Psychotherapy and Psychosomatics

Two-Year Follow-Up after Treatment with the Cognitive Behavioral Analysis System of Psychotherapy versus Supportive Psychotherapy for Early-Onset Chronic Depression

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Abstract

Background: Evidence on the long-term efficacy of psychotherapeutic approaches for chronic depression is scarce. ***Objective:*** To evaluate the effects of the Cognitive Behavioral Analysis System of Psychotherapy (CBASP) compared to Supportive Psychotherapy (SP) 1 year and 2 years after treatment termination. ***Methods:*** In this study, we present 1- and 2-year follow-up assessments of a prospective, multicenter,

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evaluator-blinded, randomized clinical trial of outpatients with early-onset chronic major depression ($n = 268$). The initial treatment included 32 sessions of CBASP or SP over 48 weeks. The primary outcome was the rate of "well weeks" (Longitudinal Interval Follow-Up Evaluation; no/minimal symptoms) after 1 year and 2 years. The secondary outcomes were, among others, clinician- and self-rated depressive symptoms, response/remission rates, and quality of life. **Results:** Of the 268 randomized patients, 207 (77%) participated in the follow-up. In the intention-to-treat analysis, there was no statistically significant difference between CBASP and SP patients in experiencing well weeks (CBASP: mean [SD] of 48.6 [36.9] weeks; SP: 39.0 [34.8]; rate ratio 1.26, 95% CI 0.99–1.59, $p = 0.057$, $d = 0.18$) and in remission rates (CBASP: 1 year 40%, 2 years 40.2%; SP: 1 year 28.9%, 2 years 33%) in the 2 years after treatment. Statistically significant effects were found in favor of CBASP 1 year after treatment termination regarding the rate of well weeks, self-rated depressive symptoms, and depression-related quality of life. **Conclusions:** CBASP lost its superiority over SP at some point between the first and the second year. This suggests the necessity of maintenance treatment for early-onset chronically depressed patients remitted with CBASP during the acute therapy phase, as well as the sequential integration of other treatment strategies, including medication for those who did not reach remission.

Introduction

Looking back at more than 40 years of depression research, including over 500 randomized trials [1], evidence concerning the long-term course of major depressive disorders after acute treatment is scarce despite the known high risk of recurrence [2, 3] and a chronicity rate of approximately 30% [4, 5].

For episodic depression, the long-term effects of psychotherapy showed a significant, moderately sized advantage over medication [6, 7]. Nevertheless, after 2 or more years, relapse rates remained high (53%; 95% CI 0.37–0.68) in major depressive disorders even after response to acute-phase psychotherapy [7]. There are strikingly fewer treatment studies of chronic depression (DSM-5: persistent depressive disorder) than of episodic depression, and almost none of these studies reported long-term efficacy values.

One of the most promising approaches based on posttreatment outcome [8] is the only disorder-specific psychotherapy for chronic depression, the Cognitive Behavioral Analysis System of Psychotherapy (CBASP) [9], although not all findings investigating it have been fully supportive [10, 11]. The evidence for the long-term effectiveness of CBASP is limited. Klein et al. [12] reported the superiority of maintenance CBASP over 1 year to "assessment-only appointments," with significantly fewer patients experiencing a recurrence. Compared to medication, the CBASP did not result in more sustainable effects on depression symptoms and quality of life 4.5 years after treatment termination in a smaller, underpowered trial [13]. In a randomized controlled pilot trial [14], the differences between acute treatment with the CBASP and interpersonal psychotherapy [15] favoring the CBASP disappeared within a 1-year naturalistic follow-up. In another pilot study treating chronically depressed inpatients, the initially high remission rate of 43.1% was maintained for over 6 months after discharge, but it had dropped significantly by 1 year after discharge [16].

This is the first randomized clinical study comparing the sustained effects of the CBASP with a nonspecific psychotherapy over a longer period of time following rigorous methodological recommendations for randomized controlled trials of psychological interventions [17]. The purpose of our study was to estimate the sustainability of the CBASP compared with a nonspecific, bona fide psychological treatment (supportive psychotherapy [SP]) after 1- and 2-year follow-up periods in patients with early-onset chronic major depression [18]. Our primary hypothesis was that patients who were initially treated for 48 weeks with the CBASP would show better results 1 year and 2 years after termination than those treated with SP in terms of higher rates of "well weeks," defined as weeks with no or minimal symptoms in the Longitudinal Interval Follow-Up Evaluation (LIFE) [19]. In contrast to single-event criteria such as relapse or remission, this longitudinal criterion allows full high-resolution coverage of patients' weekly depression status during the observation period. In addition, we hypothesized that the CBASP would confer fewer residual symptoms, higher response and remission rates, better social functioning and quality of life, fewer suicide attempts, and fewer weeks of treatment utilization than SP.

Subjects and Methods

Study Design and Participants
Here, we briefly summarize the key design issues. We report further details in the study protocols of the follow-up (online sup-

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pl. Clinical Trial Protocol; for all online suppl. material, see www.karger.com/doi/10.1159/000500189) and main study [20], as well as in the publication on the results of the main study [18]. Changes in the study protocol (all minor) are listed in online supplementary eTable 1. The study was conducted as a multicenter (8 university centers throughout Germany), evaluator-blinded, prospective, parallel-group, randomized controlled trial with an active control condition of unmedicated adult outpatients with early-onset chronic major depression (*n* = 268). For the inclusion and exclusion criteria, see the online supplementary Clinical Trial Protocol. We invited all the patients included in the main study to participate in the follow-up investigation.

