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Comparing the Efficacy of CBASP with Two Versions of CBT for Depression in a Routine Care Center: A Randomized Clinical Trial

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Keywords
Cognitive-behavioral therapy · Cognitive-behavioral analysis system of psychotherapy · Depression · Chronic depression · Early onset · Childhood adversities

Abstract
Background: The cognitive-behavioral analysis system of psychotherapy (CBASP) was developed for the treatment of chronic, early-onset depression. However, it is unclear whether this approach can be recommended for depression in general (episodic and chronic), and no direct comparisons between CBASP with different versions of cognitive-behavioral therapy (CBT) exist. ***Methods:*** A randomized controlled trial compared 3 treatment conditions (all lasting 16 sessions) with a waiting list group (WL): CBASP, CBT with a focus on physical exercise (CBT-E), and CBT with a focus on pleasurable, low-energy and mindful activities (CBT-M). We included 173 patients and involved 41 therapists. Assessments were at baseline, after session 8, and at the end of treatment. ***Results:*** Our primary outcome Beck Depression Inventory-II indicated a general advantage of the CBT arms compared to CBASP [$F(6, 154.5) = 4.2$, $p = 0.001$], with significant contrasts in particular in favor of CBT-E. Effect sizes against WL were $d = 0.91$ (CBT-E), 0.87 (CBT-M), and 0.47 (CBASP). A triple interaction with an additional factor "chronic versus episodic depression" [$F(6, 142.7) = 2.2$, $p = 0.048$] indicated that the treatments resulted in different outcomes, with best results again for CBT-E in particular in episodic depression. Responder rates indicated significant improvements (56% in both CBT arms, 34% in the CBASP arm, 3.4% in WL; intention-to-treat samples). As compared to CBASP, response rates were significantly higher for CBT-E (OR = 2.48; 95% CI = 1.02–6.00) and CBT-M (OR = 2.46; 95% CI = 1.01–6.01). ***Conclusions:*** CBASP was more effective than WL, but less effective than the 2 CBT arms. This was mainly caused by an advantage of CBT interventions in episodic depression.

Introduction

Although psychological and psychopharmacological interventions are considered to represent best evidence-based treatments for depression, there is a necessity to further improve these interventions, in particular in light of the tremendous health care burden that is associated with the disorder [1]. Antidepressant drug treatments have notorious difficulties showing superiority above placebo interventions [2, 3], but also psychological interven-

Trial Registration: www.clinicaltrial.gov NCT01464463.

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tions are far from reaching satisfying success [4, 5]. Even for cognitive-behavioral therapy (CBT), the effects are still uncertain and should be considered with caution [5]. Two recently published studies investigating noninferiority of psychodynamic treatments versus CBT did not find differences in efficiency, mainly because both treatment conditions were associated with low response rates (e.g., 16% for psychodynamic therapy and 22% for CBT [6]; 34% observed responders in CBT vs. 27% in the psychodynamic arm [7]). Thus, in these large trials, about 70–80% of participating patients remained without sufficient success. The responder rate even dropped below 8% in one of the subgroups of these trials (severely depressed patients; psychodynamic arm [7]), further underlining the necessity to improve current treatments.

New interventions (e.g., third-wave therapies like mindfulness-based cognitive therapy, acceptance and commitment therapy) were introduced with enthusiasm and expectations to either improve success rates in general, to offer alternative approaches for those who failed with existing therapies, or to offer more effective interventions for specific subgroups of depressed patients (e.g., cognitive-behavioral analysis system of psychotherapy [CBASP] for chronically depressed patients with a history of early adverse events). However, these promises are currently not backed up by sound evidence. While most third-wave therapies are beneficial compared to waiting list (WL) groups, studies confirming the postulated advantage above the first-line treatment CBT, at least for some subgroups, are rare [8, 9].

The CBASP has been developed in particular for the treatment of patients with early-onset, chronic depression, frequently in association with a history of adverse early life events [10]. For this subgroup of depressive patients, it was postulated that CBASP works better than other psychological interventions. Just recently, CBASP has been shown to be more efficient for this target group than supportive therapy [11]. Another trial reports that CBASP could be superior to mindfulness-oriented interventions [12], at least in terms of expert ratings (Hamilton Depression Scale), but not with self-ratings (Beck Depression Inventory, BDI). However, it is unclear whether the promising results for CBASP can only be achieved for the subgroup of patients with early-onset, chronic depressive disorder and a history of early adverse events, or for all types of depressed patients. Many features that are considered crucial for CBASP interventions (such as early adverse life events, insecure attachment styles) are also prevalent in episodic depression and even in nondepressed controls [13]. Therefore CBASP could be beneficial for nonchronic subtypes as well, which has never been tested before. Moreover, no randomized controlled trials compared CBASP and traditional CBT interventions directly. Any empirically derived information about benefits of CBASP in comparison to traditional CBT[1] is lacking.

CBT in its traditional version includes behavioral activation and cognitive restructuring as principal techniques. CBT approaches are effective independently of depression severity at baseline [14]. While cognitive interventions are a standard tool of CBT depression programs, the foci of behaviorally oriented treatments can vary. An increase in physical activity has been shown to improve depression. After summarizing the evidence, it was suggested to increase physical activities in depressive patients with sessions of 30 min, 3 times per week [15]. However, other behavior changes recommended in CBT, such as relaxation, mindful self-centering, hedonic and other behaviors do not challenge physical activities at all [16]. Mindfulness-oriented interventions are hypothesized to enhance traditional CBT efficiency, although they do not focus on increasing physical activity [17]. Therefore, comparisons of other interventions with traditional CBT arms require either to select one single variant and to limit any interpretation to this single CBT variant, or to use more CBT variants to be able to generalize to the overall CBT approach.

With this study, we wanted to address the following questions. (1) Is CBASP equally or even more effective in treating depression than traditional CBT focusing on cognitive restructuring and behavioral techniques? To the best of our knowledge, CBASP has rarely been investigated in depression in general, and it has never been compared to the scientific "gold standard" treatment CBT. (2) Is there a special advantage of CBASP in chronic depression compared to other forms of depression, both times in relation to CBT interventions? This hypothesis was postulated by the proponents of CBASP after its first formulation. (3) Are CBT interventions with a stronger focus on physical activation more effective than CBT interventions with a stronger focus on more hedonic, mindful, but less physically challenging activities? Although the level of physical activity is diametrically different, both treatment foci seem to have beneficial effects, and the inclusion of both CBT variations better allows

[1] We are aware that a broader conceptualization of CBT could include CBASP as a subgroup of CBT interventions. For the current purpose, we use a more narrow definition of CBT for interventions that mainly focus on cognitive restructuring and increase of specific behaviors.

