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Research report

Efficacy of Interpersonal Psychotherapy plus pharmacotherapy in chronically depressed inpatients

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Abstract

Background: Clinical guidelines recommend the combination of pharmaco- and psychotherapy for the treatment of chronic depression, although there are only a few studies supporting an additive effect of psychotherapy.
Methods: Forty-five inpatients with a chronic Major Depressive Disorder were randomized to 5 weeks of either Interpersonal Psychotherapy (IPT) modified for an inpatient setting (15 individual and 8 group sessions) plus pharmacotherapy or to medication plus Clinical Management (CM). The 17-item Hamilton Rating Scale for Depression was the primary outcome measure. The study included a prospective naturalistic follow-up, 3- and 12-months after discharge.
Results: Intent-to-treat analyses revealed a significantly greater reduction of depressive symptoms as well as better global functioning of patients treated with IPT compared to the CM group at week 5. Response and sustained response rates differed significantly between the two treatment conditions, favouring the IPT group. Remission rates were considerably higher for IPT patients who completed the treatment (67% vs. 32%). Patients who initially responded to IPT exhibited greater treatment gains at 12 months since only 7% of these subjects relapsed compared with 25% of the CM subjects. In the long-term, additional IPT led to a lower symptom level and higher global functioning.
Limitations: The study uses data of a subset of patients from a larger trial. Both treatment groups did not receive comparable amounts of therapeutic attention. Extrapolating the data from this inpatient study to chronically depressed outpatients may not be possible.
Conclusions: Intensive combined treatment provides superior acute and long-term effects over standard treatment in chronically depressed inpatients.

Keywords: Randomized controlled study; Chronic depression; Interpersonal Psychotherapy; Combination treatment; Inpatient treatment

1. Introduction

Roughly a third of all depressive disorders take a chronic course (Arnow and Constantino, 2003). In the USA (Kessler et al., 1994) and worldwide, about 3% of the population suffers from chronic depression. It is a particularly disabling disorder which is associated with

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greater comorbidity, higher impairments in functioning, increased health care utilisation, and more frequent suicide attempts and hospitalizations than acute major depressive episodes (Arnow and Constantino, 2003). Four major forms of chronic depression according to DSM-IV criteria (i.e. duration of at least 2 years) have been described in the recent literature: 1) dysthymia, 2) chronic Major Depressive Disorder (MDD), 3) double depression (MDD superimposed on a dysthymic disorder), and 4) recurrent MDD with incomplete recovery between episodes.

Despite the prevalence of chronic depression and the high rate of partial or nonresponders to pharmacotherapy, there are only a few studies investigating the efficacy of psychotherapy for this disorder (De Jong et al., 1986; Dunner et al., 1996; Miller et al., 1999; Ravindran et al., 1999; Keller et al., 2000; Barrett et al., 2001; Hellerstein et al., 2001; De Mello et al., 2001; Browne et al., 2002; Markowitz et al., 2005). The majority of these trials include *dysthymic* patients (Dunner et al., 1996; Ravindran et al., 1999; Barrett et al., 2001; Hellerstein et al., 2001; De Mello et al., 2001; Browne et al., 2002; Markowitz et al., 2005) and do not report a benefit of psychotherapy with or without pharmacotherapy over pharmacotherapy alone in terms of symptom reduction. In fact, in most of these studies medication outperformed psychotherapy. However, the short-term nature of the psychological interventions (6–18 sessions) utilized in these studies may not have provided an adequate test of the relative effectiveness of psychotherapy and medication/combination treatment. The investigations using Interpersonal Psychotherapy (IPT; Klerman et al., 1984; for review see Parker et al., 2006) with dysthymic patients had additional shortcomings such as the use of a nonmodified version of IPT (Browne et al., 2002) and insufficient statistical power (De Mello et al., 2001; Markowitz et al., 2005).