Procedures

Both interventions followed standardized treatment manuals [18]. The CBASP is a highly structured psychotherapy integrating behavioral, cognitive, psychodynamic, and interpersonal treatment strategies [9]. SP is an active, nonspecific intervention [21] that includes psychoeducational elements and other common psychotherapy factors such as reflective listening and facilitation of affect. A meta-analysis showed that SP was effective in depression treatment, and no difference between it and other psychotherapies was found after controlling for allegiance [22]. We conducted 24 sessions of CBASP or SP over 16 weeks in the acute phase, followed by 8 continuation sessions over the next 28 weeks (32 sessions in total). The CBASP and SP were comparable in terms of the number of sessions, training of therapists, supervision, manual-based procedure, and adherence [18].

Outcome Measures

The a priori primary outcome was "well weeks," defined as weeks with no or minimal symptoms based on the 6-point Psychiatric Status Rating (PSR) scale for major depressive episodes of the LIFE. The LIFE is a reliable and valid semi-structured interview for retrospective longitudinal assessments over intervals of 6 months and longer [19, 23]. In the present study, trained interviewers conducted the LIFE interviews 1 year and 2 years after the end of the study treatment. The interrater reliability of the primary outcome measure was 0.74 (intraclass correlation coefficient) based on data from 20 raters who rated up to 12 follow-up interviews each.

The secondary outcomes we measured both in the main study [18] and at follow-up included clinician- and self-rated depressive symptoms (Hamilton Rating Scale for Depression [HRSD-24] [24], Quick Inventory of Depressive Symptomatology [QIDS-C] [25], and Self-Rated Inventory of Depressive Symptomatology [IDS-SR] [26]), clinician-rated level of functioning (Global Assessment of Functioning [GAF] [27]), and self-rated global and depression-specific quality of life (12-Item Short-Form Health Survey [SF-12] [28, 29] and Quality of Life in Depression Scale [QLDS] [30, 31]). The secondary outcomes that we only analyzed for the follow-up period included suicidal behavior (LIFE), weeks in inpatient and outpatient treatment (LIFE), weeks receiving psychotherapy and pharmacotherapy (LIFE), remission regarding the HRSD-24 (a score of 8 or less after 1 year and 2 years), the IDS-SR (a score of 13 or less), patients' responses (a reduction of 50% or more) regarding the HRSD-24 and the IDS-SR, and patients' self-assessed occurrence of life events (Münchner Ereignisliste [MEL] [32]). Blinded, trained, and experienced clinical psychologists conducted all the

ratings (see online suppl. Clinical Trial Protocol). They instructed the patients not to mention the kind of therapy they had received or the name of their therapist.

Statistical Analysis

We performed the primary analyses on the intention-to-treat (ITT) sample, which included all of the randomized patients (i.e., we imputed values for patients who did not provide any follow-up data in order to retain the randomized groups). We imputed missing outcomes using multiple imputation with an iterative Markov chain Monte Carlo method (fully conditional specification) based on demographic and clinical baseline data, group membership, and values for all outcomes throughout the main and the follow-up study [33]. We created 20 imputed data sets, analyzed them separately, and combined the results using Rubin's rules.

We used the same analytical strategy for all outcomes by fitting a (generalized) linear mixed model with a treatment group (CBASP, SP), measurement point (as available; at randomization; at treatment onset; at 12, 20, and 48 weeks after treatment onset; and at the 1- and 2-year follow-up), their interaction term, depression severity at inclusion in the main study (HRSD), deviation from the scheduled time point of measurement in days, and trial site as independent fixed effects. We treated the measurement points as repeated measures with an autoregressive residual covariance structure. We tested the hypothesis contrasting the effects of the CBASP and SP by investigating the statistical significance of the main effect of the treatment group for follow-up-only measurements and of the group × time interaction term for measures also administered in the main study. We analyzed count measures (including the primary outcome) using a negative binomial distribution and a log link [34, 35]. For binary measures, we used a binomial distribution with a logit link, and for continuous measures, we used a normal distribution with an identity link.

As post hoc analyses, we investigated (a) the number of patients who deteriorated since the end of the treatment (defined as an increase of 5 or more points in HDRS score from the end of treatment to the 2-year follow-up) and (b) the time to relapse (defined as 2 consecutive weeks of fulfilling the criteria for depression in the LIFE interview) in patients who remitted (i.e., had an HRSD-24 score of 8 or less) after 48 weeks of treatment in the main study. We compared the deterioration rates and relapse rates between the groups using Pearson's χ^2 test, and cumulative survival between treatment groups with the Mantel-Cox log-rank test.