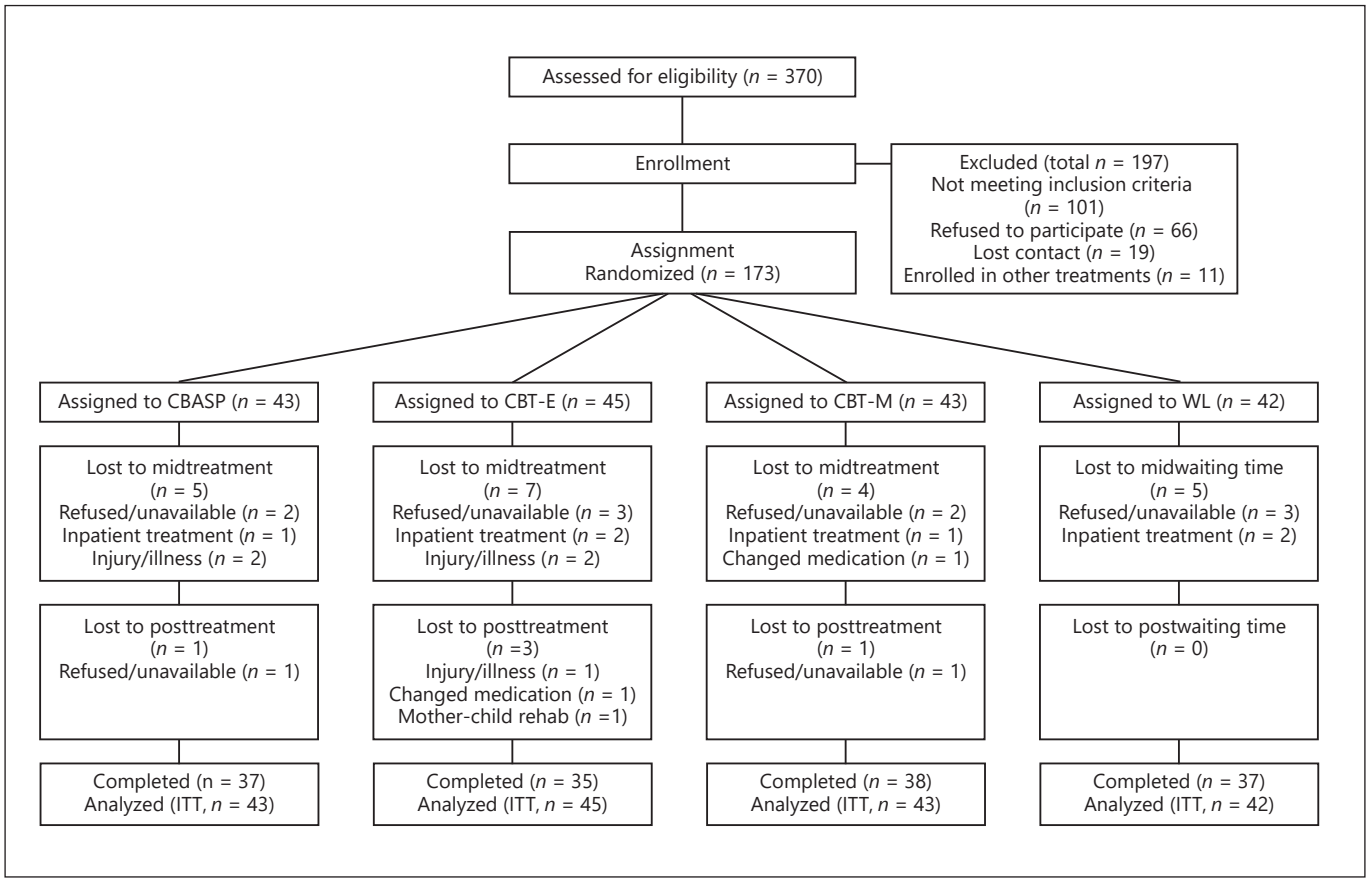

Fig. 1. Journal article reporting standards flowchart. CBASP, cognitive behavioral analysis system of psychotherapy; CBT-E, cognitive behavioral therapy emphasizing physical exercises during behavioral activation; CBT-M, cognitive behavioral therapy emphasizing mindfulness exercises during behavioral activation; ITT, intention-to-treat; WL, waitlist control group.

generalization to the CBT family of interventions. In a 4-arm trial, we wanted to investigate these questions, and additionally, compare these interventions to a waiting control condition. We also wanted to investigate various potential moderators such as "childhood maltreatment," because childhood maltreatment has been shown to predict differences in response rates between interventions [18, 19].

Methods

Setting

Patient acquisition and treatment took place in the psychotherapy outpatient clinic of the psychology department, University of Marburg, Germany. This psychotherapy center was established as part of the public health care system for providing psychological treatments, but also psychotherapy training and research. About 300–400 patients per week visit this center. Access is open to the public, and treatment costs are covered by the general public health care system in Germany; therefore patients from all social classes have unrestricted, direct access. Patients can also be referred by their physicians in private practices or clinics.

Patients

A total of 173 patients were randomized to 4 treatment arms (CONSORT patient flow; Fig. 1). Inclusion criteria were a DSM-IV diagnosis of major depression (either chronic or episodic) as verified with SCID interviews, a BDI score of >14, the potential ability to practice physical exercise, and the ability to read and answer German self-rating scales. For the purpose of this study, we defined "chronic depression" according to DSM-IV (major depression with ongoing depressive symptoms for most of the day for more than 2 years; if improvements during these 2 years occurred, they did not sum up to more than 2 months in total); all other types of major depression were labeled as "episodic depression." Early onset was defined similar to the study of Schramm et al. [11] if the first depressive episode started before the age of 21. Exclusion criteria were a history of psychotic disorders, serious addictions, or regular drug intake affecting immune status. Patients who took

antidepressants were considered for participation under the assumption that their dosage was stable for a minimum of 2 weeks and during study participation. Data collection lasted from August 2011 to October 2016.

For power/sample size estimation, we wanted to detect differences of treatment effects between groups with an effect size of $d \geq 0.30$. With an alpha error of $p < 0.05$ and a power to 0.90, G*Power [20] recommends 136 patients to detect significant interactions between 4 groups and 3 assessment points. Compensating for an estimated 20% dropout rate, we therefore calculated with a sample size of 170 patients.