However, in all studies including in- or outpatients with *more severe* chronic MDD additive benefits of psychotherapy have been reported (De Jong et al., 1986; Miller et al., 1999; Keller et al., 2000). In the only large trial, Keller et al. (2000) compared a psychotherapy method specifically developed for the treatment of chronic depression (Cognitive Behavioral Analysis System of Psychotherapy, CBASP; McCullough, 2000) to medication in 681 chronic MDD patients. The combination of CBASP and nefazodone was significantly more effective and produced greater improvement in psychosocial functioning (Hirschfeld et al., 2002) than either monotherapy. Nonetheless, work is needed to clarify the impact of the "severity" of the disorder, and "form", "intensity", and "duration" of the psychotherapeutic intervention on the treatment outcome of chronic depression.

For the present reanalysis, we used the data set of a larger trial (Schramm et al., 2007) in which IPT modified for an inpatient setting plus pharmacotherapy showed superior effects over psychiatric standard treatment (Clinical Management plus medication) in 124 predominantly severely depressed inpatients. A chronic course of depression (MDE longer than 2 years, double depression, or MDEs with no interepisode remission) was diagnosed in 36% ($n=45$) of the 124 patients. For the present secondary analysis of the data, two samples were studied: the total sample of chronically depressed patients (intention-to-treat; ITT: IPT, $n=24$ and CM, $n=21$) and the subsample who completed therapy (completer sample: IPT, $n=18$ and CM, $n=19$). Follow-up analyses were restricted to patients who completed the therapeutic program ($n=37$). Our hypothesis was that inpatients with a chronic MDD would gain more from an intensive 5 week program with IPT plus medication compared to a standard treatment in the acute treatment phase and in the long-term.

2. Methods

2.1. Patients

Methods, study design and treatment conditions of the initial study have been described in detail elsewhere (Schramm et al., 2007) and will be briefly summarized. Subjects were 18 to 65 year old inpatients referred by their physician to our department. A minimum score of 16 on the 17-item version of the Hamilton Rating Scale for Depression (HAMD; Hamilton, 1960) was required to participate in the study. In total, 124 patients with a diagnosis of MDD according to the Structured Clinical Interview for DSM IV (SCID; First et al., 1997) were randomized to 5 weeks of either IPT or CM, both combined with standard pharmacotherapy. Randomization was by computer program (dynamic allocation using minimization method) using age, gender, and disorder-related stratification variables. Patients were excluded if they had a history of bipolar I disorder or psychotic symptoms, substance dependency, a mental disorder due to organic factors, a borderline or antisocial personality disorder or if they had another Axis I diagnosis that was primary. Contraindications to the study medication (sertraline or, as the second line treatment, amitriptyline or amitriptyline-*N*-oxide) and being actively suicidal were also exclusion criteria.

The study was approved by the Ethical Committee at the University of Freiburg. Written informed consent

was obtained from each subject following a complete description of the study.

2.2. Treatment conditions

The IPT program was conducted according to a modified version of the original IPT manual by Klerman et al. (1984) for the use in an inpatient setting (Schramm, 2001). The program included three weekly individual sessions and eight additional IPT-group sessions. All IPT therapists (5 psychiatric residents and 5 clinical psychologists) had completed (or were in an advanced stage of) 3 years of psychotherapy training. Prior to the study, the therapists attended a training in IPT and were monitored for adherence by receiving weekly group supervisions. The patients in the ITT sample (with chronic MDD) attended a mean of 11.54 individual sessions (SD, 3.43; range: 4–15; completers: $M=13.06$; SD, 1.66; range: 10–15).

The patients in the CM condition also received three weekly sessions according to a brief guideline (adapted from Reynolds et al., unpublished manuscript, 1988). CM was defined as a psychoeducative, supportive and empathic intervention of 15–20 min in length and was delivered by psychiatric residents. The main components of CM involved the management of symptoms and of medication side effects, the psychoeducation of the patient and close persons, simple problem solving or advice, and to instill hope and optimism (for more detail see Supplementary appendix). All residents ($n=26$) had a didactic training in CM for at least half a day. Audiotaped CM sessions were continually checked for adherence using the therapist rating scale (Wagner et al., 1992).