To test the robustness of the findings, we performed two sets of sensitivity analyses: (1) as planned a priori, we repeated all the analyses in the sample treated per protocol in the main study [18] using all available data without imputation, and (2) post hoc, we repeated all the analyses using available cases irrespective of whether they were treated per protocol or not without imputation. We calculated or approximated standardized effect sizes (Cohen's *d*) for all group comparisons. For continuous outcomes, we divided the adjusted mean difference by the pooled observed standard deviations [36]. We used approximating formulas for count [37] and binary [38] endpoints. For all the analyses, we used a two-sided alpha level of 0.05. Consequently, except for the results of the ITT analysis of the rate of well weeks, all our findings should be considered as exploratory. We performed analyses with IBM SPSS 25 (IBM Corp., Armonk, NY, USA).
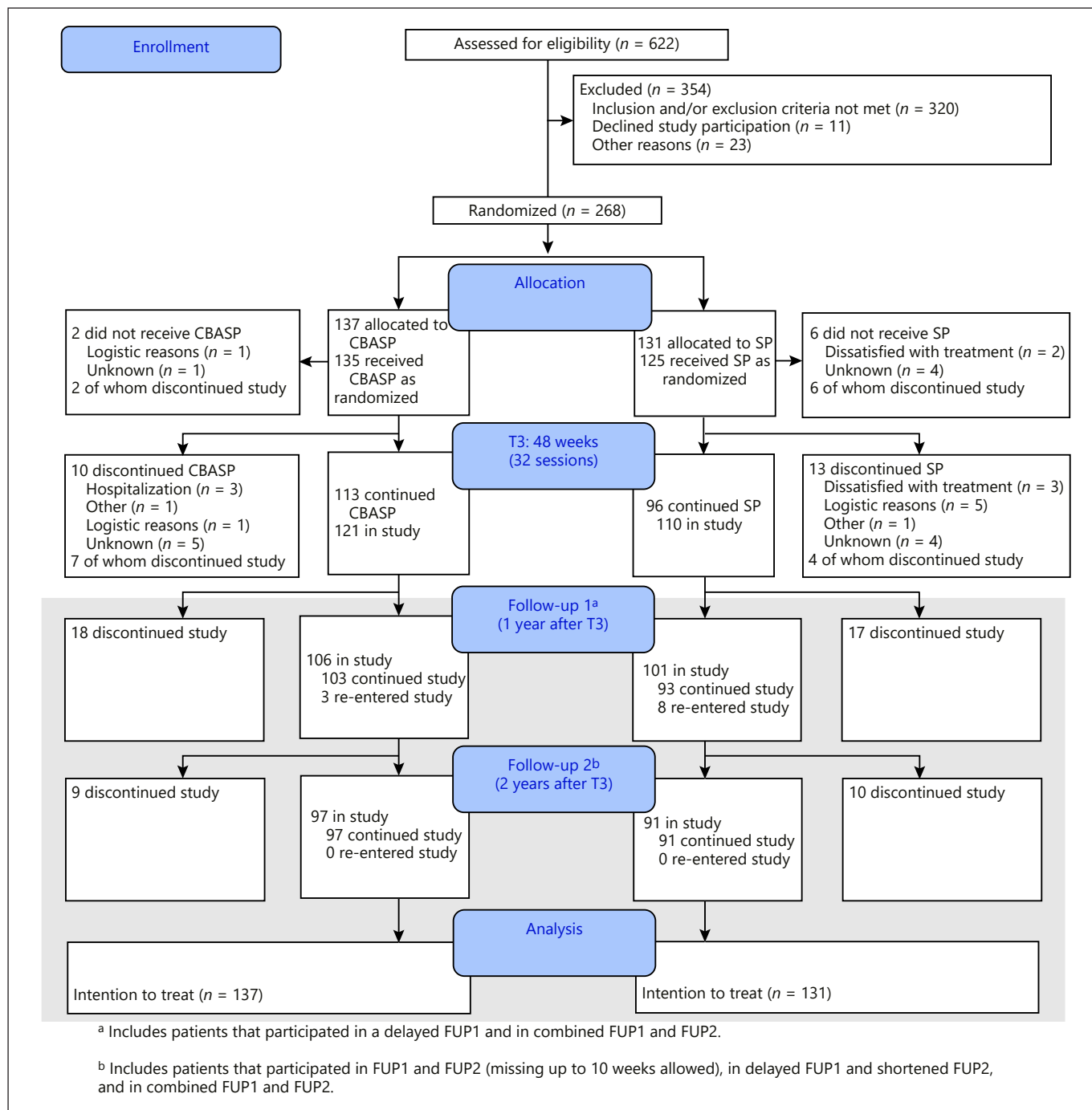
Fig. 1. Patient selection flowchart. CBASP, Cognitive Behavioral Analysis System of Psychotherapy; SP, supportive psychotherapy; FUP, follow-up.

Results

Sample

Of the 268 randomized patients, 207 (77.2%) participated in the 1-year follow-up investigation and 188 (70.1%) participated in the 2-year follow-up measurement (Fig. 1). The characteristics of the follow-up sample do not suggest differential attrition between the treatments from randomization (Table 1).

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Table 1. Sample characteristics