Procedure

The study is the clinical part of the Outcome of Psychological Interventions in Depression project (OPID trial). Before starting data acquisition, IRB approval (German Society of Psychology IRB committee) was received, and study registration (www.clinicaltrial.gov NCT01464463) took place. In addition to the clinical trial reported here, biological parameters of some subgroups were investigated, in particular immunological parameters. These biological results are reported elsewhere [21]. After prescreening via phone, patients participated in a diagnostic session with SCID and sociodemographic interviews, as well as BDI screening and approving inclusion/exclusion criteria. All participants gave oral and written informed consent. Patients were randomized to 1 of 4 conditions (3 treatment arms, 1 WL), lasting over 16 weeks. A computer-generated randomization sequence with a 1:1:1:1 allocation ratio was used to randomize patients [22]. Randomization was supervised by administration personnel who was not involved in treatment. The 4 conditions were: (i) CBT including a 4-week block encouraging physical exercise (CBT-E), (ii) CBT including a 4-week block focusing on pleasurable low-energy activities and mindfulness exercises (CBT-M), (iii) CBASP, and (iv) a WL control condition. Treatments included 16 weekly sessions of 50 min. As these treatments took place in a natural treatment environment, patients had the option to continue psychotherapy after these 16 weeks, although a minimum break of 6 months was recommended. Due to this unsystematic posttreatment effect, no follow-up data will be reported here.

Treatments

CBASP. The CBASP manual was similar to the manual developed during a large CBASP multicenter trial [11], but the number of sessions was slightly modified to 16 sessions to be comparable to the CBT arms. The CBASP is a highly structured psychotherapy. Its main focus is on social problem solving, including learning to recognize the consequences of one's own behavior on other persons. The first part of CBASP is characterized by the analysis of past significant relationships and consequently developed interaction patterns, and this information is used to generate a transference hypothesis, which expresses the patient's expectations of therapist's reactions to his/her behavior (see online suppl. material Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000487893). A focus is on highlighting how current interaction experiences are different from past experiences, and to enable patients to detect expectation-violating reactions of the therapist. The subsequent major part of CBASP consists of situational analyses of real life interaction sequences with interventions to improve the overlap between effects of current interaction behavior and interaction goals. Therefore patients' demonstrated interaction behavior, consequences, as well as hopes and intentions for this interaction are continuously reflected [23, 24]. Role plays can help to shape patient behavior to better achieve interaction goals. Whenever possible, the therapist proactively employs the transference hypothesis to help patients discriminate the therapist's behavior from that of hurtful significant others in the past ("interpersonal discrimination exercises").

CBT-E and CBT-M. After an initial phase of psychoeducation, introduction of cognition, emotion, and behavior models, and other preparatory interventions (see online suppl. material Table 1; weeks 1–4), the patients received behavioral activation (weeks 5–8) with either physical exercise (CBT-E) or pleasant low-energy activities, including mindful sensory perception tasks (CBT-M), followed by cognitive therapy (weeks 9–16). For CBT-E, CBT was modified to increase physical activity according to the recommendations of the World Health Organization. Both CBT treatments (i.e., CBT-E and CBT-M) were manual-based and included well-evaluated principles as published elsewhere [25].

Patients participated in weekly treatment sessions for 16 weeks, with an expected duration of 50 min per session. For further details of the intervention arms, see online supplementary material Table 1.

Waitlist. Patients in the WL condition (i.e., passive control condition) did not receive any treatment during the 16 weeks and were transferred to standard psychotherapy afterwards.

Assessment Instruments

The SCIDs [26] were conducted by 2 experienced and licensed psychologists (F.E., K.D.); interviewers were always independent of therapists. As primary outcome, we chose a priori self-rated depressive symptom severity according to the BDI-II [27]. Compared to this type of self-ratings, expert ratings (like the Hamilton Depression Scale) seem to be more prone to overestimations of treatment effects and investigator bias [2, 28]. Secondary outcomes were general symptomatology (Symptom Checklist, SCL, general symptom index [29]), perseverative thinking (Perseverative Thinking Questionnaire [30]), therapeutic relationship, satisfaction with treatment outcome (Health Alliance Questionnaire [31]) as well as metabolic equivalent minutes per week for moderate-intensity and vigorous-intensity activity (International Physical Activity Questionnaire, long form) [32]. To assess early childhood abuse and neglect, we used the 28-item version of the Childhood Trauma Questionnaire [33]. Individuals were classified according to their report of any early adverse events. Furthermore, this classification was applied for 5 adverse event subtypes such as sexual, physical and emotional abuse, as well as physical and emotional neglect.

CBT interventions and CBASP postulate different mechanisms of change. Therefore we constructed visual analogue scales that should assess these expected differences of treatment mechanisms and changes. For instance, CBT is expected to improve self-efficacy, and CBT-E is expected to modulate physical activity more specifically than the other interventions. CBASP postulates 4 specific effects on interaction domains, namely closeness/intimacy, emotional need, making mistakes and expression of negative emotionality, and improvements are expected to be driven by improvements of feeling socially connected, reductions of negative reactions of others, and improved expression of needs. For all of these variables, visual analogue scales were constructed using a 100-mm

Table 1. Means and standard deviations (in parentheses) of outcomes at baseline, midtreatment, and posttreatment assessments

