains are consolidated. Patients are told from the outset that their treatment will be time-limited and final session is previously established.

Two graduate therapists provided the BDT; they were both psychiatrists who had completed a personal training in psychodynamic psychotherapy. Sessions were weekly, lasting 45 min., individually administered and in a face-to-face interview. The number of sessions, ranging from 15 to 30, was determined at intake by the therapist on the basis of focus characteristics. Any missed session was included as part of the psychotherapeutic protocol. An experienced BDT therapist who reviewed case notes and supervised treatment adherence according to manuals weekly monitored each BDT therapist.

2.4. Evaluations

The primary efficacy assessment was the HAM-D-17; secondary efficacy measures included the 5 Clinical Global Impression-Severity scale (CGI-S), the Clinical Global Impression-Improvement scale (CGI-I), the Global Assessment of Functioning (GAF), and the Longitudinal Interval Follow-Up Evaluation (LIFE) (Keller et al., 1987).

The baseline evaluation (T0), conducted after admission (end of acute phase), included the HAM-D-17, the Clinical Global Impression-Severity scale (CGI-S), the Clinical Global Impression-Improvement scale (CGI-I), and the Global Assessment of Functioning (GAF).

Following evaluations were conducted with the same rating scales at the end of the continuation phase (T1), at 24 (T2) and 48 (T3) months after the end of continuation phase. Moreover, 8 evaluations were conducted at 6-month intervals during the naturalistic follow-up (from T1) with the Longitudinal Interval Follow-Up Evaluation. In addition, all patients were informed to contact their psychiatrist every time they

experienced a worsening of symptoms: in this case, another evaluation was conducted with the same rating scales.

The primary efficacy measure was time to recurrence of major depression. Patients with a HAM-D-17 score ≥ 12 were considered to be at risk for recurrence and were reevaluated within 14 days. The definition of recurrence included having a HAM-D-17 score ≥ 12 at 2 consecutive visits or at the last valid visit prior to patient's discontinuation from the study, and meeting DSM-IV criteria for major depressive disorder as judged by a senior investigator. The LIFE was used to facilitate recall and dating of episodes of psychopathology.

Two raters assessed all patients: they were 2 psychiatrists who did not participate in the study as therapists and were kept blind with respect to the treatment assignment. Patients were advised not to talk to the evaluators about the type of treatment they were on. In the early phase of the study, interrater agreement on the diagnosis, as well as the classification regarding the clinical features of MDD, were ascertained.

The interrater reliability of DSM-IV diagnosis was good ($\kappa=0.79$, 95% confidence interval=0.71–0.87). To determine interrater reliability the two raters simultaneously assessed 10 depressed subjects before the start of this study, score obtained by our raters on HAM-D correlated above 0.90.

2.5. Statistical analysis

All statistical analyses were performed by SPSS software version 15.0.

The results from any statistical comparison of the treatment groups were presented as 2-sided p values rounded to 3 decimal places. The criterion for statistical significance in all comparison was a p value ≤ 0.05 .

Paired t-test was performed to test the comparability of continuous variables in the two groups (index age, educational level, HAM-D, CGI-S, GAF). Pearson Chi-squared calculations were used to compare among groups: sex ratio, marital and occupational status, rates of recurrences.

The intent-to-treat and the completer cohorts statistical analyses of the HAM-D, CGI-S, CGI-I, and the GAF at T0 were conducted to examine differences between the treatment groups.

Time until recurrence, the primary efficacy outcome, was calculated using the date of the baseline visit (T0) at the start date and the date of the first of the 2 consecutive visits used to diagnose recurrence as the end date. Time to recurrence was evaluated using Kaplan–Meier methods and compared between the combined therapy and medication monotherapy groups using log-rank tests.

Secondary efficacy variables included the mean HAM-D, CGI-S, CGI-I, and GAF total scores and the rates of relapse and recurrence of the completers cohort (i.e., patients that did not continue to meet criteria for achieved remission).

3. Results

The study group comprised 92 subjects who completed the acute treatment (with combined treatment or with only medication) and who achieved remission from their first episode of unipolar major depression. Remission rates did not significantly differ between the two treatment groups at the end of acute phase (64.1% of remitters to combined treatment and 61.4% of remitters to only medication). The mean number of psychotherapeutic session of the $n=40$ completers assigned to combined treatment was 18.32 (± 8.46).