	Randomized sample			Sample participating in follow-up		
	CBASP (n = 137)	SP (n = 131)	total (n = 268)	CBASP (n = 106)	SP (n = 101)	total (n = 207)
Mean age (SD), years	44.65 (12.06)	45.18 (11.60)	44.91 (11.82)	44.62 (12.17)	46.47 (11.17)	45.52 (11.70)
Female	96 (70.1%)	81 (61.8%)	177 (66.0%)	77 (72.6%)	63 (62.4%)	140 (67.6%)
Family status						
Married, cohabiting	52 (38.0%)	54 (41.2%)	106 (39.6%)	41 (38.7%)	41 (40.6%)	82 (39.6%)
Single	61 (44.5%)	56 (42.7%)	117 (43.7%)	47 (44.3%)	44 (43.6%)	91 (44.0%)
Separated, divorced or widowed	24 (17.5%)	21 (16.0%)	45 (16.8%)	18 (17.0%)	16 (15.8%)	34 (16.4%)
Formal educational level[a]						
Low or medium	46 (33.6%)	50 (38.2%)	96 (35.8%)	37 (34.9%)	40 (39.6%)	77 (37.2%)
High or very high	91 (66.4%)	81 (61.8%)	172 (64.2%)	69 (65.1%)	61 (60.4%)	130 (62.8%)
Employment						
Full-time	54 (39.4%)	35 (26.7%)	89 (33.2%)	45 (42.5%)	29 (28.7%)	74 (35.7%)
Part-time or in training	54 (39.4%)	47 (35.9%)	101 (37.7%)	42 (39.6%)	33 (32.7%)	75 (36.2%)
Not employed[b]	29 (21.2%)	49 (37.4%)	78 (29.1%)	19 (17.9%)	39 (38.6%)	58 (28[b])
Subtype of chronic depression[c]						
Double depression	59 (43.7%)	60 (48.0%)	119 (45.8%)	43 (41.3%)	45 (46.4%)	88 (43.8%)
Chronic major depression	42 (31.1%)	40 (32.0%)	82 (31.5%)	32 (30.8%)	32 (33.0%)	64 (31.8%)
Recurrent major depression without complete remission between episodes	34 (25.2%)	25 (20.0%)	59 (22.7%)	29 (27.9%)	20 (20.6%)	49 (24.4%)
Mean age at onset (SD), years	12.96 (4.46)	13.05 (4.39)	13.00 (4.41)	12.89 (4.37)	12.82 (4.42)	12.86 (4.38)
Any comorbid axis I disorder	56 (40.9%)	61 (46.6%)	117 (43.7%)	42 (39.6%)	45 (44.6%)	87 (42.0%)
Any comorbid axis II disorder	44 (32.1%)	59 (45.0%)	103 (38.4%)	36 (34.0%)	50 (49.5%)	86 (41.5%)
Any comorbid axis I or II disorder	82 (59.9%)	100 (76.3%)	182 (67.9%)	64 (60.4%)	78 (77.2%)	142 (68.6%)
Previous antidepressive treatments						
Medication	71 (51.8%)	77 (58.8%)	148 (55.2%)	54 (50.9%)	59 (58.4%)	113 (54.6%)
Psychotherapy	78 (56.9%)	75 (57.3%)	153 (57.1%)	61 (57.5%)	59 (58.4%)	120 (58.0%)
Combination	26 (19.0%)	27 (20.6%)	53 (19.8%)	20 (18.9%)	20 (19.8%)	40 (19.3%)
Previous inpatient treatment	66 (48.2%)	72 (55.0%)	138 (51.2%)	49 (46.2%)	58 (57.4%)	107 (51.7%)
Treatment resistance[d]						
Medication	10 (7.3%)	18 (13.7%)	28 (10.4%)	6 (5.7%)	14 (13.9%)	20 (9.7%)
Psychotherapy	7 (5.1%)	19 (14.9%)	26 (9.7%)	5 (4.7%)	16 (15.8%)	21 (10.1%)
Medication washout necessary	34 (24.8%)	39 (29.8%)	73 (27.2%)	28 (26.4%)	29 (28.7%)	57 (27.5%)
Previous suicide attempts[e]	31 (24.0%)	45 (36.0%)	76 (29.9%)	23 (22.8%)	35 (35.7%)	58 (29.1%)
Family history of depression	85 (62.0%)	79 (60.3%)	164 (61.2%)	68 (64.2%)	65 (64.4%)	133 (64.3%)
Early trauma[f, i]	93 (71.5%)	97 (77.0%)	190 (74.2%)	71 (70.3%)	79 (79.8%)	150 (75%)
Emotional abuse[f, j]	72 (55.4%)	79 (62.7%)	151 (59.0%)	55 (54.5%)	65 (65.7%)	120 (60.0%)
Physical abuse[f, j]	27 (20.8%)	28 (22.2%)	55 (21.5%)	17 (16.8%)	26 (26.3%)	43 (21.5%)
Sexual abuse[g, j]	28 (21.5%)	29 (23.4%)	57 (22.4%)	23 (22.8%)	24 (24.7%)	47 (23.7%)
Emotional neglect[f, j]	82 (63.6%)	85 (67.5%)	167 (65.5%)	63 (62.4%)	72 (72.7%)	135 (67.5%)
Physical neglect[f, j]	41 (31.5%)	71 (32.5%)	82 (32.0%)	28 (27.7%)	34 (34.3%)	62 (31%)
Treatment preference[h]						
Medication alone	1 (0.7%)	2 (1.6%)	3 (1.1%)	1 (1.0%)	2 (2.1%)	3 (1.4%)
Psychotherapy alone	104 (77.0%)	94 (74.0%)	198 (75.6%)	80 (76.9%)	73 (75.3%)	153 (73.9%)
Combined treatment	13 (9.6%)	18 (14.2%)	31 (11.8%)	10 (9.6%)	12 (12.4%)	22 (10.6%)
No preference	17 (12.6%)	13 (10.2%)	30 (11.5%)	13 (12.5%)	10 (10.3%)	23 (11.1%)
HRSD screening score	27.15 (5.49)	26.99 (5.76)	27.07 (5.61)	27.07 (5.27)	27.28 (6.01)	27.17 (5.63)
HRSD score at start of follow-up (end of study treatment)	14.00 (9.72)	16.49 (9.96)	15.19 (9.90)	14.76 (9.56)	17.51 (9.96)	16.06 (9.82)

Unless otherwise indicated, data are presented as n (%). SD, standard deviation; CBASP, Cognitive Behavioral Analysis System of Psychotherapy; SP, supportive psychotherapy. [a] "Low" corresponds to at least 9 years of education (no formal education or Hauptschule), "medium" corresponds to at least 10 years of education (Realschule or Polytechnische Oberschule), "high" corresponds to at least 12 or 13 years of education (Gymnasium or Fachoberschule), and "very high" corresponds to at least 15 years of education (university degree). [b] Includes retired, housemaker, unemployed, and other. [c] n = 201 with data available for long-term follow-up. [d] Defined as at least 2 self-reported failures/nonresponses to a medication (more than 4 weeks) or to a psychotherapy (more than 8 sessions). [e] n = 199 with data available for long-term follow-up. [f] n = 200 with data available for long-term follow-up. [g] n = 198 with data available for long-term follow-up. [h] n = 201 with data available for long-term follow-up. [i] At least moderate to severe in 1 of 5 dimensions assessed with the Childhood Trauma Questionnaire. [j] At least moderate to severe in the respective dimension of the Childhood Trauma Questionnaire. [k] n = 196 with data available for long-term follow-up.