	CBASP	CBT-E	CBT-M	WL
BDI-II				
Baseline	27.28 (7.91)	27.87 (9.64)	27.98 (8.94)	26.93 (9.20)
Midtreatment	20.89 (9.04)	18.63 (9.37)	19.38 (9.73)	26.07 (9.85)
Posttreatment	17.68 (10.63)	14.20 (11.46)	14.97 (10.70)	23.38 (10.78)
SCL: global severity index				
Baseline	1.12 (0.50)	1.10 (0.50)	1.15 (0.54)	1.11 (0.58)
Midtreatment	0.95 (0.53)	0.84 (0.59)	0.82 (0.50)	1.11 (0.60)
Posttreatment	0.72 (0.49)	0.58 (0.42)	0.63 (0.47)	0.83 (0.48)
PTQ: perseverative thinking				
Baseline	37.93 (9.65)	40.44 (11.88)	41.13 (18.79)	37.27 (11.60)
Midtreatment	30.61 (13.91)	32.12 (13.34)	32.37 (14.55)	32.41 (12.40)
Posttreatment	26.32 (15.03)	29.68 (12.12)	29.47 (14.14)	32.30 (15.44)
HAq-P: therapeutic relationship				
Midtreatment	31.76 (3.97)	31.27 (3.61)	29.92 (6.55)	–
Posttreatment	32.93 (2.85)	33.17 (10.84)	32.84 (3.22)	–
HAq-P: satisfaction with therapy outcome				
Midtreatment	24.98 (6.10)	25.70 (5.70)	24.76 (6.22)	–
Posttreatment	27.53 (5.33)	28.00 (5.42)	28.55 (4.78)	–
HAq-T: therapeutic relationship				
Midtreatment	28.22 (5.50)	24.29 (5.37)	26.21 (5.58)	–
Posttreatment	29.03 (6.29)	28.32 (5.69)	26.64 (6.18)	–
HAq-T: satisfaction with therapy outcome				
Midtreatment	21.31 (4.38)	21.17 (4.87)	20.42 (4.71)	–
Posttreatment	22.61 (5.40)	24.72 (15.84)	21.47 (5.55)	–
IPAQ: moderate physical activity				
Baseline	2,863.27 (3,319.74)	1,894.07 (2,199.77)	2,506.89 (2,501.13)	2,312.25 (2,352.96)
Midtreatment	2,210.00 (1,181.01)	1,747.82 (2,393.59)	1,457.82 (2,090.33)	1,412.31 (1,643.28)
Posttreatment	2,319.63 (2,267.54)	2,156.92 (3,733.30)	1,999.55 (2,566.36)	1,965.44 (2,208.74)
IPAQ: vigorous physical activity				
Baseline	953.85 (2,044.44)	749.77 (1,416.77)	1,132.68 (2,173.96	1,061.46 (2,171.01)
Midtreatment	383.03 (744.25)	1,614.19 (2,339.86)	615.34 (1,196.89)	969.23 (1,992.66)
Posttreatment	898.82 (1,409.00)	1,476.92 (2,696.32)	664.24 (1,238.66)	1,149.09 (2,370.39)
VAS: mood (extremely bad to very good)				
Baseline	3.79 (1.43)	4.02 (2.07)	3.99 (1.95)	4.19 (1.88)
Midtreatment	4.50 (2.37)	5.55 (1.96)	5.00 (2.23)	3.93 (2.17)
Posttreatment	5.28 (2.54)	5.98 (2.65)	5.50 (2.43)	4.26 (2.06)
VAS: self-efficacy (very low to very high)				
Baseline	4.04 (2.02)	4.07 (2.27)	4.19 (2.51)	4.34 (2.14)
Midtreatment	4.96 (2.54)	5.84 (2.40)	5.26 (2.40)	5.11 (2.17)
Posttreatment	4.98 (2.47)	6.43 (2.65)	5.71 (2.34)	4.80 (1.94)
VAS: increase in activity (not at all to very)				
Baseline	3.66 (1.91)	3.44 (2.44)	2.93 (2.34)	3.53 (2.38)
Midtreatment	5.10 (2.55)	6.88 (2.36)	5.31 (2.69)	4.35 (2.60)
Posttreatment	5.99 (2.46)	6.43 (2.65)	6.01 (2.49)	4.35 (2.58)
VAS: rumination (not at all to strong)				
Baseline	5.66 (2.83)	5.49 (2.74)	6.17 (3.11)	6.50 (2.95)
Midtreatment	4.83 (2.74)	4.52 (3.22)	4.85 (2.92)	4.50 (3.27)
Posttreatment	4.49 (2.80)	3.85 (2.88)	4.21 (2.67)	5.19 (3.33)
VAS: feeling socially connected (not at all to strong)				
Baseline	3.91 (1.87)	3.86 (2.09)	3.44 (1.88)	4.00 (2.24)
Midtreatment	4.61 (2.27)	4.86 (1.71)	4.42 (2.06)	3.91 (1.92)
Posttreatment	4.83 (2.35)	5.93 (2.10)	4.75 (2.15)	4.84 (1.95)
VAS: expressing needs (very poor to very good)				
Baseline	4.04 (2.08)	3.39 (2.61)	3.41 (2.48)	3.71 (2.69)
Midtreatment	4.45 (2.41)	5.02 (2.69)	4.36 (2.44)	4.59 (2.81)
Posttreatment	4.96 (2.38)	5.42 (2.71)	5.00 (2.96)	4.30 (2.69)
VAS: external reactions to own mistakes (extremely negative to very emphatic)				
Baseline	3.73 (1.95)	3.08 (1.98)	3.38 (2.49)	3.23 (2.33)
Midtreatment	4.11 (2.29)	3.84 (2.11)	4.22 (2.28)	4.24 (2.24)
Posttreatment	5.43 (2.55)	5.23 (2.59)	4.62 (2.53)	5.08 (2.42)
VAS: the expression of negative emotions as viewed by external sources (extremely inappropriate to very acceptable)				
Baseline	4.56 (2.12)	4.24 (2.07)	4.38 (2.34)	4.99 (2.25)
Midtreatment	4.61 (2.02)	4.36 (2.13)	4.58 (2.14)	5.43 (1.69)
Posttreatment	5.37 (2.37)	5.02 (2.17)	4.88 (2.53)	5.85 (2.28)

BDI, Beck Depression Inventory; CBASP, cognitive behavioral analysis system of psychotherapy; CBT-E, cognitive behavioral therapy emphasizing physical exercises during behavioral activation; CBT-M, cognitive behavioral therapy emphasizing mindfulness exercises during behavioral activation; CTQ, Childhood Trauma Questionnaire; HAq-P, Helping Alliance Questionnaire, patient version; HAq-T, Helping Alliance Questionnaire, therapist version; IPAQ, International Physical Activity Questionnaire; PTQ, Perseverative Thinking Questionnaire; SCL, Symptom Checklist; VAS, visual analogue scale; WL, waiting list control condition.

scale, with "zero" representing the negative pole, and "100" representing the positive pole (for items, see Table 1).

Therapists

A large number of therapists conducting the treatments can help to improve generalizability of trial results. Therefore, we recruited a total of 41 psychologists to participate in this trial. To keep treatment allegiance comparable, therapists selected the treatment conditions they wished to participate in and practice with patients. All therapists were master degree psychologists with a specialization in clinical psychology and psychotherapy, either fully approved in psychological psychotherapy (which is a 3-year postgraduate training in psychotherapy after the master's degree), or in advanced postgraduate training for CBT. The amount of basic CBT training was similar between CBT and CBASP therapists. CBASP training consisted of 48 h of workshops, and 2 therapies under supervision. Video-taped CBASP sessions were rated for adherence by CBASP trainers; if these ratings were considered satisfactory, therapists received approval for CBASP therapies. All therapists practicing CBASP in this trial fulfilled the criteria of the German CBASP association and were approved accordingly. CBASP was an already established intervention in this treatment setting, because the clinic was also part of another multicenter CBASP trial [11]. All CBT therapists had a minimum of 30 h in specific CBT techniques for depression, plus a special training in the application of the CBT manual for this trial.