Both treatment groups received standardized pharmacotherapy in addition to IPT or CM by the treating physician who was aware to the patient's treatment status. The first line treatment was sertraline ($n=24$ chronic depressives in the ITT sample; $n=20$ among completers). In the case of a known nonresponse to sertraline in the patient's treatment history, amitriptyline or amitriptyline-*N*-oxide was applied as the second line treatment ($n=19$ in the ITT sample; $n=15$ among completers). Two patients (1 CM, 1 IPT) who started treatment with sertraline received additional amitriptyline or amitriptyline-*N*-oxide after the second week due to an unsatisfactory response to sertraline. In the ITT sample the mean final dosage for sertraline was 80.2 mg/day (SD, 32.9; range: 50–150 mg/day) and among completers 77.5 mg/day (SD, 31.3; range: 50–150 mg/day). For amitriptyline or amitriptyline-*N*-oxide the mean final dosage in the ITT sample was 160.8 mg/day (SD, 58.2; range: 75–300 mg/day), among completers 167.0 mg/day (SD, 63.4; range: 75–300 mg/day). As rescue medications lorazepam (max. 3 mg) or oxazepam (max. 30 mg) were allowed for a maximum of three weeks. A benzodiazepine was administered to 13 (28.9%) of the 45 patients in the ITT sample and 11 (29.7%) of the completers, this difference was not significant in either sample. The number of patients using sertraline or amitriptyline was similar in both treatment conditions, and in both the ITT and the completer samples. Furthermore, there was no significant difference in the mean final dosage between IPT and CM patients for both types of medication in both samples. All patients participated in usual hospital activities such as daily ward rounds, occupational therapy groups, and physiotherapy.

2.3. Assessments

The 17-item version of the HAMD (Hamilton, 1960) served as the primary outcome measure. Secondary measures included the Beck Depression Inventory (BDI; Beck et al., 1961), and the Global Assessment of Functioning (GAF; Endicott et al., 1976). In the follow-up period weekly psychiatric status ratings (PSRs), based on DSM-IV symptoms of depression, were recorded retrospectively by the patient. Criteria for the PSR (according to the Longitudinal Interview Follow-up Evaluation; Keller et al., 1987) format ranged from "1 = no symptoms" to "6 = meets full criteria of major depression".

Treatment *response* was defined a priori as a reduction in symptom severity of 50% or higher on the HAMD, *remission* as a score of 7 or less on the HAMD. Following initial posttreatment response, patients were considered to have *relapsed* if they had a HAMD score of ≥ 15 in combination with a PSR score of ≥ 5 for a minimum of two weeks. *Sustained response* was defined as responding to acute inpatient treatment, maintaining the response and staying free from relapse, and not being rehospitalized during the course of follow-up. *Sustained remission* was defined as a score of 7 or less on the HAMD plus a PSR score of 1 or 2 for at least two weeks following initial remission with no relapse and no rehospitalization during the follow-up period.

The SCID (First et al., 1997) was conducted by trained and experienced clinical psychologists. The efficacy of treatment was evaluated 5 weeks after beginning of treatment, and 3 and 12 months post-hospitalization in terms of a naturalistic follow-up. The follow-up evaluations were performed by clinical psychologists who were blind to treatment condition, had not been involved in the inpatient care, and worked outside the hospital building. The patients were instructed not to mention anything that might reveal their treatment group to the evaluator. Interrater

reliability for the HAMD was obtained from all evaluators from a random sample of 13 audio- or videotaped HAMD interviews (intraclass correlation coefficient: 0.94).

2.4. Statistics

The treatment groups (ITT: $n=45$; completers: $n=37$) were pairwise compared. For differences in demographic and clinical characteristics at baseline, the χ^2-test and the unpaired t-test were used. The primary analysis for examining changes over time was a repeated-measure analysis of variance. The overall efficacy of treatment was assessed by an analysis of covariance (ANCOVA) controlling for pretreatment scores on all outcome measures by treatment condition at week 5. In the completer sample, "age" was also used as a covariate because there was a statistical significant difference between groups. In the case of attrition between baseline and posttreatment for the ITT sample, "last observation carried forward" was used. Completer analysis at month 3 and 12 was conducted to examine differences between groups.

Data for response, remission, and relapse for the percentage of patients who reached cutoff scores were analyzed using Fisher's exact test. The effect of potential predictors (such as severity, comorbidity on axis I or II, etc.) on the response rate was examined by means of a binary logistic regression (method forward LR). The effect sizes (ES) were calculated using Cohen's d statistic (Olejnik and Algina, 2000). All statistical tests were two-tailed, and significance was declared at the .05 level.

