

Contents lists available at ScienceDirect

Journal of Affective Disorders



journal homepage: www.elsevier.com/locate/jad

Research report

Cognitive behavioral analysis system of psychotherapy versus interpersonal psychotherapy for early-onset chronic depression: A randomized pilot study $\stackrel{>}{\sim}$

Elisabeth Schramm^{*}, Ingo Zobel, Petra Dykierek, Sabine Kech, Eva-Lotta Brakemeier, Anne Külz, Mathias Berger

Department of Psychiatry and Psychotherapy, University Medical Centre Freiburg, Germany

ARTICLE INFO

Article history: Received 11 June 2010 Received in revised form 3 August 2010 Accepted 3 August 2010 Available online 6 September 2010

Keywords: Randomized controlled study Chronic depression Cognitive Behavioral Analysis System of Psychotherapy Interpersonal psychotherapy

ABSTRACT

Background: The only psychotherapy specifically designed and evaluated for the treatment of chronic depression, the Cognitive Behavioral Analysis System of Psychotherapy (CBASP), has never been directly compared to another depression-specific psychological method.

Methods: Thirty patients with early-onset chronic depression were randomized to 22 sessions of CBASP or Interpersonal Psychotherapy (IPT) provided in 16 weeks. Primary outcome was the score on the 24-item Hamilton Rating Scale for Depression (HRSD) assessed posttreatment by an independent blinded evaluator. Secondary endpoints were, among others, remission (HRSD \leq 8) rates and the Beck Depression Inventory (BDI). The study included a prospective naturalistic 12-month follow-up.

Results: Intent-to-treat analyses of covariance (ANCOVA) revealed that there was no significant difference in posttreatment HRSD scores between the CBASP and the IPT condition, but in self-rated BDI scores. We found significantly higher remission rates in the CBASP (57%) as compared to the IPT (20%) group. One year posttreatment, no significant differences were found in the self-reported symptom level (BDI) using ANCOVA.

Limitations: The study used only a small sample size and no placebo control. The generalizability of the results may be limited to patients with a preference for psychological treatment.

Conclusions: While the primary outcome was not significant, secondary measures showed relevant benefits of CBASP over IPT. We found preliminary evidence that in early-onset chronic depression, an approach specifically designed for this patient population was superior to a method originally developed for the treatment of acute depressive episodes. Long-term results suggest that chronically depressed patients may need extended treatment courses.

© 2010 Elsevier B.V. All rights reserved.

1. Introduction

Up to one third of all mood disorders take a chronic (defined as 2 years or more) course (Klein and Santiago, 2003; Klein, 2008) which implies that 2.5–6% of the Western population suffer from chronic depression (Kessler et al., 1994, 2005; Torpey and Klein, 2008). Compared to acute major depressive episodes chronic depression is associated with greater comorbidity, more significant impairments in functioning, more interpersonal deficits, increased health care utilization, more frequent suicide attempts and hospitalizations, more early adversity, and earlier onset (for review see Arnow and Constantino, 2003; Torpey and Klein 2008; Angst et al., 2009). Not surprisingly, patients with chronic depression are also more difficult to treat with both pharmacological and psychological

 $[\]stackrel{\text{\tiny{fr}}}{\to}$ Parts of the study were presented at the 3rd International conference of the International Society for Interpersonal Psychotherapy, March 2009 in New York.

^{*} Corresponding author. University Medical Center Freiburg, Dept. of Psychiatry and Psychotherapy, Hauptstr. 5, 79104 Freiburg, Germany. Tel.: +49 761/270 6967; fax: +49 761/270 6966.

E-mail address: Elisabeth.Schramm@uniklinik-freiburg.de (E. Schramm).

^{0165-0327/\$ –} see front matter © 2010 Elsevier B.V. All rights reserved. doi:10.1016/j.jad.2010.08.003

approaches (Kocsis, 2003; Markowitz, 1995). In more than 70% of all cases, chronic depression begins before the age of 21 years (Cassano et al., 1992; Keller et al., 2000), is usually associated with early trauma (Lizardi et al., 1995, Wiersma et al., 2009), and frequently persists for the entire lifespan. Early-onset chronic depression results in a more substantial human capital loss than late-onset (Berndt et al., 2000). In addition, the disorder has a more malignant course than late-onset depression (Klein et al., 1999) and shows a high rate of relapse after an initial response to medication treatment (Agosti, 1999).

Although psychotherapy is commonly applied to long-term depressed patients in clinical practice (Angst et al., 2009), there has been only limited research on the efficacy of psychological interventions for chronic forms of depression. In a recent metaanalysis, psychotherapy had a small but significant effect on chronic depression when compared to control groups (Cuijpers et al., 2010). The approach with the strongest empirical support is the Cognitive Behavioral Analysis System of Psychotherapy (McCullough, 2000), the only psychotherapeutic method specifically designed for this disorder. One large trial (n = 681; Keller et al., 2000) showed that for a subgroup of chronic depressives with an early childhood trauma (Nemeroff et al., 2003), CBASP was particularly effective with and without additional medication. In contrast, medication (nefazodone) alone had a weak effect in this subgroup of patients as only 33% reached remission (48% with CBASP). Similarly, imipramine but also more traditional psychotherapies (IPT, and Cognitive Behavioral Therapy/CBT) performed relatively poorly in the subgroup of early-onset chronic depression as shown by a reanalysis (Agosti and Ocepek-Welikson, 1997) of the data from the NIMH-Collaborative study. In another trial (Markowitz et al., 2005) with early-onset patients suffering from dysthymia IPT modified for dysthymic disorders was no more successful than the control condition (supportive psychotherapy). However, in our own study (Schramm et al., 2008) a more intensive course of IPT plus medication in hospitalized patients with severe chronic major depression was superior to a standard psychiatric treatment.