Eight therapists exclusively contributed to the CBASP arm, while 3 therapists did both CBASP and CBT treatments. Sixteen therapists exclusively contributed to 1 of the 2 CBT arms, while 14 contributed to both.

Patients were blinded to the purpose and study hypothesis. "Informed consent" included the information that participants would be randomized to 1 of 3 treatment conditions all of them expected to offer effective depression treatments, or to a WL group.

Treatment Fidelity

Therapies were based on written manualized treatment protocols for all 3 interventions, describing the content of every single session. The CBASP protocol was a modified version of the one used in the study of Schramm et al. [11] which revealed good results compared to supportive therapy but was limited to 16 sessions for the current purpose. CBT protocols derived from standard CBT protocols, mainly introduced, manualized, and disseminated in Germany by Hautzinger [25, 34]. All therapists were specifically trained to use the corresponding treatment protocol. During the study, all therapists received continuous supervision (after every 4th treatment session; either 45 min of individual supervision or 90 min of group supervision with a maximum of 4 supervisees per session) by certified supervisors especially trained for the corresponding intervention. Supervisors were required to ensure treatment fidelity. Every therapist had to show 1 video of a treatment session per patient to the supervisor to further check treatment fidelity with the treatment condition. No rating scale for treatment fidelity has been used.

When departures from the treatment manuals occurred for the first time per patient, supervisors addressed these deviances from the manuals. A structured plan was developed how to reapproach the manual. If a clear deviance was noted by the supervisor for the second time, it was decided whether the variation was either (a) due to a solvable problem in therapy leading to further attempts to improve treatment fidelity or (b) due to an unsolvable mismatch of the patient's problem focus to the study protocol, resulting in an exclusion of this patient from the study. In the flowchart of Figure 1, these excluded patients were part of the "refused/unavailable" category, which encompassed up to 3 patients per group (7%).

Dropouts

Completer rates were high (85% at the end of treatment), with only 4–7 patients per group who had been lost by the time of midterm assessment (8.8–15.6%), and another 0–3 patients who were lost by the end of treatment (0.0–6.7%) (Fig. 1).

Statistics

Statistical analyses were carried out with IBM SPSS statistics version 23.0 for Windows (SPSS Inc., Chicago). Baseline characteristics between groups were compared using analysis of variance, *t* tests (if necessary with the Welch correction) and χ^2 tests as appropriate. Intervention effects on outcomes were analyzed on an intention-to-treat basis using multilevel models with full information maximum likelihood estimation [35] according to current recommendations [36]. Models were tested with different covariance structures, and for each model, the covariance structure that provided the best fit was selected [37, 38]. Models were based on 3 time points (baseline, midtreatment, posttreatment). As in previous research [39], models for the primary outcome were adjusted for depressive symptom severity from initial screening which are not influenced by specific treatment expectations (i.e., BDI scores when inclusion criteria were examined). Data from all 173 randomized participants were analyzed (for study flow, see Fig. 1). Given the exploratory nature of this study, analyses were not corrected for multiple testing [40]. Only in case of significant ($p < 0.05$) treatment effects (i.e., group × time interactions) or interactions with a potential moderator (i.e., moderator × group × time interactions), post hoc contrasts were calculated to specify these effects by testing group differences (i.e., CBASP vs. CBT-E vs. CBT-M vs. WL) at week 8 (midtreatment) and at week 16 (posttreatment). To indicate the standardized difference for these group differences, we calculated between-group effect sizes (Cohen *d*) by dividing the difference of the model-estimated marginal means by the square root of the pooled standard deviation (derived from standard errors of the estimated marginal means) (see online suppl. material Table 2 for effect sizes of post hoc contrasts). Models include terms of interest, lower order terms, main effects, as well as a random intercept. All outcomes were tested for normality. For a number of outcomes with moderately right-skewed distributions (Table 2), square root transformations were applied to normalize data and to improve model fit [38].

In addition to multilevel models, we analyzed the pattern of responders and deterioration rates in the primary outcome (i.e., BDI-II) using binary logistic regressions. These analyses were performed for an intention-to-treat sample, as well as for completer outcome data. For intention-to-treat analysis, multiple imputation was used to create 5 imputed data sets followed by 5 independent analyses. Imputations were based on all variables from Table 3, treatment allocation, and on primary and secondary outcomes. Response and deterioration rate were not estimated directly but calculated from imputed data for posttreatment BDI-II scores. Logistic regression results from imputed data sets were combined using the SPSS standard procedure, following the strategies and recommendations of comparable publications [41, 42].

Table 2. Results for secondary outcomes from intention-to-treat analyses using multilevel modeling: main effects, lower-order terms and patterns of change from baseline, to midtreatment, to posttreatment assessments by treatment group

Outcome	*F* (df)	*p* value
SCL: global severity index[a]		
Group	1.59 (3, 173.6)	0.194
Time	95.97 (2, 258.1)	<0.001
Group × time	3.32 (6, 256.8)	0.004
PTQ: perseverative thinking		
Group	0.42 (3, 168.3)	0.739
Time	32.23 (2, 114.0)	<0.001
Group × time	0.62 (6, 110.4)	0.718
HAq-P: therapeutic relationship[b]		
Group	0.52 (2, 105.8)	0.596
Time	6.78 (1, 103.1)	0.011
Group × time	0.50 (2, 102.9)	0.610
HAq-P: satisfaction with therapy outcome[b]		
Group	0.17 (2, 109.1)	0.846
Time	30.92 (1, 101.2)	<0.001
Group × time	0.53 (2, 101.1)	0.588
HAq-T: therapeutic relationship[b]		
Group	1.55 (2. 108.5)	0.216
Time	1.47 (1, 100.9)	0.228
Group × time	0.05 (2, 100.5)	0.956
HAq-T: satisfaction with therapy outcome[b]		
Group	0.57 (2. 108.3)	0.567
Time	4.11 (1, 101.8)	0.045
Group × time	0.44 (2, 101.8)	0.645
IPAQ: moderate physical activity[a]		
Group	1.19 (3, 179.1)	0.314
Time	6.00 (2, 163.7)	0.003
Group × time	1.32 (6, 163.9)	0.250
IPAQ: vigorous physical activity[a]		
Group	1.35 (3, 172.9)	0.259
Time	0.68 (2, 160.0)	0.510
Group × time	2.74 (6, 161.0)	0.015
VAS: mood		
Group	2.68 (3, 162.8)	0.049
Time	14.75 (2, 163.7)	<0.001
Group × time	2.03 (6, 160.3)	0.064
VAS: self-efficacy		
Group	1.36 (3, 174.9)	0.257
Time	22.51 (2, 272.0)	<0.001
Group × time	1.39 (6, 268.3)	0.218
VAS: increase in activity		
Group	4.48 (3, 159.0)	0.005
Time	43.71 (2, 285.3)	<0.001
Group × time	2.99 (6, 279.9)	0.008
VAS: rumination[a]		
Group	0.96 (3, 177.5)	0.411
Time	15.22 (2, 277.3)	<0.001
Group × time	0.51 (6, 273.7)	0.798
VAS: feeling socially connected		
Group	1.12 (3, 169.1)	0.341
Time	22.32 (2, 254.2)	<0.001
Group × time	2.12 (6, 251.7)	0.052