The mean number of psychotherapeutic sessions of the completers ($n=40$) assigned to combined treatment was 18.32 (± 8.46). The mean dose of citalopram was not significantly different in the two treatment groups (33.89 mg/die ± 3.9 for the sample assigned to combined treatment and 34.26 mg/die ± 4.1 for the sample assigned to pharmacotherapy). Likewise, the mean dose of paroxetine was not significantly different in the two treatment groups (34.21 mg/die ± 3.5 for the sample assigned to combined treatment and 33.83 mg/die ± 3.6 for the sample assigned to pharmacotherapy). Of the 92 subjects, 89 (93.7%) were followed for

the entire 5-year study period. One of the 41 remitters (2.4%) to combined treatment and two of the 51 remitters (3.9%) to medication monotherapy developed manic or hypomanic episodes during the study ($\chi^2 = .158$; $df=1$; $p=.582$). These patients' diagnoses were changed to bipolar disorder, and they were excluded from all further analyses. The treatment conditions of both the intent-to-treat and the completer cohorts did not differ in background demographic and clinical characteristics (Table 1).

Table 1
Baseline demographics and cohort characteristics

	Brief dynamic therapy plus pharmacotherapy	Pharmacotherapy	Analysis		
			χ^2/t	<i>df</i>	<i>p</i>
<i>Intent-to-treat (n=92)</i>	<i>(n=41)</i>	<i>(n=51)</i>			
Sex, <i>n (%)</i> :			.201	1	.674
Males	15 (36.6)	21 (41.2)			
Females	26 (63.4)	30 (58.8)			
Age, years: mean (s.d.)	36.0 (± 11.6)	35.8 (± 10.7)	.082	90	.935
Marital status, <i>n (%)</i> :			.648	2	.723
Married	18 (43.9)	23 (45.1)			
Divorced	9 (22.0)	8 (16.3)			
Never married	14 (34.1)	20 (39.2)			
Educational level: mean (s.d.)	11.4 (± 3.3)	11.1 (± 4.0)	.426	90	.671
Working for pay, <i>n (%)</i> :			4.238	1	.053
Yes	35 (85.4)	34 (66.7)			
No	6 (14.6)	17 (33.3)			
HAM-D: mean (s.d.)	5.5 (± 1.2)	5.6 (± 1.3)	-.290	90	.772
CGI-S: mean (s.d.)	1.2 (± 0.4)	1.2 (± 0.4)	-.071	90	.943
GAF: mean (s.d.)	86.3 (± 5.2)	85.7 (± 6.0)	.542	87	.589
<i>Completers (n=89)</i>	<i>(n=40)</i>	<i>(n=49)</i>			
Sex, <i>n (%)</i> :			.316	1	.663
Males	14 (35.0)	20 (40.8)			
Females	26 (65.0)	29 (59.2)			
Age, years: mean (s.d.)	36.3 (± 11.5)	35.9 (± 10.7)	.146	87	.884
Marital status, <i>n (%)</i> :			.681	2	.712
Married	18 (45.0)	22 (44.9)			
Divorced	9 (22.5)	8 (16.3)			
Never married	13 (32.5)	19 (38.8)			
Educational level: mean (s.d.)	11.3 (± 3.3)	10.8 (± 3.9)	.685	87	.495
Working for pay, <i>n (%)</i> :			.3668	1	.083
Yes	34 (85.0)	33 (67.3)			
No	6 (15.0)	16 (32.7)			
HAM-D: mean (s.d.)	5.5 (± 1.2)	5.6 (± 1.3)	-.326	87	.746
CGI-S: mean (s.d.)	1.2 (± 0.4)	1.2 (± 0.4)	-.105	87	.917
GAF: mean (s.d.)	86.5 (± 5.2)	85.8 (± 6.1)	.552	84	.583

At the end of the study we found that combined treatment was associated with a significantly higher proportion of patients with sustained remission (Log Rank=4.11; $df=1$; $p=.0425$), based on the HAM-D definition (Fig. 2). The probability of relapse during the continuation phase (T1) and the probability of