3. Results

3.1. Baseline patient characteristics

There were no significant differences between both treatment groups with respect to baseline demographic and clinical characteristics (Table 1), except for age in the completer sample (IPT: 39.11±11.90 years; CM: 46.68±9.46 years, $p=.039$).

More than half of the patients in the total sample (53%; 24 of 45) suffered from a double depression, with this increasing to over three quarters (75.8%, $n=18$) in

Table 1
Baseline demographic and sample characteristics of the patients for the IPT and the CM group

	ITT sample ($n=45$)					Completer sample ($n=37$)				
	IPT ($n=24$)	CM ($n=21$)	χ^2/t	df	p	IPT ($n=18$)	CM ($n=19$)	χ^2/t	df	p
Age, mean (SD), y	40.0 (10.77)	45.9 (9.38)	1.93	43	.06	39.1 (11.9)	46.7 (9.5)	2.15	35	.04
Female	14 (58.3)	16 (76.2)	1.61	1	.34	11 (61.1)	16 (84.2)	2.50	1	.11
Family status										
Single	9 (37.5)	7 (33.3)				8 (44.4)	6 (31.6)			
Married	12 (50.0)	9 (42.9)				7 (38.9)	8 (42.1)			
Separated, divorced or widowed	3 (12.5)	5 (23.8)	.38	2	.83	3 (16.7)	5 (26.3)	2.33	2	.80
Education, mean (SD), y	10.8 (1.64)	10.7 (1.78)	.18	43	.86	10.8 (1.7)	10.6 (1.8)	.39	35	.67
Working	15 (62.5)	14 (66.7)	.09	1	.99	12 (66.7)	12 (63.2)	.05	1	.55
Early onset	8 (33.3)	4 (19.0)	1.17	1	.33	5 (27.8)	3 (15.8)	.78	1	.45
Number of episodes										
1. episode	8 (33.3)	5 (23.8)				6 (33.3)	5 (26.3)			
2. episodes and more	16 (66.7)	16 (76.2)	.50	1	.53	12 (66.7)	14 (73.7)	.22	2	.73
Melancholia	15 (62.5)	13 (61.9)	.00	1	.99	11 (61.1)	13 (68.4)	.22	1	.45
Bipolar II	1 (4.2)	1 (4.8)	.01	1	.99	1 (5.6)	1 (5.3)	.00	1	.99
History of suicidal attempt	7 (29.2)	3 (14.3)	2.53	1	.43	6 (33.3)	3 (15.8)	2.90	1	.23
Comorbidity axis I	19 (79.2)	16 (76.2)	.06	1	.99	14 (77.8)	14 (73.7)	.08	1	.54
Double Depression	14 (58.3)	10 (47.6)	.52	1	.56	10 (55.6)	8 (42.1)	.67	1	.31
Comorbidity axis II										
Traits	7 (30.4)	8 (38.1)				6 (33.3)	7 (36.8)			
Disorder	9 (39.1)	4 (19.0)	2.15	2	.34	7 (38.9)	3 (15.8)	2.80	2	.25
Previous treatment										
Psychotherapy	18 (75.0)	16 (76.2)	.01	1	.99	13 (91.0)	14 (73.7)	.01	1	.61
Pharmacotherapy	16 (66.7)	18 (85.7)	2.20	1	.18	9 (50.0)	11 (57.9)	.23	1	.44
Hospitalization	10 (41.7)	13 (61.9)	1.83	1	.17	7 (38.9)	13 (68.4)	3.24	1	.07

Abbreviations: IPT, interpersonal psychotherapy; CM, clinical management; y years.
Unless otherwise indicated, data are presented as number (percentage).

the completer sample. The remaining patients had a MDD with a chronic course according to DSM IV. The majority of the total sample (96%) was evaluated as markedly and severely ill by the treating physician using the Clinical Global Impression Scale (CGI; National Institute of Mental Health, 1985) as a part of clinical routine. Most of the patients were characterized by features of severe depressive disorder (see Tables 1 and 2) such as initial HAMD scores of 20 or more (mean HAMD score: 24.6; SD, 4.6), as employed in the Elkin et al. (1989) report, scores of 49 or below in the Global Assessment of Functioning (GAF; Endicott et al., 1976) Scale (mean GAF score: 46.2; SD, 8.9) and melancholic subtypes (62.2%) as suggested by Thase (2000). Almost two third of the patients ($n=28$) suffered from marked suicidal thoughts as indicated by a HAMD item score of three or higher. The majority (89%) had received outpatient treatment before admission, while approximately half of the patients (51%) reported at least one previous hospitalization for the treatment of depression.