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Table 2. Observed data and results of the intention-to-treat analysis for the count outcomes

	Observed data						Intention-to-treat effect estimate			
	CBASP			SP			rate ratio	95% CI	*p*	*d*
	n	mean	SD	*n*	mean	SD				
Well weeks (primary outcome)										
Total	99	48.61	36.93	92	38.99	34.79	1.26	0.99 to 1.59	0.057	0.18
Year 1	106	23.49	20.24	101	17.82	18.67	1.36	1.05 to 1.76	0.021	0.24
Year 2	99	24.22	20.89	92	20.46	19.52	1.17	0.89 to 1.54	0.27	0.12
Weeks in treatment										
Total	99	54.53	42.24	92	58.23	44.45	0.91	0.76 to 1.09	0.31	−0.07
Year 1	106	23.83	23.52	101	29.08	23.11	0.84	0.68 to 1.03	0.092	−0.14
Year 2	99	30.18	23.75	92	30.47	24.20	0.99	0.81 to 1.22	0.95	−0.01
Weeks in outpatient treatment										
Total	99	53.12	41.11	92	56.88	44.07	0.91	0.76 to 1.10	0.33	−0.07
Year 1	106	22.87	22.77	101	27.91	22.84	0.84	0.68 to 1.05	0.12	−0.13
Year 2	99	29.81	23.73	92	30.02	23.98	0.99	0.80 to 1.22	0.92	−0.01
Weeks in inpatient treatment[a]										
Total	99	2.07	6.14	92	1.54	4.83	1.01	0.22 to 4.60	0.99	0.01
Year 1	106	1.14	4.29	101	1.17	4.10	1.47	0.32 to 6.77	0.62	0.30
Year 2	99	0.85	4.21	92	0.64	2.79	0.69	0.14 to 3.29	0.64	−0.29
Weeks in pharmacological treatment										
Total	99	38.90	42.00	92	38.65	44.02	0.98	0.75 to 1.29	0.90	−0.01
Year 1	106	15.54	21.99	101	18.72	22.82	0.87	0.65 to 1.18	0.37	−0.10
Year 2	99	22.82	24.26	92	21.00	24.06	1.10	0.80 to 1.52	0.54	0.08
Weeks in psychotherapeutic treatment										
Total	99	33.63	38.44	92	37.95	42.08	0.88	0.66 to 1.17	0.37	−0.10
Year 1	106	15.08	20.85	101	17.10	20.83	0.92	0.66 to 1.27	0.62	−0.06
Year 2	99	18.00	22.68	92	20.95	23.86	0.84	0.59 to 1.18	0.30	−0.14

CBASP, Cognitive Behavioral Analysis System of Psychotherapy; CI, confidence interval; *d*, Cohen's *d*; SD, standard deviation; SP, supportive psychotherapy. [a] Estimates calculated in available data due to convergence problems in some imputed data sets.

The baseline (pre-randomization) characteristics of the available sample did not differ substantially between CBASP and SP patients regarding age (mean [SD] age = 45.52 [11.70] years), family status (married/cohabiting: *n* = 82, 39.6%), formal educational level (high/very high: *n* = 130, 62.8%), age at depression onset (mean [SD] age = 12.86 [4.38] years), previous psychological treatment (*n* = 120, 58.0%), previous combined psycho- and pharmacological treatment (*n* = 40, 19.3%), and family history of depression (*n* = 133, 64.3%). However, SP patients reported slightly fewer females (CBASP: 72.6%; SP: 62.4%), double the unemployment rate (CBASP: 17.9%; SP: 38.6%), more comorbid axis I or II disorders (CBASP: 60.4%; SP: 77.2%), more previous inpatient treatments (CBASP: 46.2%; SP: 57.4%), higher treatment resistance to medication (CBASP: 5.7%; SP: 13.9%) and psychotherapy (CBASP: 4.7%; SP: 15.8%), more previous suicide attempts (CBASP: 22.8%; SP: 35.7%), and more early trauma (CBASP: 70.3%; SP: 79.8%).

Outcomes
Patients in the CBASP group had a 26% higher chance of experiencing a well week in the 2 years after treatment than patients in the SP group (mean [SD] of 48.6 [36.9] weeks in the CBASP group vs. 39.0 [34.8] weeks in the SP group; estimated rate ratio = 1.26, 95% CI 0.99–1.59, *p* = 0.057, *d* = 0.18), a difference not reaching statistical significance (Table 2). In the first year, however, patients were statistically significantly more likely to experience a well week in the CBASP group (CBASP: *n* = 23.5 [20.24]; SP: *n* = 17.82 [18.67]; estimated rate ratio = 1.36, 95% CI 1.05–1.76, *p* = 0.021, *d* = 0.24). The detailed descriptive results for well weeks throughout the follow-up period are depicted in Figure 2, showing a fairly stable proportion of patients reporting a well week throughout the follow-up phase (ranging from 40 to 50% in the CBASP group and from 30 to 45% in the SP group). There were no significant differences between the groups regarding treatment utiliza-