Nevertheless, as an augmentation strategy for non- or partial responders to a medication algorithm (Kocsis et al., 2009) 12 sessions of CBASP did not fare better than the control conditions (supportive therapy or a medication switch). The data suggest that chronic depression requires more frequent sessions (Thase et al., 1994) and a longer duration of treatment (Gelenberg et al., 2003) and therefore the results of the study by Kocsis et al. (2009) need to be interpreted with caution.

In summary, while the results of the outlined trials are mixed, CBASP performed best in the subgroup of patients it was originally developed for by McCullough (2000): chronically depressed patients with early trauma (most of whom can be assumed to have early onset). The CBASP approach aims specifically at overcoming interpersonal, cognitiveemotive and other maturational deficits which resulted from early maltreatment by focusing on the therapeutic relationship. The IPT model which was originally designed for acute depressive episodes assumes that, independent from the causes, depression always occurs in a context of acute interpersonal stress (vulnerability-stress-model). Resolving current problem areas associated with the depression is the focus of IPT. It is the first comparison of these two theoretically distinct, depression-specific interventions in chronic depression. Our primary hypothesis was that in patients with early-onset chronic depression CBASP which is specifically tailored to the needs and deficits of this patient group would be superior to IPT in terms of *reduction of depressive symptoms* when applied in an intense manner (22 sessions in 16 weeks). The secondary hypothesis was that CBASP would lead to higher *remission rates* than IPT.

2. Methods

2.1. Patients

Subjects were 18 to 65 years old, mostly physicianreferred outpatients of the Department of Psychiatry and Psychotherapy of the University Medical Center Freiburg, Germany. Eligible patients met DSM-IV criteria for a current episode of chronic MDD, MDD superimposed on a preexisting dysthymic disorder, recurrent MDD with incomplete remission between episodes in a patient with a current MDD and a total duration of at least 2 years, or dysthymia. In addition, early onset (before the age of 21) according to DSM-IV and a score of at least 16 on the 24-item Hamilton Rating Scale of Depression (HRSD, Hamilton, 1967) at screening and if given, after a 2-week drug-free period, at baseline were required. Furthermore, patients needed to be fluent in the German language and give their written informed consent.

In total, 30 patients with a diagnosis of early-onset chronic depression according to the Structured Clinical Interview for DSM-IV (SCID; First et al., 1997) were randomized to 22 individual sessions of either CBASP or IPT over a time period of 16 weeks. Randomization was conducted according to a central computerized randomization schedule, with a 1:1 treatment allocation ratio, stratified by early trauma, in blocks of variable size, to guarantee concealment. "Early trauma" was defined as an experience of emotional/physical/sexual abuse, and emotional/physical neglect before the age of 18 to a degree of at least "moderate to severe" on the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1994). Early trauma was used as a stratification variable because according to McCullough's (2000) theory we assumed an impact of traumatization on outcome.

Patients were excluded if they had an acute risk for suicide (as opposed to suicidal thoughts or chronic suicidality) assessed according to clinical practice guidelines. Further exclusion criteria were: a history of psychotic symptoms, bipolar disorder, or organic brain disorders, a primary diagnosis of another axis I disorder including anxiety disorders (e.g. posttraumatic stress disorder), or substance dependence as evaluated with the Structured Clinical Interview for DSM-IV (SCID-I and II; First et al., 1997), antisocial, schizotypal, or borderline personality disorder, a serious medical condition, severe cognitive impairment, absence of a response to previous adequate trial of CBASP, and/or IPT, or other ongoing psychotherapy or medication.

The study was approved by the ethical committee at the University of Freiburg. The protocol was registered at a University Register of Clinical Studies Web site (UKF000931).

2.2. Treatment conditions

The CBASP program follows a manual (McCullough, 2000; German version: Schramm et al., 2006). The approach is specifically tailored for the treatment of chronic forms of depression, particularly with early-onset by focusing on the problems resulting from an inhibition of maturation in early childhood and by using the therapeutic relationship in a personal disciplined way. CBASP is highly structured and integrates behavioral, cognitive, and interpersonal strategies to teach patients interpersonal problem solving skills.

IPT is also manualized (Klerman et al., 1984; Weissman et al., 2000; German version: Schramm, 1998), but less structured than CBASP. It is a time-limited approach originally developed for the treatment of acute major depressive episodes. IPT focuses on current interpersonal and psychosocial life-events or problem areas associated with the depression. The style of therapy resembles that of psychodynamic short-term approaches. The therapeutic relationship is defined as supportive and helpful; however, transference issues are not discussed with the patients. In the present study, we applied the modification of IPT for use with chronic depression by Markowitz (1998).