Other axis I diagnoses according to the SCID I among ITT patients were 7 of substance abuse (not primary), 6 of anxiety, 2 of somatoform, 1 of attention-deficit, and 3 of eating disorders, with no statistical difference between the treatment groups. Axis II disorders or traits (SCID II; First et al., 1996) were diagnosed in 28 (63.3%) of the patients with no significant difference between the treatment conditions (see Table 1).

3.2. Acute phase results

3.2.1. General acute treatment effects

Repeated-measure analysis of variance revealed a significant improvement and large effect sizes in both treatment groups from baseline to week 5 (Table 2) for clinician rated (HAMD, ITT: $F[1,43]=87.31$, $p=.001$, $ES_{pre-post}$ IPT: $d=3.57$ and CM: $d=1.98$; completer: $F[1,35]=98.84$, $p=.001$, $ES_{pre-post}$ IPT: $d=3.71$ and CM: $d=2.04$) and self-rated depression (BDI, ITT: $F[1,43]=69.64$, $p=.001$, $ES_{pre-post}$ IPT: $d=2.18$ and CM: $d=1.46$; completer: $F[1,33]=60.50$, $p=.001$, $ES_{pre-post}$ IPT: $d=3.57$ and CM: $d=1.45$). In the ITT analysis, mean HAMD scores of the IPT group dropped from 25.58 to 9.95 (BDI: 31.75 to 16.65) and in the CM

Table 2
Posttreatment and follow-up scores for the IPT and the CM group

Posttreatment								
		Baseline Mean (SD)	Posttreatment Mean (SD)	Δ pre–post Mean (SD)	*F*	*df*	*p*	ES
ITT sample ($N=45$)								
HAMD	IPT	25.58 (4.38)	9.95 (7.44)	15.63 (8.73)				
	CM	23.48 (4.76)	14.05 (7.93)	9.43 (8.40)	4.82	1/42	.034	.90
BDI	IPT	31.75 (6.92)	16.65 (12.22)	15.10 (11.08)				
	CM	34.24 (9.93)	19.74 (13.25)	14.50 (12.80)	.97	1/42	.331	.37
GAF	IPT	45.13 (7.84)	66.29 (14.30)	21.16 (13.41)				
	CM	47.38 (10.11)	60.05 (13.63)	12.67 (16.19)	4.99	1/42	.031	.70
Completer sample ($N=37$)								
HAMD	IPT	25.44 (4.87)	7.39 (5.43)	18.06 (8.08)				
	CM	23.00 (4.75)	13.32 (7.83)	9.68 (8.71)	11.22	1/34	.002	1.23
BDI	IPT	30.11 (4.96)	13.39 (10.43)	16.72 (11.17)				
	CM	33.68 (10.31)	18.68 (13.19)	15.00 (13.44)	2.80	1/34	.066	.65
GAF	IPT	46.56 (6.72)	72.44 (9.70)	25.89 (11.37)				
	CM	48.16 (9.78)	61.79 (13.14)	13.63 (16.32)	13.84	1/34	.001	1.26

Follow-up								
		IPT Mean (SD)	CM Mean (SD)	Δ Mean (SE)	*t*	*df*	*p*	ES
HAMD	F1	5.00 (4.29)	10.00 (7.85)	5.00 (2.14)	2.34	26.90	.027	1.05
	F2	5.87 (5.10)	11.28 (10.54)	5.41 (2.81)	1.93	25.45	.065	1.14
BDI	F1	10.47 (8.85)	15.94 (12.31)	5.48 (3.81)	1.44	31	.160	.51
	F2	9.87 (8.41)	20.06 (16.71)	10.19 (4.60)	2.22	24.22	.036	.99
GAF	F1	78.38 (10.55)	68.18 (12.83)	10.20 (4.10)	2.49	31	.019	1.21
	F2	76.87 (9.10)	65.61 (19.89)	11.26 (5.25)	2.15	24.72	.042	1.15