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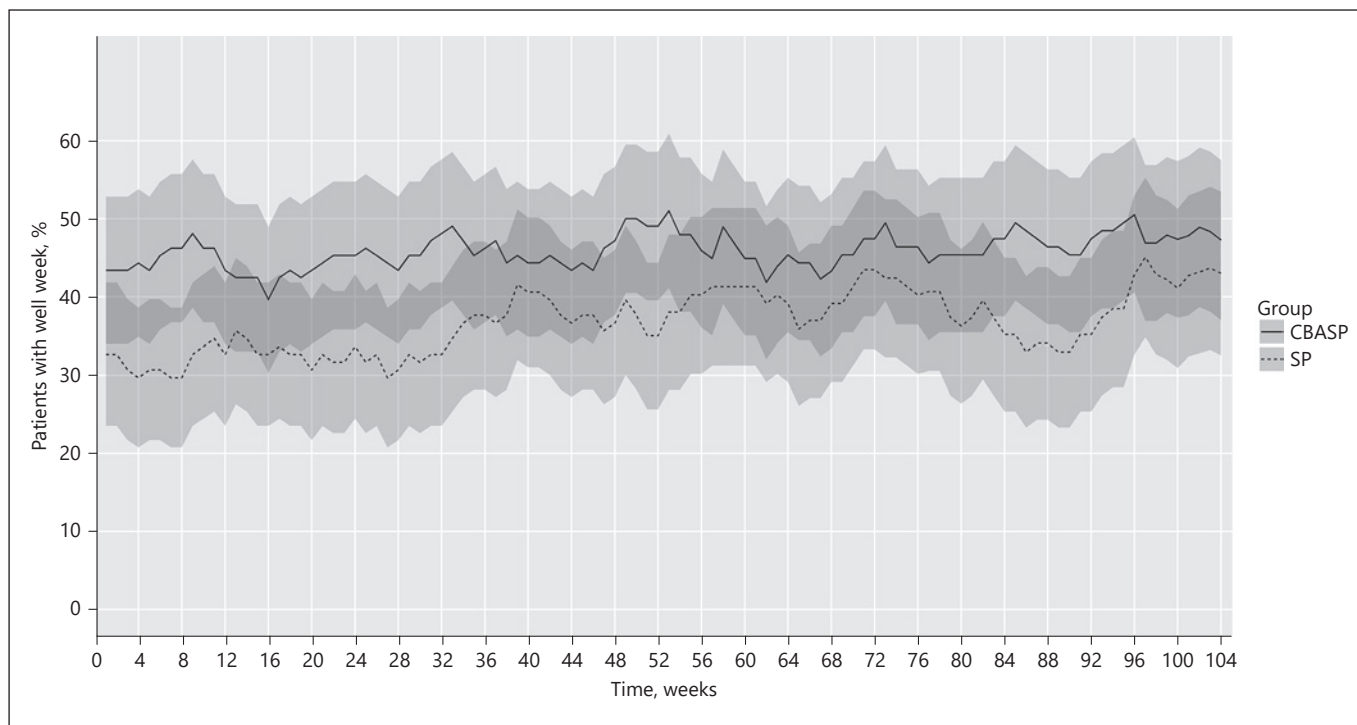Psychother Psychosom 2019;88:154–164
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Fig. 2. Course of well weeks. CBASP, Cognitive Behavioral Analysis System of Psychotherapy; SP, supportive psychotherapy.

tion (including inpatient and outpatient or pharmacological and psychotherapeutic).

Considering the investigated continuous outcomes (Table 3), the CBASP showed advantages over SP regarding self-rated depression severity after the first year (IDS-SR estimated mean difference = –5.57 points, 95% CI –10.04 to –1.10, p = 0.015, d = –0.39) and depression-specific quality of life after the first year (QLDS estimated mean difference = –2.46 points, 95% CI –4.90 to –0.03, p = 0.048, d = –0.25). No differences were detected after the second year. The course of the HRSD-24 scores throughout the main and the follow-up study showed that the average symptom levels achieved in the main study were largely maintained in the follow-up phase (online suppl. Fig. 1). Suicidal behavior was rarely observed during the follow-up phase (2 times in the SP group in the first year after treatment: 1 attempt, no suicide). The results regarding remission rates (CBASP: 1 year 40%, 2 years 40.2%; SP: 1 year 28.9%, 2 years 33%; online suppl. eTable 2) and life events (online suppl. eTable 3) showed no significant difference between the treatment groups.

In total, 180 patients provided HRSD data at the end of the treatment and at the 2-year follow-up and were included in the post hoc analysis of deterioration rates. A total of 22 of the 95 patients (23.2%) in the CBASP group and 15 of the 85 patients (17.6%) in the SP group deteriorated until the end of the 2-year follow-up (group difference p = 0.361). Of 72 patients remitted in the main study, 55 patients provided their follow-up data for a post hoc analysis of time to relapse. Here, 19 of the 35 remitted patients (54.2%) in the CBASP group and 6 of the 20 remitted patients (30.0%) in the SP group relapsed during the 2-year follow-up (group difference p = 0.082). With a mean of 68.0 (95% CI 55.9–80.1) weeks to relapse in the CBASP group and 79.6 (95% CI 62.4–96.7) weeks to relapse in the SP group, we did not identify a statistically significant difference between treatments (log-rank test p = 0.14).

Sensitivity analyses per protocol suggested similar results to the ITT findings, but most of them did not reach significance (online suppl. eTables 4–7). In general, the sensitivity analyses in the available cases without imputation showed effects similar to or mildly larger than those in the ITT approach, which for well weeks, clinician-rated depressive symptoms (both HRSD and QIDS), self-rated depressive symptoms, mental health-related quality of life, depression-specific quality of life, and remission and response regarding self-rated depressive symptoms reached statistical significance for one or both years of the follow-up phase (results not shown).