Both treatments included two weekly 50 min individual sessions for the first 6 weeks and weekly sessions thereafter. If there was no improvement in the depressive symptoms (reduction in the baseline HRSD score of at least 20%) after 8 weeks of treatment the patient received one additional session per week for two more weeks as a dose adjustment. Thus, a minimum of 22 and a maximum of 24 sessions were offered. There was a naturalistic 1-year follow-up after the last therapy session.

All therapists (9 female clinical psychologists) had completed (or in one case were in an advanced stage of) 3 years of psychotherapy training. Prior to the trial, the study therapists attended a minimum of 2 days of training in either IPT or CBASP. The study therapists treated 1–12 cases and were monitored for adherence by receiving regular group supervision. For this purpose, all therapy sessions were videotaped and viewed regularly by the supervisor (authors: E.S. for CBASP, and P.D. for IPT). Both the study therapists and the supervisors practiced and supervised, respectively, only one of the two approaches.

The patients in the intention-to-treat sample (ITT; n = 29) attended a mean of 21.21 individual sessions (SD = 3.12; range: 9–24; completers: M = 22.15; SD = 0.92; range: 21–24).

2.3. Assessments

The 24-item version of the HRSD (Miller et al., 1985) served as the primary outcome measure. Secondary measures included the Beck Depression Inventory (BDI; Beck et al., 1961), and the assessment of social functioning. To measure global psychological, social, and occupational functioning, the widely utilized Global Assessment of Functioning (GAF; Endicott et al., 1976) scale was used. The GAF-scale ranges from 0 to 90, with scores of 50 or below reflecting serious impairments in global functioning, whereas scores of more than 70 reflect only mild and transient impairments. Another measurement was the Social Adaptation Self-Evaluation Scale (SASS; Duschek et al., 2003), specifically designed for self-assessment of social functioning of patients with depression. This scale has been used in European clinical trials and is currently being studied in the United States. It contains 21 items covering different aspects of social interactions, global social attitude, and selfperception. The SASS has been validated and found to be simple to use and sensitive to changes in different areas of social functioning. A total score in this scale between 35 and 52 is considered as normal or healthy functioning.

Similar to the trial of Keller et al. (2000), in our study, remission was defined a priori as a posttreatment HRSD score of 8 or lower (but only at one measurement point as opposed to at weeks 10 and 12, as defined by Keller et al.). A satisfactory therapeutic response was defined as a reduction in the HRSD score by at least 50% from baseline and a score of 15 or less.

The initial screening visit involved taking a medical and psychiatric history. Diagnoses were derived by 2 trained and experienced clinical psychologists using the *Structured Clinical Interview for DSM-IV (SCID-I and II*; First et al., 1997). In addition, at baseline, the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1994) was completed. The CTQ is a 28item retrospective self-report questionnaire which determines five severity categories of emotional/physical/sexual abuse, and emotional/physical neglect. "Early trauma" is defined as one of these experiences before the age of 18 to a degree of at least "moderate to severe".

The efficacy of treatment was evaluated 16 weeks after beginning of therapy, and 12 months posttherapy in terms of a naturalistic follow-up on the basis of self-evaluation by means of the BDI, the SASS, and information on further treatment. The follow-up evaluations were performed by a trained and experienced study nurse who was blind to the treatment condition, had not been involved in the patient care, and worked outside the treatment building. The patients were instructed not to mention anything that might reveal their treatment group to the evaluator. Interrater reliability for the HRSD was obtained from all evaluators from a random sample of 6 audio- or videotaped HRSD interviews (intraclass correlation coefficient: 0.94).

2.4. Statistics

Demographic and clinical characteristics of treatment groups at baseline were compared using χ^2 test, and unpaired *t*-test.

The primary analysis was a modified intention-to-treat analysis that included all patients who attended at least one treatment visit (n = 29). Overall efficacy of treatment was assessed by conducting analysis of covariance (ANCOVA) controlling for pretreatment scores on all outcome measures by treatment condition at termination. To examine differences for outcome measures between treatment groups at 12-month follow-up, further ANCOVAs were carried out. When attrition occurred between baseline, posttreatment, and 12-month follow-up "last observation carried forward" was used. Changes over time were analyzed by use of paired *t*-tests.

Response and remission data for the percentage of patients who reached cutoff scores were analyzed using χ^2 test. Treatment effect sizes (ES) were calculated using Cohen's *d* statistic. All statistical tests were conducted using a two-tailed alpha level of 0.05.

3. Patient flow

Eighty-seven physician- (n=73) or Internet-referred (n=14) patients were initially screened by phone using a

standardized brief form which included questions about the present complaints of the patient, evidence for chronic (for at least 2 years) depressive symptoms, early onset, and previous as well as current treatments. In addition, the patients received brief information about the study procedure on the phone. Fifty-five patients were invited for a diagnostic interview, of whom 25 were not included mainly because of diagnostic reasons (see Fig. 1). Thirty were randomized (n=29 physician- and n=1 self-referred). One patient was subsequently excluded (non-starter) after it turned out that she had denied symptoms and a treatment history of a borderline syndrome. More detailed information on the patient flow is shown in Fig. 1.