Abbreviations: BDI, Beck Depression Inventory; CM, clinical management; ES, effect size calculated using Cohen´s d statistic IPT vs. CM; F1, 3-month follow-up; F2, 12-month follow-up; GAF, Global Assessment of Functioning; HAMD, Hamilton Depression Rating Scale; IPT, interpersonal psychotherapy; Δpre–post=absolute difference between baseline and week 5; Δ=absolute difference between IPT and CM.

group from 23.48 to 14.05 (BDI: 34.24 to 19.74) after 5 weeks of treatment.

Analysis of covariance showed a significant benefit of IPT over CM on the HAMD at week 5 (ITT: F [1,42]=4.82, p =.034, $ES_{IPT\text{-}CM}$: d=.90; completer: F [1,34]=11.22, p =.002, $ES_{IPT\text{-}CM}$: d=1.23). Patients in the IPT group reported also lower BDI-scores, but the difference did not reach statistical difference (Table 2).

3.3. Response and remission rates

There was a significant difference between IPT and CM regarding response rates at posttreatment (ITT: 70.8% vs. 38.1%, p =.038; completer: 83.3% vs. 42.1%, p =.017) favouring therapy with IPT. In the binary logistic regression, the potential predictors "severity of depression" (HAMD ≥ 20), "comorbidity on axis I or II", "early onset" and "history of suicidal attempt" showed no significant effect on the response rate. Differences in remission rates were not statistically significant in the ITT sample (IPT: 50.0%, CM: 28.6%, p =.123), but achieved significance in the completer sample (66.7% vs. 31.6%, p =.050) (Fig. 1a).

3.4. Global functioning

Overall functioning improved substantially from baseline to week 5 (GAF, ITT: F[1,43]=58.79, p =.001; completer: F[1,35]=71.13, p =.001) in both treatment groups. The ANCOVA showed a main treatment effect significantly favouring combined therapy (GAF, ITT: [1,42]=4.99, p =.031, $ES_{IPT\text{-}CM}$: d=.70; completer: [1,34]=13.84, p =.001, $ES_{IPT=CM}$: d=1.26).

3.5. Follow-up phase

Assessments during the naturalistic follow-up period were conducted 3 and 12 months posthospital. Both follow-up assessments were completed by 95.6% of the patients. Only 2 subjects (one in each condition) did not complete both follow-up assessments. There was no statistically significant difference on any of the demographic or clinical variables between those patients who participated in the follow-up evaluation and those who did not.

Most patients remained on pharmacotherapy during the 12 months period after discharge (IPT: 14 of 17; 82.4%, and CM: 16 of 18; 88.9%). Psychotherapy was still received by 60.5% of the patients (IPT: 11 of 17; 65%, and CM: 10 of 18; 56%). Only 9.1% of all patients had discontinued all forms of treatment by 12 months. There was no significant difference between the treatment groups regarding the use of posthospitalization pharmacotherapy or psychotherapy. For detailed data see Table 3.

3.6. General treatment effects

A significantly higher reduction of depressive symptoms on the HAMD was found at 3 months after discharge in the IPT group (mean score of 5 vs.10 in CM; t [26.90]=2.34, p =.027, $ES_{IPT\text{-}CM}$: d=1.05) (Table 2). There was a trend toward lower scores on the HAMD for IPT patients (t[25.45]=1.93, p =.065) at 12 months (mean score of 5.87 vs.11.28 in CM) and a significantly higher symptom reduction on the BDI favouring the IPT treatment (mean score of 9.87 vs. 20.06 in CM; t[24.22]=2.22, p =.036, $ES_{IPT\text{-}CM}$: d=.99).