Table 2 (continued)

Outcome	*F* (df)	*p* value
VAS: expressing needs[a]		
Group	0.84 (3, 167.8)	0.473
Time	19.16 (2, 148.7)	<0.001
Group × time	2.43 (6, 144.9)	0.029
VAS: expected reactions to own mistakes[a]		
Group	0.45 (3, 165.1)	0.719
Time	28.81 (2, 157.8)	<0.001
Group × time	0.88 (6, 158.3)	0.511
VAS: expected reactions to negative emotions[a]		
Group	1.11 (3, 167.7)	0.347
Time	4.57 (2, 254.0)	0.011
Group × time	0.35 (6, 251.2)	0.907

HAq-P, Helping Alliance Questionnaire, patient version; HAq-T, Helping Alliance Questionnaire, therapist version; IPAQ, International Physical Activity Questionnaire; PTQ, Perseverative Thinking Questionnaire; SCL, Symptom Checklist; VAS, visual analogue scale. [a] Based on square-root transformed data. [b] Treatment groups and changes from midtreatment to posttreatment only.

Results

Baseline Scores

Table 3 confirms that baseline comparisons of all relevant variables did not reveal any significant group differences. An average BDI-II of 29 indicated that more than half of the patients suffered from severe depression (BDI ≥29; the average BDI-II score of the 78 trials included in the meta-analysis of Cuijpers et al. [43] was 25.7). About one third of the sample fulfilled the criteria for chronic depression or early-onset depression, and about two thirds reported any kind of early childhood adverse events (mainly emotional neglect).

Primary Outcome: BDI-II

Analyses for depressive symptom severity were adjusted for BDI scores at study entry. We found a significant interaction between treatment group and assessment time (Tables 1 and 4; Fig. 2). At the end of treatment (after 16 weeks), patients of all 3 treatment arms reported substantial lower BDI scores than patients in the WL condition. These treatment effects were large for CBT-E (d = 0.91) and CBT-M (d = 0.87) and small to moderate for CBASP (d = 0.47). Patients in both CBT arms showed stronger reductions in BDI scores than patients in the CBASP arm. While this trend is partially evident at midtreatment assessments (after 8 weeks), only the comparison between the CBT-E group and CBASP was significant at the end of treatment, while CBT-M tended to be superior to CBASP. Thus, CBT-E resulted in significantly better outcome scores than CBASP, as indicated by post hoc comparisons (Fig. 2). Effect sizes for differences between CBASP and CBT arms at the end of the treatment were small to moderate (see suppl. Table 2 for effect sizes for post hoc contrasts).

The inventors of CBASP postulated that this treatment would be especially effective in patients with chronic, early-onset depression, and, respectively, in patients with adverse early childhood experiences. Therefore, we analyzed separate models for each potential moderator by adding the interaction terms (treatment × time × moderator) and lower order terms to our main outcome models (Table 4). The interaction with persistence of depression became significant. This interaction was mainly explained by the results for episodic depression: here, already at midterm, patients in the CBT-E arm showed more improvement than in the CBASP arm ($p < 0.05$). At end of treatment, both CBT arms had significantly lower BDI scores than the WL ($p < 0.05$); the advantage of CBT-E versus CBASP is further confirmed ($p < 0.05$), while an advantage of CBT-M compared to CBASP can only be shown on a trend level ($p < 0.10$; see online suppl. material Table 2 and Fig. 2). For chronic depression, cell sizes become too small to reveal meaningful results (13–18 per group). At midterm, the CBT arms were significantly improved compared to the WL ($p < 0.05$), while the advantage of CBASP versus WL was only at a trend level ($p <$ 0.10). CBT-M tended to be superior to WL in this sub-

Table 3. Sample characteristics

Characteristic	CBASP (n = 43)	CBT-E (n = 45)	CBT-M (n = 43)	WL (n = 42)	p value
Age (mean ± SD), years	40.4 (13.0)	35.9 (11.1)	36.3 (12.7)	38.8 (13.7)	0.30[d]
Female, n (%)	29 (67.4)	24 (53.3)	23 (53.5)	20 (47.6)	0.30[e]
BDI-II: depressive symptom severity at screening	28.12 (8.14)	30.54 (8.60)	29.19 (8.32)	28.29 (10.09)	0.56[d]
Upper secondary education[a], n (%)	19 (44.1)	23 (51.1)	24 (55.8)	15 (35.7)	0.30[e]
Chronic major depression[b], n (%)	13 (30.2)	13 (28.9)	18 (41.9)	18 (42.9)	0.48[e]
Early-onset major depression[c], n (%)	15 (34.9)	12 (26.6)	18 (41.9)	12 (28.6)	0.48[e]
Antidepressant medication, n (%)					
Total	19 (44.1)	19 (42.2)	17 (39.5)	18 (42.9)	0.98[e]
SSRIs	8 (18.6)	7 (15.6)	5 (11.6)	9 (21.4)	0.66
SNRIs	4 (9.3)	5 (11.1)	3 (7.0)	3 (7.1)	0.88
SARIs	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0.39
Agomelatine	0 (0.0)	0 (0.0)	2 (4.7)	3 (7.1)	0.12
NaSSAs	2 (4.7)	2 (4.4)	4 (9.3)	2 (4.8)	0.73
TCAs	4 (9.3)	2 (4.4)	3 (7.0)	2 (4.8)	0.78
St John's wort	2 (4.7)	2 (4.4)	1 (2.3)	1 (2.4)	0.89
NDRIs	1 (2.3)	2 (4.4)	2 (4.7)	2 (4.8)	0.93
DSM-IV axis I comorbidity, n (%)					
Anxiety disorders	11 (25.6)	15 (33.3)	7 (16.3)	10 (23.8)	0.33[e]
Somatoform disorders	5 (11.6)	5 (11.1)	7 (16.3)	8 (19.0)	0.68[e]
CTQ: childhood trauma, n (%)					
At least one trauma	34 (79.1)	32 (71.1)	31 (72.1)	24 (57.1)	0.13[e]
Emotional abuse	11 (25.6)	17 (37.7)	6 (14.0)	8 (19.0)	0.07[e]
Physical abuse	7 (16.3)	5 (11.1)	1 (2.3)	4 (9.5)	0.19[e]
Sexual abuse	5 (11.6)	1 (2.2)	4 (9.3)	5 (11.9)	0.32[e]
Emotional neglect	25 (58.1)	18 (40.0)	21 (48.8)	14 (33.3)	0.09[e]
Physical neglect	12 (27.9)	9 (20.0)	7 (16.3)	8 (19.0)	0.60[e]