4. Results

4.1. Baseline patient characteristics

There were no significant differences between both treatment groups with respect to baseline demographic and clinical characteristics (Table 1). Fifty-five percent of the patients were female. The mean age of the sample was 40.2 years (SD, 11.5; range: 20–60). More than half of the patients in the total sample (55%; 16 of 29) suffered from a double depression. The remaining patients had a major depressive disorder with a chronic course according to DSM IV (n=9, 31%) and four (13%) patients suffered from dysthymia. The mean duration of illness was 20.3 years (SD, 11.3), and the mean pretreatment 24-HRSD score was 23.2 (SD, 5.4).

The majority (72.4%; n=21) had previously received psychotherapy, more than half of the patients (58.6%; n=17) reported having used pharmacotherapy and 20.7% (n=6) had received no prior treatment. A history of treatment resistance was defined as at least two self-reported failures/ non-response to a medication and/or a psychotherapy course. Nearly half of the patients (44.8%, n=13) indicated no response to at least 2 previous trials of psychotherapy, whereas 41.4% (n=12) reported treatment resistance to antidepressants. Seven (24.1%) of those patients were resistant to both medication and psychotherapy trials.

Other current axis I diagnoses (41.3%) according to the SCID-I among ITT patients were 1 of substance abuse (not primary) and 11 of anxiety disorders, with no significant difference between the treatment groups. Axis II disorders or traits (SCID-II; First et al., 1997) were diagnosed in 24 (82%)



Fig. 1. Flow diagram for the study. Abbreviations: IPT = interpersonal psychotherapy; CBASP = Cognitive Behavioral Analysis System of Psychotherapy.

Table 1

Characteristics of the sample at baseline, by treatment group.

Characteristics	tics ITT sample (n=29)				
	CBASP	IPT	$\chi^{2/t}$	df	p value
	(n = 14)	(<i>n</i> =15)			
Age mean (SD), years	41.1(12.7)	39.4(10.6)	0.38	27	.70
Female	8(57.1)	8(53.3)	0.42	1	.83
Family status					
Married/With partner	8(57.1)	10(66.7)	0.28	1	.59
Education, mean (SD), years	11.7(1.8)	11.9(1.5)	0.34	27	.73
Working	9(64.3)	10(66.7)	0.01	1	.89
Duration of depression, mean (SD), years	21.2(12.6)	19.6(30.3)	0.37	27	.71
Comorbidity axis I	5(35.7)	7(46.7)	0.35	1	.55
Comorbidity axis II	12(85.7)	12(80.0)	0.16	1	.68
Previous treatment ^a	12(85.7)	11(73.3)	0.67	1	.41
Treatment resistance					
Psychotherapy	5(35.7)	8(53.3)	0.90	1	.34
Medication	7(50.0)	5(33.3)	0.82	1	.36
Early trauma ^b	11(78.6)	12(80.0)	0.09	1	.92

Abbreviations: IPT = Interpersonal Psychotherapy; CBASP = Cognitive Behavioral Analysis System of Psychotherapy; ITT=intent-to-treat.

Unless otherwise indicated, data are presented as number (percentage).

^a Pharmacotheraphy and/or psychotheraphy.

^b At least moderate–severe in the CTQ.

of the patients and did not differ significantly between the treatment conditions (see Table 1).

Seventy-nine percent (n = 23) of the patients reported at least moderate to severe early trauma in their childhood according to the CTQ with no significant difference between the two treatment groups. Reports of "emotional neglect" were most common (n = 16) followed by "emotional abuse" (n = 15). Physical neglect was present in eight patients, sexual abuse in seven, and four reported physical abuse. Two of the 6 patients who were below the cutoff for moderate interpersonal trauma reported early separation by death of a parent (separation was not assessed by the CTQ).

4.2. Acute phase results

In the ITT analysis (n = 29; 1 non-starter), mean HRSD-24 scores in the CBASP group dropped from 23.00 to 11.21 (BDI: 25.43 to 10.79) and in the IPT group from 23.27 to 18.87 (BDI: 28.47 to 21.27) after 16 weeks of treatment (Table 2). Only in the CBASP group did the change in the mean HRSD scores reach statistical significance (T[13]=3.53, p=.004). Mean BDI scores were significantly lower posttreatment in both groups than at pretreatment (CBASP: T[13]=5.01, p<.001; IPT: T[14]=2.34, p=.034).

Analysis of covariance did not show a significant benefit of CBASP over IPT on the HRSD-24 (see Table 2 and Fig. 1) whereas a significantly higher reduction in self-rated depressive symptoms was found in the CBASP group posttreatment (mean BDI score of 10.79 vs. 21.27 in IPT; F[1,26] = 4.34, p = .047, ES_{IPT-CM}: d = .87). To detect the effect size of 0.68 as found in the HRSD-24 in this study by a two-tailed *t*-test with a power (1- β) of 0.80 and type I error probability level of $\alpha = 0.05$ for significance, 70 patients (35 per group) are needed.