Table 3. Observed data and results of the intention-to-treat analysis for the continuous outcomes

	Observed data						Intention-to-treat effect estimate			
	CBASP			SP			mean difference	95% CI	p	d
	n	mean	SD	n	mean	SD				
Clinician-rated depressive symptom severity (HRSD)										
Randomization	137	27.15	5.49	130	27.05	5.74	–			
Treatment onset	135	24.30	7.75	128	25.07	6.59	–			
End of treatment	120	14.00	9.72	110	16.49	9.96	–			
1 Year after treatment	100	12.84	9.37	97	15.68	9.71	–2.33	–5.09 to –0.43	0.097	–0.24
2 Years after treatment	97	12.44	8.86	91	15.05	9.63	–1.31	–4.87 to 2.26	0.47	–0.14
Clinician-rated depressive symptom severity (QIDS)										
Randomization	137	14.39	3.85	130	14.90	3.45	–			
Treatment onset	135	13.10	4.41	128	14.08	4.06	–			
End of treatment	120	7.42	5.51	110	8.69	5.74	–			
1 Year after treatment	106	7.03	5.22	101	8.51	5.10	–0.91	–2.46 to 0.64	0.25	–0.18
2 Years after treatment	91	6.69	5.05	87	7.90	5.62	–0.86	–2.80 to 1.09	0.38	–0.16
Clinician-rated level of functioning (GAF)										
Treatment onset	131	54.94	9.69	124	53.67	8.55	–			
End of treatment	115	67.67	13.72	109	63.89	12.84	–			
1 Year after treatment	104	69.03	14.29	97	65.39	13.31	3.72	–0.64 to 8.07	0.094	0.27
2 Years after treatment	74	70.42	14.37	73	68.15	13.09	3.63	–1.81 to 9.07	0.19	0.26
Self-rated depressive symptom severity (IDS-SR)										
Treatment onset	129	37.31	10.27	126	40.49	8.42	–			
End of treatment	106	22.48	13.73	96	29.29	13.89	–			
1 Year after treatment	98	24.94	14.13	97	31.04	14.71	–5.57	–10.04 to –1.10	0.015	–0.39
2 Years after treatment	97	24.60	13.83	90	31.24	15.29	–4.37	–9.62 to 0.89	0.10	–0.30
Global physical health-related quality of life (SF-12-PCS)										
Treatment onset	126	45.92	10.10	121	46.23	10.16	–			
End of treatment	101	47.46	10.56	95	46.25	10.46	–			
1 Year after treatment	93	46.21	9.89	93	45.41	10.66	1.33	–2.08 to 4.74	0.44	0.04
2 Years after treatment	95	45.54	10.47	85	44.78	10.66	0.06	–3.51 to 3.63	0.97	0.00
Global mental health-related quality of life (SF-12-MCS)										
Treatment onset	126	26.34	7.43	121	25.24	7.61	–			
End of treatment	101	38.10	13.65	95	34.23	12.41	–			
1 Year after treatment	93	38.25	13.00	93	35.41	11.52	2.86	–0.99 to 6.71	0.15	0.23
2 Years after treatment	95	40.25	12.94	85	36.32	11.70	3.30	–0.76 to 7.37	0.11	0.27
Depression-specific quality of life (QLDS)										
Treatment onset	130	17.86	7.92	126	20.44	7.27	–			
End of treatment	106	10.41	9.17	98	13.60	9.77	–			
1 Year after treatment	98	11.02	9.66	96	13.60	9.81	–2.46	–4.90 to –0.03	0.048	–0.25
2 Years after treatment	97	9.80	9.17	89	12.68	9.82	–1.81	–4.59 to 0.97	0.20	–0.19

CBASP, Cognitive Behavioral Analysis System of Psychotherapy; CI, confidence interval; d, Cohen's d; GAF, Global Assessment of Functioning; HRSD, Hamilton Rating Scale for Depression; IDS-SR, Self-Rated Inventory of Depressive Symptomatology; QIDS, Quick Inventory of Depressive Symptomatology; QLDS, Quality of Life in Depression Scale; SD, standard deviation; SF-12-MCS, Mental Component Summary of the 12-Item Short-Form Health Survey; SF-12-PCS, Physical Component Summary of the 12-Item Short-Form Health Survey; SP, supportive psychotherapy.

Discussion

The observed data suggest that, on average, both the CBASP and SP resulted in sustainably reduced levels of depressive symptoms, a higher level of social functioning, and an increased quality of life over the 2-year follow-up period. The clinician-rated response and remission rates slightly increased over time in both groups. Nevertheless, more than half of the patients had not achieved remission 2 years after intensive psychological therapy, and patients

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in both conditions on average spent about half of the time in psycho- or pharmacotherapy, indicating a need for further treatment. For early-onset chronically depressed patients, 48 weeks or 32 sessions of acute therapy may not be sufficient for acute [18] and long-term results.

The superiority of CBASP over SP with regard to the rate of well weeks, self-rated depressive symptoms, and depression-related quality of life had diminished at some point between the first and the second year after treatment. This finding suggests that the skills the chronic patients acquired through CBASP treatment [39] may have faded over time. A similar but much more steeply declining long-term course has been reported in other CBASP studies [14, 16] after the initial acute treatment had ended. A possible explanation might be that the therapists in our study were not allowed to continue therapy after 48 weeks, and that the CBASP is not yet well disseminated in outpatient care. A maintenance regimen that includes booster sessions may help to reinforce the strategies learned with the CBASP, particularly in the face of life events. In one study utilizing monthly maintenance sessions with the CBASP over the course of 1 year after acute treatment, the CBASP proved superior over "assessment-only sessions" [12]. Persistent benefits were also demonstrated if a sequential model integrating pharmacotherapy was endorsed [40, 41]. Another reason for the unexpectedly small differences between the therapies after 2 years may be that SP is a strong comparator including powerful common efficacy factors for psychotherapy [22], in comparison to a wait list control or assessment-only sessions.