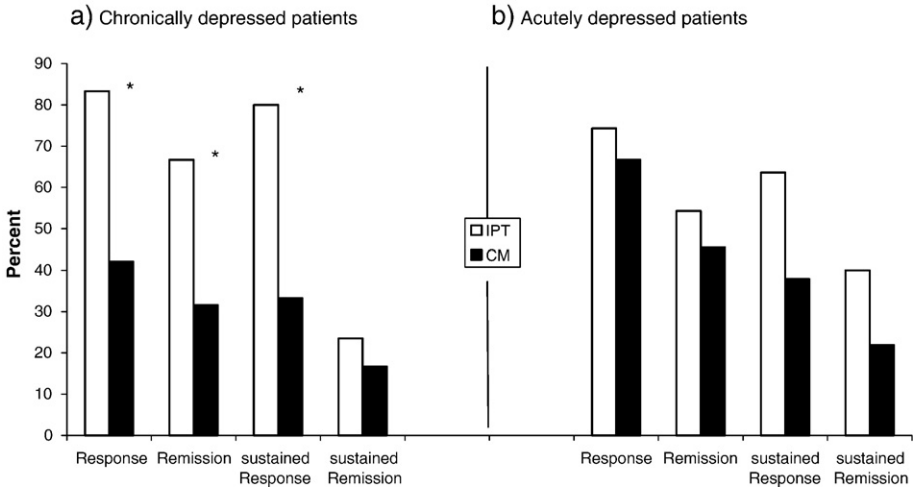

Fig. 1. Response and remission rates over time (12 months) in the completer sample using the HAMD. Abbreviations: CM, clinical management; HAMD, Hamilton Depression Rating Scale; IPT, Interpersonal Psychotherapy. ∗Group comparison between IPT and CM, $p \leq .05$.

Table 3
Posthospitalization treatment and rehospitalization rates in the naturalistic follow-up period

	N	IPT	CM	p value
		No (%)	No (%)	
Pharmacotherapy				
3 month	33	16 (94)	16 (89)	.522
12 month	35	14 (82)	16 (89)	.352
Psychotherapy				
3 month	35	12 (71)	11 (61)	.408
12 month	35	11 (65)	10 (56)	.418
Rehospitalization				
3 month	35	0 (0)	0 (0)	
12 month	35	2 (12)	3 (17)	.528

Abbreviations CM, clinical management. IPT, interpersonal psychotherapy.

3.7. Relapse rates and rehospitalizations

Up to 12 months after discharge, 1 of 15 patients (6.7%) who had responded after 5 weeks of combined treatment relapsed compared with 2 of 8 patients (25%) in the CM group (p =.263). Rehospitalization due to acute psychiatric symptoms occurred in 14.2% of the patients (5 of 35) during the entire course of follow-up, with no statistical difference between groups (IPT: 2 of 17; 11.7% and CM: 3 of 18; 16.7%; see Table 3).

3.8. Sustained response and remission

The sustained response rate at 3 months was 81.3% (13 of 16) in the IPT group compared with only 33.3% (6 of 18) in the CM group. This difference was statistically significant (p =.007) and was maintained at 12 months (IPT: 80.0%, 12 of 15 vs. CM: 33.3%, 6 of 18; p =.013) (Fig. 1). Rates of sustained remission were higher in the IPT group but did not reach statistical significance at either 3 months (IPT: 23.5%, 4 of 17 vs. CM: 16.7%, 3 of 18; p =.691) or 12 months (IPT: 23.5%, 4 of 17 vs. CM: 16.7%, 3 of 18; p =.691).

3.9. Global functioning

The initial combination treatment revealed more improved global functioning, as measured by the GAF than the standard treatment at 3 and 12 months (t[31]=2.49, p =.019, $ES_{IPT\text{-}CM}$: d=1.21 and t[24.72]=2.15, p =.042, $ES_{IPT\text{-}CM}$: d=1.15; see Table 2).

3.10. Comparison with the subset of acutely depressed patients

For better understanding of our results we compared the subset of chronically depressed patients with the subset of acutely depressed patients regarding the clinically most relevant data, namely response and remission. As shown in Fig. 1b, significant differences between CM and IPT were only found in the subset of chronically depressives.