4.2.1. Response and remission rates

In the ITT-sample, there was a statistically significant difference between CBASP and IPT regarding response rates at posttreatment (64.3% vs. 26.7%, $\chi^2[1] = 4.144$, p = .042)

favouring therapy with CBASP. The remission rates also differed significantly between both groups with higher rates for the CBASP patients (ITT sample: CBASP: 57.1% vs. IPT: 20.0%, χ^2 [1]=4.24, *p*=.039).

4.2.2. Global and social functioning

The ANCOVA did not show a significant main treatment effect for both the GAF and the SASS (see Table 2). Both groups showed significant changes over time in the GAF scores (CBASP: T[13] = -3.86, p = .002; IPT: T[14] = -4.45, p = .001) but not in the SASS scores.

4.3. Follow-up phase

The 12-month follow-up assessment was completed by 75.9% (n = 22; 8 CBASP = 57%, 14 IPT = 93%) of the patients. Of those unable to be followed up, two patients refused and 5 were no longer available. Two of the 8 CBASP patients (25%) and 2 of the 14 IPT patients (14.3%) started pharmacotherapy during the 12-month period after termination of study treatment. Some form of psychotherapy (mostly CBT or psychodynamic therapy) was received by 45.5% overall (CBASP: 3 of 8; 37.5%, and IPT: 7 of 14; 50%). Almost half (41.4%; CBASP: n = 5, IPT: n = 7) had discontinued all forms of treatment by 12 months. There was no significant difference between the treatment groups regarding the use of posttreatment pharmacotherapy or psychotherapy. There was also no significant difference in long-term outcome on the BDI between those patients who continued with some form of treatment vs. those who discontinued (independent from the condition they previously received).

4.3.1. Treatment effects

Analysis of covariance did not show a significant benefit of CBASP over IPT on the BDI or on the SASS at 1-year follow-up (see Table 2). Both groups showed significant changes over time in the BDI scores (CBASP: T[13] = 5.01, p < .001; IPT: T[14] = 2.34, p = .034). However, only in the CBASP group,

Table 2

Baseline,	posttreatment	and fo	llow-up	scores	for the	CBASP	and the	PTI PT	group	(ITT)	sam	ole n	1 = 29).
										· ·				

Post treatment											
		Baseline Mean (SD)	Post trea	tment Mean (SD)	$\Delta Mean$ (SE)	F	df	р	ES		
HRSD-24	CBASP IPT	23.00 (5.11) 23.27 (5.86)	11) 11.21 (10.84) 86) 18.87 (11.71)		7.46 (4.01)	3.46	1/26	.074	.68		
BDI	CBASP IPT	25.43 (9.45) 28.47 (8.27)	10.79 (8.40) 21.27 (14.62)		8.68 (4.17)	4.34	1/26	.047	.87		
GAF	CBASP IPT	58.43 (8.22) 59.27 (11.08)	70.78 (9. 69.40 (16	25) 6.12)	2.09 (3.92)	0.28	1/26	.597	.10		
SASS	CBASP IPT	29.29 (7.57) 27.87 (7.53)	3329 (7.69) 29.67 (9.35)		2.96 (2.67)	1.01	1/26	.324	.18		
Follow-up											
		Follow-up Mean	Follow-up Mean (SD)		F	df	р		ES		
BDI	CBASP	12.92 (11.83)									
SASS	IPT CBASP	18.66 (14.53) 36.57 (9.51)		3.82 (4.64)	0.67	1/26		418	.43		
	IPT	31.53 (12.21)		3.89 (3.48)	1.24	1/26		274	.46		

Abbreviations: BDI = Beck Depression Inventory; CBASP = Cognitive Behavioral Analysis System of Psychotherapy; ES = effect size calculated using Cohen's *d* statistic CBASP vs. IPT; GAF = Global Assessment of Functioning; HRSD-24 = Hamilton Depression Rating Scale; IPT = Interpersonal Psychotherapy; SASS = Social Adaptation Self-Evaluation Scale (higher values mean better adaptation); Δ = absolute difference between CBASP and IPT.

the changes in the SASS scores over time from baseline to 1-year follow-up reached statistical significance (T[13] = -2.41, p = .031).

5. Discussion

An intensive treatment involving 22 CBASP sessions was superior to IPT in early-onset chronic depression in terms of remission and response rates and self-reported depressive symptoms. The difference in the level of clinician rated depressive symptoms did not reach statistical significance. Only in CBASP patients, however, were the changes in the HRSD scores over time significant.