The strengths of this study include the use of a large, multicenter sample with patient recruitment from different departments and the high rate of patient participation in the follow-up measurements. This is the first published study comparing the long-term effects of the CBASP with those of a nonspecific psychotherapy. Further unique features and strengths of this investigation – besides including core factors for chronic depression, such as moderate substance abuse, chronic suicidality, and early trauma – include the relatively long duration of follow-up of 2 years. In addition, the primary outcome measure LIFE enabled us to retrospectively gather information about the long-term course on a weekly basis rather than just cross-sectionally.

The results of this study should be interpreted with caution because of the limitation that patients were recruited from academic centers only; thus, our findings may not generalize to routine settings in public health care. In addition, we observed a moderate baseline imbalance between the groups, with somewhat more impaired patients in the SP group. However, since we used depression severity before treatment as a covariate in all the analyses, it is very unlikely that the variables indicating group differences had substantial influences on the outcomes that had not been captured by baseline symptom severity. Furthermore, the relatively complex statistical models, imputing values for over 20% of the participants for the ITT analyses, as well as the difficult-to-justify assumptions behind imputation and analysis, may evoke some uncertainty regarding the validity of the findings. However, the negative binomial model has been shown to be a good choice for count variables [34, 35], multiple imputation may work with up to 50% of missing data [42], and we confirmed the general pattern of findings across a large number of outcomes and in two sets of sensitivity analyses. Another limitation is that we did not assess the specific kind and dosage of antidepressant medication as well as possible withdrawal syndromes during follow-up. The medication status, however, is known to affect relapse rates [43]. Yet, the medication status in the follow-up period of the present trial was similar in both treatment groups; thus, it could not confound the main objective of the study, which was to estimate the comparative long-term effectiveness of the CBASP versus SP.

The CBASP is a disorder-specific psychological treatment with evidence for persistent effectiveness in outcomes in chronic depression. Notwithstanding the positive results, this trial also reminds us that even an intensive/specific approach applied over 1 year does not provide a satisfying solution for long-term stabilization in early-onset patients with a history of early trauma [18]. A substantial number of patients did not achieve remission 2 years after having received CBASP treatment, and the average participant still scored in the mildly depressed range. Additional research should clarify whether further treatment, including augmentation with pharmacotherapy or modular interventions based on individual patient characteristics [44] in the acute phase, might result in a higher rate of remission and consequently a lower rate of relapse. In addition, considering management options that proved helpful in treating other chronic diseases may be promising. These comprise integrative care approaches organized in disease management programs and long-term support with low-threshold therapeutic contacts. For example, a fully automated internet-delivered augmentation strategy (SUMMIT) was superior to treatment as usual in patients with recurrent depression over 24 months after discharge [45].

In summary, we found disorder-specific psychotherapy to confer stronger long-term effects than nonspecific psychotherapy in terms of the number of well weeks, self-rated depressive symptoms, and quality of life in early-onset chronically depressed patients 1 year, but not 2 years, after therapy termination. An extended and flexible treatment regimen with booster sessions or sequential strategies may improve long-term outcomes in chronically depressed patients.

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Statement of Ethics

The study is being conducted in compliance with the protocols, good clinical practice, and the applicable regulatory requirements. The Institutional Review Board/Institutional Ethics Committee (IRB/IEC) of the University of Freiburg approved this research, and the ongoing trial is under continued review by the IRB/IEC. We asked the local IRB/IECs of each participating site for confirmation prior to study initiation. All participants had provided written informed consent prior to undergoing clinical interviewing, randomization, and intervention.

Disclosure Statement

E. Schramm received modest book royalties and honoraria for workshops and presentations related to the CBASP. D. Schoepf received honoraria for CBASP workshops and presentations. J.P. Klein received payments for workshops and books (Beltz, Elsevier, and Hogrefe) on the topic of psychotherapy for chronic depression. H. Walter and K. Schnell received funding from the German Research Foundation for an add-on study of the reported randomized controlled trial. K. Schnell received advisory fees from Servier Pharmaceuticals and payments for workshops and books (Schattauer, Elsevier, and Kohlhammer) on psychotherapy for chronic depression. M. Backenstrass received honoraria for workshops and presentations related to the CBASP. M. Hautzinger received advisory fees from Servier Pharmaceuticals, Springer publishers, Hogrefe publishers, and Beltz publishers. No other disclosures were reported.

Author Contributions

E. Schramm and L. Kriston had full access to all the data in the study, and they take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: E. Schramm, L. Kriston, I. Zobel, M. Berger, M. Hautzinger, and M. Härter. Acquisition, analysis, or interpretation of data: E. Schramm, L. Kriston, M. Elsaesser, I. Zobel, J. Bailer, K. Wambach, M. Backenstrass, J.P. Klein, D. Schoepf, K. Schnell, A. Gumz, B. Löwe, H. Walter, P. Bausch, T. Fangmeier, R. Meister, M. Hautzinger, and M. Härter. Drafting of the manuscript: E. Schramm, L. Kriston, M. Elsaesser, and M. Härter. Critical revision of the manuscript for important intellectual content: E. Schramm, L. Kriston, M. Elsaesser, I. Zobel, J. Bailer, K. Wambach, M. Backenstrass, J.P. Klein, D. Schoepf, K. Schnell, A. Gumz, B. Löwe, H. Walter, P. Bausch, T. Fangmeier, R. Meister, M. Wolf, K. Domschke, M. Berger, M. Hautzinger, and M. Härter. Statistical analysis: L. Kriston, T. Fangmeier, R. Meister, and M. Hautzinger. Administrative, technical, or material support: E. Schramm, I. Zobel, J. Bailer, K. Wambach, M. Backenstrass, J.P. Klein, D. Schoepf, K. Schnell, A. Gumz, B. Löwe, P. Bausch, H. Walter, K. Domschke, M. Berger, R. Meister, M. Hautzinger, and M. Härter.

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