BDI, Beck Depression Inventory; CBASP, cognitive behavioral analysis system of psychotherapy; CBT-E, cognitive behavioral therapy emphasizing physical exercises during behavioral activation; CBT-M, cognitive behavioral therapy emphasizing mindfulness exercises during behavioral activation; CTQ, Childhood Trauma Questionnaire; NDRIs, norepinephrine-dopamine reuptake inhibitors; NaSSAs, noradrenergic and specific serotonergic antidepressants; SARIs, serotonin antagonist and reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; WL, waiting list control condition. [a] School education of at least level 3 according to the International Standard Classification of Education. [b] Depressive symptoms must have persisted for at least 2 years. [c] Age of onset of less than 21 years. [d] By analysis of variance. [e] By χ^2 test.

group at the end of treatment. The other moderator "early onset of depression" (triple interaction; $p < 0.11$) and "early adverse events" (triple interaction; $p < 0.07$; Table 4) indicated similar effects as "persistence of depression," although on a trend level.

We applied the frequently used criterion of a 50% reduction to define treatment response [43]. Figure 3 illustrates results from the responder analysis. For the intention-to-treat analysis, response rates of patients were significantly different between treatment groups, with 34.0% (n = 14.6) in the CBASP group, 56.0% (n = 25.2) in the CBT-E and 55.8% (n = 24.0) in the CBT-M group. As compared to WL (3.4%; n = 1.4), response rates were significantly higher in CBASP (OR = 15.42, 95% CI = 1.98–120.04, p = 0.009), in CBT-E (OR = 38.20, 95% CI = 4.71–310.09, p = 0.001), as well as in CBT-M (OR = 37.91, 95% CI = 4.72–304.87, p = 0.001). As compared to CBASP, response rates were significantly higher in CBT-E (OR = 2.48, 95% CI = 1.02–6.00, p = 0.044) and in CBT-M (OR = 2.46, 95% CI = 1.01–6.01, p = 0.048). CBT-E response rates were similar to CBT-M (OR = 1.01, 95% CI = 0.42–2.41, p = 0.987). The pattern of differences was similar when analyzing completer data.

Secondary Outcome Variables

Significant patterns of change (Tables 1 and 2) were found for SCL-global symptom severity, vigorous physical activity, as well as for 2 visual analogue scales (per-

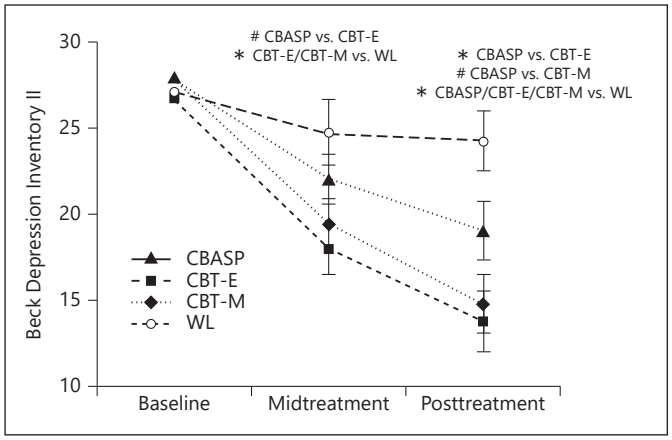

Fig. 2. Depressive symptom severity (adjusted for screening values at study entry) from baseline to week 8 (midtreatment) and to week 16 (posttreatment) by treatment group. Values are estimated marginal means (with SEM) from intention-to-treat analysis using multilevel modeling. Post hoc contrasts for cognitive behavioral analysis system (CBASP), cognitive behavioral therapy emphasizing physical exercises during behavioral activation (CBT-E), and cognitive behavioral therapy emphasizing mindfulness exercises during behavioral activation (CBT-M) versus waitlist (WL). * $p < 0.05$; # $p < 0.1$.

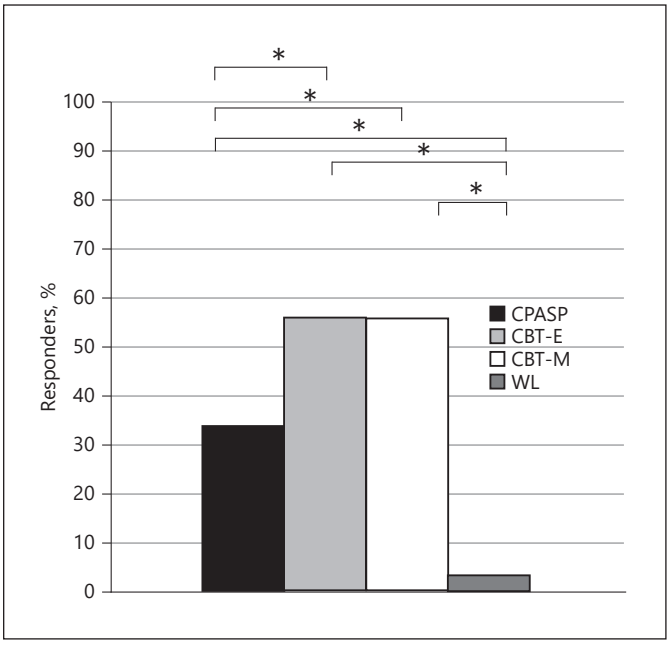

Fig. 3. Percentages of patients with at least 50% reduction in depressive symptom severity after 16 weeks of treatment/waiting time for the intention-to-treat sample. Significance of differences based on binary logistic regression models. CBASP, cognitive behavioral analysis system of psychotherapy; CBT-E, cognitive behavioral therapy emphasizing physical exercises during behavioral activation; CBT-M, cognitive behavioral therapy emphasizing mindfulness exercises during behavioral activation; WL, waitlist control condition. * $p < 0.05$.

ceived increase in activity, perceived ability to express needs). At the end of treatment, both CBT arms led to significantly lower SCL scores than the WL, while CBASP was not significantly superior to WL and tended to be inferior to CBT-E (see online suppl. Fig. 1). CBT-E was associated with a temporary significant increase in vigorous physical activity after the period of behavioral activation (see online suppl. Fig. 3). As compared to the WL, all active treatments resulted in significantly higher levels of perceived activity at the end of treatment (see online suppl. Fig. 4). Finally, the perceived ability to express needs was higher in CBT-E than in the WL condition after 16 weeks of treatment (see online suppl. Fig. 5).