Remission has been adopted by recent guidelines for the treatment of depression as the optimal outcome (Thase, 2009). In our study, remission rates for CBASP (57%) were markedly higher not only compared to the IPT condition (20%) but also compared to an integrative therapy program which included IPT (35%; Murray et al., 2009). These findings suggest that in early-onset chronically depressed individuals, an approach specifically designed for this patient population is more effective than a method originally developed for acute major depressive episodes. Our results also surpassed the rates found by Keller et al. (2000) for CBASP monotherapy (24%), even in the subgroup of early traumatized patients (Nemeroff et al., 2003) where the remission rate for CBASP was 48%. They were also markedly higher compared to those recently published for the REVAMP study (Kocsis et al., 2009) where the augmentation of medication-non-responders (or partial responders) with CBASP resulted in a remission rate of 37%. Given the high rate of chronicity (the mean duration of illness was 20.3 years) and comorbidity in our study as important risk factors for incomplete remission (Thase, 2009) our results are of clinical significance. This is particularly relevant for patients who cannot or do not want to take medication.

Why does CBASP appear to work better in one setting, and worse in the other (Kocsis et al., 2009)? First, as the authors of

the REVAMP study noted, their sample consisted of patients who were mainly interested in receiving pharmacotherapy but did not (or not completely) respond to it. Also, participants in the Keller trial had a 2/3 chance of being treated with medication. It is known (Kocsis et al., 2009) that treatment preference has an important impact on outcomes. Participants in our trial had a preference for psychological treatment which may partially explain the better outcomes found in the present study (Keller et al., 2000; Kocsis et al., 2009). Second, the mean dose of 12.5 and about 16 sessions of CBASP reported by Kocsis et al. (2009) and Keller et al. (2000) respectively, might have been too low as suggested by a recent meta-analysis by Cuijpers et al. (2010). These authors reported that at least 18 treatment sessions are needed for patients with chronic depression to realize optimal effects of psychotherapy. In our study, 22 sessions of CBASP resulted in high remission rates. Third, the strategies and procedures of the CBASP are specifically tailored for the needs of early traumatized patients (for example, the Interpersonal Discrimination Exercise in CBASP aims to heal early trauma by teaching the patient to discriminate interpersonally between abusive significant others and the therapist), and therefore early-onset and/or early traumatized chronically depressed patients may gain most from this approach.

Even 22 sessions applied in a short time period did not seem to be sufficient to maintain the effects after 1 year. To reach long-term remission from chronic depression a longer course of psychotherapy may be necessary. This is in line with recommendations of several authors and guidelines for not only more intensive, but also more extended treatment courses (Dunner, 2001; Conradi et al., 2007; Cuijpers et al., 2010).

Consistent with previous studies of chronically depressed outpatients using IPT (De Mello et al., 2001; Browne et al., 2002; Markowitz et al., 2005), our trial revealed only weak effects of IPT for this diagnosis. Only when applied as an intense (3 weekly individual plus 8 group sessions) and modified inpatient treatment program (Schramm et al., 2008) including family involvement, additional group sessions, and medication, IPT seemed to work well for chronic major depression. It remains unclear if CBASP would have provided even more benefits when used in this manner and context. In the present study and on an outpatient basis, our experience throughout the trial was that the IPT-manual fails to adequately offer specific strategies to deal with typical difficult behavior of chronic patients such as extreme detachment, passivity, and/or hostility. These are more adequately addressed with targeted CBASP-techniques.

Several limitations to this study are worth noting. First, the study used only a small pilot sample and may be underpowered. Particularly the results of the follow-up period need to be interpreted with caution. Second, acute response and remission rates were defined on the basis of a single assessment covering only 1 week's time. In addition, we did not use a placebo control. However, in chronically depressed patients placebo treatment leads to only low rates of response (12%; Kocsis et al., 1988). Finally, these findings were obtained for patients with a preference for psychotherapy and may not be directly generalizable to all chronically depressed patients.

In summary, while limited by some factors, the results of this study suggest that with intensive CBASP early-onset chronically depressed patients have a good chance of remission. However, to maintain the effects a longer course of therapy might be necessary. Future studies will examine under what treatment circumstances CBASP is most effective, focusing on which dosage and duration of treatment are optimal.

Role of funding source

The study was partially funded by the Research Committee of the University Medical Centre Freiburg, Germany. The Research Committee of the University Medical Center Freiburg had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Disclosure of conflict of interest

There was no other financial support and no competing interest.

Acknowledgement

We thank Lasse Sander for proofreading of the manuscript.

References

- Agosti, V., 1999. One year clinical and psychosocial outcomes of early-onset chronic depression. J. Affect. Disord. 54 (1), 171–175.
- Agosti, V., Ocepek-Welikson, K., 1997. The efficacy of imipramine and psychotherapy in early-onset chronic depression: a reanalysis of the National Institute of Mental Health Treatment of Depression Collaborative Research Program. J. Affect. Disord. 43 (3), 181–186.
- Angst, J., Gamma, A., Rössler, W., Ajdacic, V., Klein, D., 2009. Long-term depression versus episodic major depression: results from the prospective Zurich study of a community sample. J. Affect. Disord. 115 (1), 112–121.
- Arnow, B.A., Constantino, M.J., 2003. Effectiveness of psychotherapy and combination treatment for chronic depression. J. Clin. Psychology 59 (8), 893–905.
- Beck, A.T., Ward, C.H., Mendelson, M., 1961. An inventory for measuring depression. Arch. Gen. Psychiatry 4, 561–571.
- Berndt, E.R., Koran, L.M., Finkelstein, S.N., Gelenberg, A.J., Kornstein, S.G., Miller, I.M., Thase, M.E., Trapp, G.A., Keller, M.B., 2000. Lost human capital from early-onset chronic depression. Am. J. Psychiatry 157 (6), 940–947.
- Bernstein, D.P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., Sapareto, E., Ruggiero, J., 1994. Initial reliability and validity of a new retrospective measure of child abuse and neglect. Am. J. Psychiatry 151 (8), 1132–1136.
- Browne, G., Steiner, M., Roberts, J., Gafni, A., Byrne, C., Dunn, E., Bell, B., Mills, M., Chalklin, L., Wallik, D., Kraemer, J., 2002. Sertraline and/or