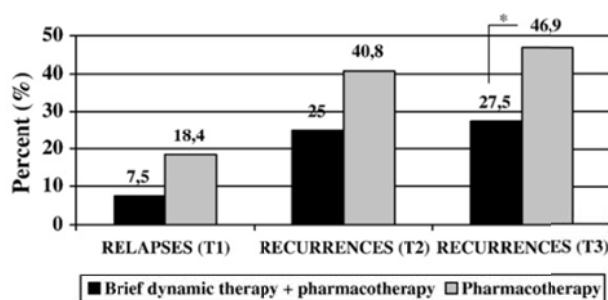


Fig. 3. Cumulative proportion of relapse and recurrence rates in the complete cohorts using HAM-D. $\chi^2: 3.525$; $df=1$; $p=.048$.

recurrence during the prospective naturalistic 48-month follow-up are presented in Fig. 3: among patients who were remitters at the end of acute treatment phase, 46.9% of those treated with combined therapy maintained remission at the end of the naturalistic 48-month follow-up, compared with 27.5% of those treated with only medication ($\chi^2 = 3.525$; $df=1$; $p=.048$). Some secondary efficacy outcomes showed significant differences between the

combined and medication groups throughout the study. End point scores on these measures are summarized in Table 2.

Table 2
Follow-up scores for combined therapy and medication therapy groups

	BDT+PT (n=40)	PT (n=49)	<i>t</i>	<i>df</i>	<i>P</i>
	Mean (±SD)	Mean (±SD)			
HAM-D					
T1 (end of continuation phase)	7.08±5.49	10.16±8.24	-2.029	87	.045
T2 (24-months follow-up)	9.07±7.14	13.53±9.36	-2.477	87	.015
T3 (48-months follow-up)	9.72±7.14	14.88±9.82	-2.772	87	.007
CGI-S					
T1 (end of continuation phase)	1.23±0.48	1.88±1.38	-2.853	87	0.005
T2 (24-months follow-up)	1.53±1.01	2.41±1.52	-3.137	87	0.002
T3 (48-months follow-up)	1.78±1.20	2.67±1.62	-2.901	87	0.005
CGI-I					
T1 (end of continuation phase)	1.27±0.75	1.78±1.24	-2.230	87	.028
T2 (24-months follow-up)	1.70±1.20	2.16±1.43	-1.628	87	.107
T3 (48-months follow-up)	1.78±1.25	2.47±1.473	-2.365	87	.020
GAF					
T1 (end of continuation phase)	85.85±5.80	82.08±9.74	2.154	87	0.034
T2 (24-months follow-up)	81.80±9.66	79.00±10.54	1.293	87	0.199
T3 (48-months follow-up)	81.30±10.00	77.27±10.60	1.831	87	0.070

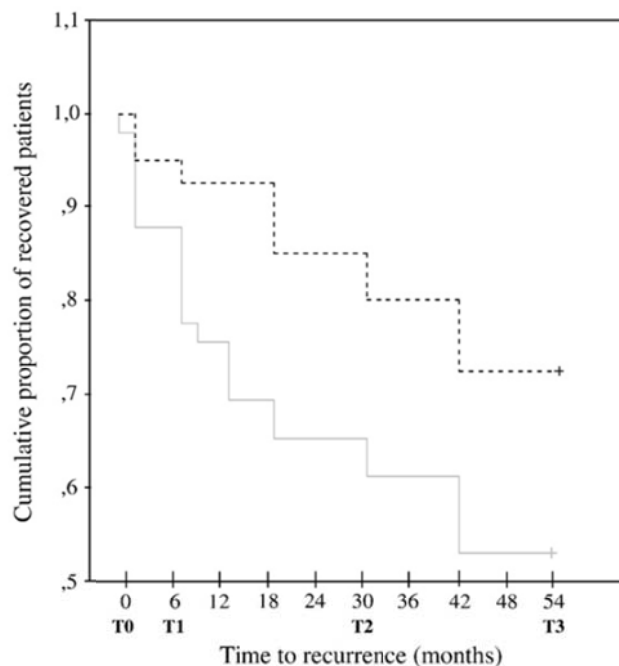


Fig. 2. Kaplan-Meier. ---: BDT+PT; ____:PT; Log rank=4.11; *p*=.042.