4. Discussion

A brief, but intensive treatment program combining medication with Interpersonal Psychotherapy had significant acute and long-term benefits over a standard psychiatric intervention in chronically depressed inpatients. Outcomes both at the end of 5 weeks of inpatient treatment and across a year of follow-up consistently favoured the group that received the combination therapy, although not all, particularly self-reported effects achieved statistical significance. Response rates to combination treatment (71%) – as high as those found in the outpatient study of Keller and colleagues (Keller et al., 2000) – were observed in the present trial while only 38% of the patients in the standard therapy group responded. In addition, the remission rate of 67% among those patients who completed the multicomponent 5-week program was significantly higher than in the CM condition (32%) and in the trial of Keller et al. (2000) (42%). The response was sustained by most of the IPT patients over the 12 month period following hospital discharge, an important finding given the chronic nature of the depressive disorder. Furthermore, patients initially treated with IPT reported a significantly lower level of depressive symptoms and showed higher global functioning at the 12 months follow-up.

The long-term superiority of the initial combination therapy over the standard treatment, as indicated by significant differences on both symptom and psychosocial levels 3 and 12 months posthospitalization, is particularly impressive given the short period of *acute* treatment and the relatively strong comparison condition. However, it should be noted that the vast majority of patients in both treatment groups continued pharmaco- and/or psychotherapy on an outpatient basis, in line with previous recommendations of several authors for longer and more intensive treatment courses for patients with a chronic or recurrent depressive disorder (Segal et al., 2001; Dunner, 2001; Conradi et al., 2007).

In contrast to previous studies with *dysthymic* patients using IPT (De Mello et al., 2001; Browne et al., 2002; Markowitz et al., 2005), our trial revealed a significant

additional effect of IPT. The differences between the present study and the others lie not only in the intensity of the treatment program and the inpatient setting, respectively, and the high rate (more than 85%) of continued treatment but also in the fact that we did not include purely dysthymic patients. In addition, we used a modified form of IPT including the option of family involvement in some of the individual sessions, and group sessions with interpersonal and behavioural components. All these factors may have increased the efficacy of the additional psychotherapy.

Several limitations to this study are worth noting. First, the study is a secondary analysis including only a subgroup of the whole sample and may therefore be underpowered. Second, acute response and remission rates were defined on the basis of a single assessment covering only one week's time. In the follow-up phase, there were only two assessment points regarding the application of the HAMD-scale. However, weekly psychiatric status ratings recorded by the patient to identify change in depressive symptoms over time were included in the definition of relapse, and of sustained response and remission. Third, since both treatment groups did not receive comparable amounts of therapeutic attention, it is unclear if the effect is attributable to IPT per se as opposed to extra time with a therapist. We consider it unlikely that the amount of time spent with a health professional was a major factor, as due to the inpatient setting ceiling effects in terms of amount of therapeutic contact were reached in both treatment groups. The possibility that CM-therapists did not provide decent clinical management can be excluded since an audiotape-analysis of the quality of CM sessions revealed high adherence (Zobel et al., unpublished manuscript). Fourth, the average doses of both types of medication were relatively low, reflecting the prescription habits in Germany. A higher dose may have led to a higher response rate and diminished the effect of IPT treatment. In addition, the treating physicians who prescribed the medication were not blind with respect to the treatment status of the patient since the study was performed in a routine clinical setting. Finally, these findings were obtained for inpatient treatment and may not be directly transferable to other medical systems, or to other countries. Patients in the German Health System are much more frequently hospitalized as compared to most other countries which limits the generalizability of this investigation. Extrapolating the data from this inpatient study to chronically depressed outpatients may be limited. However, the current cohort appears to be comparable to those seen in psychiatric outpatient settings in the United States.

In summary, while limited by some factors, the results of this study provide hope that with intensive treatment chronically depressed patients have a good chance of getting well relatively quickly and with lasting effects. The acute and long-term response rates and high effect sizes found in this study suggest that combined treatment provides a clinically meaningful benefit over monotherapy. Future studies should examine whether CBASP (McCullough, 2000), the most specific and so far most promising psychotherapy approach for chronic depression, is more effective than IPT if also applied in an intensive fashion.

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Conflict of interest

Dr. van Calker has received honoraria for lecturing from AstraZeneka, Pfizer, Eli Lilly, Merz, Sanofi, Organon, Neuraxpharm, Wyeth, Bristol-Myers Squibb. All other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jad.2007.10.013.

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