interpersonal psychotherapy for patients with dysthymic disorder in primary care: 6-month comparison with longitudinal 2-year follow-up of effectiveness and costs. J. Affect. Disord. 68 (2–3), 317–330.

- Cassano, G.B., Akiskal, H.S., Perugi, G., Musetti, L., Savino, M., 1992. The importance of measures of affective temperaments in genetic studies of mood disorders. J. Psych. Res. 26 (4), 257–268.
- Conradi, H.J., De Jonge, P., Kluiter, H., Smit, A., van der Meer, K., Jenner, J.A., van Os, T.W., Emmelkamp, P.M., Ormel, J., 2007. Enhanced treatment for depression in primary care: long-term outcomes of a psycho-educational prevention program alone and enriched with psychiatric consultation or cognitive behavioural therapy. Psych. Med. 37, 849–862.
- Cuijpers, P., van Straten, A., Schuurmans, J., van Oppen, P., Hollon, S.D., Andersson, G., 2010. Psychotherapy for chronic major depression and dysthymia: a meta-analysis. Clin. Psychology Rev. 30 (1), 51–62.
- De Mello, M.F., Myczcowisk, L.M., Menezes, P.R., 2001. A randomized controlled trial comparing moclobemide and moclobemide plus interpersonal psychotherapy in the treatment of dysthymic disorder. J. Psychother. Pract. Res. 10, 117–123.
- Dunner, D.L., 2001. Acute and maintenance treatment of chronic depression. J. Clin. Psychiatry 62 (6), 10–16.
- Duschek, S., Schandry, R., Hege, B., 2003. Soziale Aktivität Selbstbeurteilungs-Skala (SASS). Diagnostik sozialer Funktionsstörungen bei depressiven Störungen. Beltz Test GmbH, Göttingen.
- Endicott, J., Spitzer, R.L., Fleiss, J.L., Cohen, J., 1976. The Global Assessment Scale. A procedure for measuring overall severity of psychiatric disturbance. Arch. Gen. Psychiatry 33, 766–771.
- First, M., Spitzer, R., Gibbon, M., Williams, J., 1997. Structured Clinical Interview for DSM-IV Axis I Disorders: Patient Edition. Biometrics Research Dept, New York State Psychiatric Institute, New York, NY.
- Gelenberg, A.J., Trivedi, M.H., Rush, A.J., Thase, M.E., Howland, R., Klein, D.N., Kornstein, S.G., Dunner, D.L., Markowitz, J.C., Hirschfeld, R.M., Keitner, G.I., Zajecka, J., Kocsis, J.H., Russell, J.M., Miller, I., Manber, R., Arnow, B., Rothbaum, B., Munsaka, M., Banks, P., Borian, F.E., Keller, M.B., 2003. Randomized, placebo-controlled trial of nefazodone maintenance treatment in preventing recurrence in chronic depression. Biol. Psychiatry 54, 806–817.
- Hamilton, M., 1967. Development of a rating scale for primary depressive illness. Br. J. Soc. Clin. Psychol. 6, 278–296.
- Keller, M.B., McCullough, J.P., Klein, D.N., Arnow, B., Dunner, D.L., Gelenberg, A.J., Markowitz, J.C., Nemeroff, C.B., Russell, J.M., Thase, M. E., Trivedi, M.H., Zajecka, J., 2000. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J. Med. 342, 1462–1470.
- Kessler, R.C., McGonagle, K.A., Zhao, S., Nelson, C.B., Hughes, M., Eshleman, S., Wittchen, H.U., Kendler, K.S., 1994. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch. Gen. Psychiatry 51, 8–19.
- Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E., 2005. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch. Gen. Psychiatry 62, 593–602.
- Klein, D.N., 2008. Dysthymia and chronic depression. In: Craighead, W.E., Miklowitz, D.J., Craighead, W.E. (Eds.), Psychopathology: History, Diagnosis, and Empirical Foundations. John Wiley & Sons, Hoboken, NJ, pp. 329–365.
- Klein, D.N., Santiago, N.J., 2003. Dysthymia and chronic depression: Introduction, calssification, risk factors, and course. J. Clin. Psychology 59 (8), 807–816.
- Klein, D.N., Schatzberg, A.F., McCullough, J.P., Keller, M.B., Dowling, F., Goodman, D., Howland, R.H., Markowitz, J.C., Smith, C., Miceli, R., Harrison, W.M., 1999. Early- versus late-onset dysthymic disorder: comparison in out-patients with superimposed major depressive episodes. J. Affect. Disord. 52 (3), 187–196.
- Klerman, G.L., Weissman, M., Rounsaville, B.J., Chevron, E.S., 1984. Interpersonal Psychotherapy of Depression. Basic Books, New York, NY.
- Kocsis, J.H., 2003. Pharmacotherapy for chronic depression. J. Clin. Psychology 59 (8), 885–892.
- Kocsis, J.H., Frances, A.J., Voss, C., Mann, J.J., Mason, B.J., Sweeney, J., 1988. Imipramine treatment for chronic depression. Arch. Gen. Psychiatry 45, 253–257.
- Kocsis, J.H., Gelenberg, A.J., Rothbaum, B.O., Klein, D.N., Trivedi, M.H., Manber, R., Keller, M.B., Leon, A.C., Wisniewski, S.R., Arnow, B.A., Markowitz, J.C., Thase, M.E., REVAMP Investigators, 2009. Cognitive Behavioral Analysis System of Psychotherapy and Brief Supportive Psychotherapy for augmentation of antidepressant nonresponse in chronic depression: the REVAMP trial. Arch. Gen. Psychiatry 66 (11), 1178–1188.
- Lizardi, H., Klein, D.N., Ouimette, P.C., Riso, L.P., Anderson, R.L., Donaldson, S.K., 1995. Reports of the childhood home environment in early-onset dysthymia and episodic major depression. J. Abnorm. Psychol. 104 (1), 132–139.