4. Discussion

This is the first randomised trial involving a clinical sample of patients with major depressive disorder, single episode, in which two types of acute therapy – combined therapy (brief dynamic therapy added to medication) and medication alone – are compared in terms of long-term outcome measures. The entire cohort was homogeneous in terms of subgroups of major depressive disorder being single episode and remitters to acute treatment with pharmacotherapy. Moreover, all patients without a focal problem appropriate for brief dynamic therapy had been excluded from the study (*n*=20; 11.7%). In terms of generalizability and external validity, the homogeneity of the study sample could be considered a strength

of the study for two main reasons. First, long-term observational studies have found that the risk of recurrence in major depressive disorder increases with the number of previous episodes and decreases with the duration of recovery (Mueller et al., 1999; Solomon et al., 2000) other factors that may increase the risk of recurrence include the presence of residual symptoms despite a therapeutic response (Judd et al., 2000), and the persistence of psychosocial impairment (Solomon et al., 2004). The selection of unipolar single episode with complete remission to acute treatment limits all possible bias due to these factors. Second, as the timing of additional psychotherapy initiation seems to play an important role, the recruitment of first episode unipolar depression may aid in solving this important issue. Another strength of the study is the absence of patients lost to follow-up.

The results at the prospective naturalistic 48-month follow-up indicate that the most favourable outcome was obtained from combined therapy. The addition of brief dynamic therapy to medication was more effective in the long-term recurrences prevention. Moreover, some secondary efficacy measures (CGI-S, CGI-I, and GAF) also reflected greater efficacy with combined therapy in comparison with medication alone. The significant lower recurrence rates in a 48-month period without treatment in the group of patients treated with the addition of BDT to medication in the acute treatment (27.5% in comparison with 46.9%) support the view of the advantage in the long-term outcome of adding psychotherapeutic intervention to pharmacotherapy in the acute therapy of unipolar major depression. De Jonghe et al. (2001) already underlined that combined therapy could be preferable to pharmacotherapy alone in the acute treatment of ambulatory patients with major depression but, our results support that psychotherapy may offer particularly a prophylactic effect not provided by medication in a long-term perspective, as Imel et al. (2008) suggest.

As we previously pointed out, (Maina et al., 2005; Maina et al., 2007) the primary objective of BDT, which is to enhance the patient's insight into repetitive conflicts (intrapsychic and interpersonal) and trauma, appeared to be a specific therapeutic factor: it underlies and sustains the patient's problems not only during the treatment sessions. Given the short time period of acute treatment (six months), the long-term advantage of adding this psychotherapeutic intervention to pharmacotherapy is impressive.

This study has several limitations. First, the inclusion and exclusion criteria may limit the generalizability of the results. Second, since both treatment groups did not receive comparable amounts of therapeutic attention, it may be unclear whether the effect is attributable to brief dynamic therapy per se as opposed to extra time with a therapist. Nevertheless, we previously found the specific advantage of BDT as a main efficacy factor, since the addition of an aspecific supportive treatment reaching the same amount of therapeutic contact was significantly less effective (Maina et al., 2007). Third, while we observe better outcomes in patients originally assigned to combined treatment than in those originally assigned to pharmacotherapy alone, we cannot determine if this represents a true treatment effect (combined treatment conveys additional protection against relapse) or a selection effect (reaching remission after combined treatment selects those with a better prognosis than does reaching remission with pharmacotherapy alone). Finally, these findings were obtained for outpatient treatment and may not be directly transferable to other medical systems. However, the current cohort appears to be comparable with those seen in acute psychiatric outpatients setting in Italy.

Future studies should examine whether it is more beneficial to add brief dynamic therapy in recurrent major depressive disorders. Moreover, future randomized controlled trials to compare BDT with other forms of specific psychotherapy (Cognitive-behavioural Therapy and Interpersonal Psychotherapy) in terms of efficacy and cost-effectiveness are needed.

Role of funding source

Nothing declared.

Conflict of interest

No conflict declared.

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