- Markowitz, J.C., 1995. Psychotherapy of dysthymic disorder. In: Kocsis, J.H., Klein, D.N. (Eds.), Diagnosis and Treatment of Chronic Depression. Guilford Press, NY, pp. 146–168.
- Markowitz, J.C., 1998. Interpersonal Psychotherapy of Dysthymic Disorder. American Psychiatric Press, Washington.
- Markowitz, J.C., Kocsis, J.H., Bleiberg, K.L., Christos, P.J., Sacks, M., 2005. A comparative trial of psychotherapy and pharmacotherapy for "pure" dysthymic patients. J. Affect. Disord. 89, 167–175.
- McCullough, J.P., 2000. Treatment for Chronic Depression. Cognitive Behavioral Analysis System of Psychotherapy. Guilford Press, New York, NY.
- Miller, I.W., Bishop, S., Norman, W.H., Maddever, H., 1985. The modified Hamilton Rating Scale for Depression: reliability and validity. Psychiatry Res. 14, 131–142.
- Murray, G., Michalak, E.E., Axler, A., Yaxley, D., Hayashi, B., Westrin, A., Ogrodnczuk, J.S., Tam, E.M., Yatham, L.N., Lam, R., 2009. Relief of chronic or resistant depression (Re_ChORD): a pragmatic, randomized, opentreatment trial of an integrative program intervention for chronic depression. J. Affect. Disord. Doi:10.1016.
- Nemeroff, C.B., Heim, C.M., Thase, M.E., Klein, D.N., Rush, A.J., Schatzberg, A.F., Ninan, P.T., McCullough, J.P., Weiss, P.M., Dunner, D.L., Rothbaum, B.O., Kornstein, S., Keitner, G., Keller, M.B., 2003. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms

of major depression and childhood trauma. Proc National Acad Sci U.S.A. 100 (24), 14293–14296.

- Schramm, E., 1998. Interpersonelle Psychotherapie-zur Behandlung depressiver und anderer psychischer Störungen, 2 ed. Schattauer, Stuttgart.
- Schramm, E., Caspar, F., Berger, M., 2006. Spezifische Psychotherapie f
 ür chronische Depression–Cognitive Behavioral Analysis System of Psychotherapy nach McCullough. Nervenarzt 77 (3), 355–371.
- Schramm, E., Schneider, D., Zobel, I., van Calker, D., Dykierek, P., Kech, S., Härter, M., Berger, M., 2008. Efficacy of interpersonal psychotherapy plus pharmacotherapy in chronically depressed inpatients. J. Aff. Disord. 109, 65–73.
- Thase, M.E., 2009. Update on partial response in depression. J. Clin. Psych. 70 (6), 4–9.
- Thase, M.E., Reynolds, C.F., Frank, E., Simons, A.D., Garamoni, G.D., McGeary, J., 1994. Response to cognitive-behavioral therapy in chronic depression. J. Psychother. Pract. Res. 3, 204–214.
- Torpey, D.C., Klein, D.N., 2008. Chronic depression: update on classification and treatment. Curr. Psychiatry Rep. 10, 458–464.
- Weissman, M.M., Klerman, G., Markowitz, J.C., 2000. Comprehensive Guide to Interpersonal Psychotherapy. Basic Books, New York, NY.
- Wiersma, J.E., Hovens, J.G., van Oppen, P., Giltay, E.J., van Schaik, D.J., Beekman, A.T., Penninx, B.W., 2009. The importance of childhood trauma and childhood life events for chronicity of depression in adults. J. Clin. Psychiatry 70 (7), 983–989.