Role of Concurrent Drug Administration

Between 39.5 and 42.9% of patients were on stable antidepressant medication, and 2 patients were excluded because of changes in drug regimen (Fig. 1). Exploratory analyses were performed to ensure that antidepressant use did not affect the impact of interventions on depressive symptom severity (BDI-II). Antidepressant use did not moderate the impact of treatment group on depressive symptom severity [$F(6, 146.01) = 0.86$, $p = 0.527$]. Furthermore, when considering antidepressants as a covariate, group × time interaction [$F(6, 154.74) = 4.21$, $p = 0.001$] remained significant, and significances for post hoc contrasts were similar to our main analysis (Fig. 2). Even results for an analysis without patients on antidepressants [interaction of treatment group × assessment time, $F(6, 89.12) = 3.04$, $p = 0.009$] were comparable to the whole sample analysis, despite the lower sample size.

Negative Outcomes/Deterioration

While psychotherapy trials notoriously missed to analyze negative outcomes in the past, this problem has been more and more emphasized during the last few years [44–46]. Therefore we reanalyzed the number of patients who displayed deterioration until the end of treatment. As criterion for deterioration, we used the recommended threshold of a 17.5% increase in BDI scores which has been evaluated as minimal clinically important difference of the BDI [47]. For the intention-to-treat analysis, deterioration rates of patients were not significantly different

Table 4. Results for depressive symptom severity as a primary outcome from intention-to-treat analyses using multilevel modeling: main effects, lower-order terms and adjusted patterns of change from baseline, to midtreatment, to posttreatment assessments by treatment group and by potential moderators

BDI-II[a]	*F* (df)	*p* value
Group	5.09 (3, 155.1)	0.002
Time	66.00 (2, 155.1)	<0.001
Group × time	4.18 (6, 154.5)	0.001
Moderator: chronic depression		
Group	4.25 (3, 146.3)	0.007
Time	50.80 (2, 142.8)	<0.001
Chronic depression	3.20 (1, 146.3)	0.076
Group × time	3.09 (6, 142.7)	0.007
Group × chronic depression	0.45 (3, 146.3)	0.716
Time × chronic depression	1.21 (2, 142.8)	0.300
Group × time × chronic depression	2.18 (6, 142.7)	0.048
Moderator: early-onset depression		
Group	4.59 (3, 152.3)	0.004
Time	53.72 (2, 151.9)	<0.001
Early-onset depression	1.60 (1, 153.4)	0.208
Group × time	3.07 (6, 150.2)	0.007
Group × early-onset depression	0.06 (3, 152.2)	0.981
Time × early-onset depression	0.37 (2, 152.0)	0.692
Group × time × early-onset depression	1.79 (6, 150.2)	0.106
Moderator: early trauma		
Group	5.14 (3, 147.1)	0.002
Time	47.18 (2, 143.7)	<0.001
Early trauma	0.17 (1, 147.0)	0.684
Group × time	3.58 (6, 144.7)	0.002
Group × early trauma	0.86 (3, 147.4)	0.461
Time × early trauma	0.92 (2, 143.7)	0.400
Group × time × early trauma	2.00 (6, 144.7)	0.069

BDI, Beck Depression Inventory. [a] Adjusted for depressive symptom severity at study entry (i.e., BDI screening values).

between treatment groups, with 9.8% ($n = 4$) in the CBASP group, 8.9% ($n = 4$) in the CBT-E and 5.7% ($n = 3$) in the CBT-M group. As compared to WL (14.3%; $n = 6$), deterioration rates were lower (yet not reaching statistical significance) in CBASP (OR = 0.62, 95% CI = 0.14–2.86, p = 0.540), in CBT-E (OR = 0.58, 95% CI = 0.15–2.26, p = 0.432), as well as in CBT-M (OR = 0.44, 95% CI = 0.10–2.00, p = 0.281). As compared to CBASP, deterioration rates were not significantly different in CBT-E (OR = 0.93, 95% CI = 0.17–4.97, p = 0.929), and in CBT-M (OR = 0.71, 95% CI = 0.137–3.63, p = 0.675). Deterioration rates were not significantly different between CBT-E and CBT-M (OR = 1.32, 95% CI = 0.26–6.70, p = 0.740). The pattern of differences was similar when analyzing completer data.

Discussion

While our results confirmed improvements for all 3 treatment arms compared to the WL, we also found some advantages in favor of the CBT conditions. For our primary outcome BDI-II, CBASP resulted in less success compared to the CBT arms if all depressed patients were included. Our CBT arms showed comparable success to the meta-analytical results including more than 70 depression studies of Cuijpers et al. [43], with response rates of 56% for both CBT-E and CBT-M, and also the CBASP results are similar to other CBASP studies, underlining that we conducted the treatments comparably to corresponding primary trials. Therefore, for the first time, a direct comparison between traditional CBT approaches and CBASP was possible.

Preliminary meta-analyses about CBASP confirm its efficacy [48], although the average effect size compared to treatment as usual was small (g = 0.34–0.44), and similar to drug treatments in chronic depression [39]. Inpatient adaptations report large effect sizes in uncontrolled one-arm designs, again in chronic depression [49], but uncontrolled factors could have also contributed to these large effect sizes. Post hoc analyses of one of the first large trials using CBASP [50] confirmed early childhood adversities to predict better outcome in CBASP treatments than in pharmacological therapies [18]. Moreover, CBASP had a positive maintenance effect of treatment benefits in chronic depression compared to no maintenance strategies [51].

A moderation analysis of our results with "chronic versus episodic depression" confirmed that results for interventions are different depending on this moderator ($p < 0.05$). For the chronic subgroup of depression, our analyses did not confirm any superiority of CBASP, although results are only based on small sample sizes for these subgroups. For episodic depression, a clear advantage for CBT-E could be confirmed in post hoc tests. The rationale of CBASP postulates that transference-focused work in therapy should help the patient to change behavior and experiences in interactions, while behavior-analytical parts should provide feedback about the discrepancy of personal interaction goals, interaction behavior, and interaction effects. Our results indicate that such an approach is less recommended for episodic depression. Reasons for this could be a postulated greater relevance of present conflicts, stressors, or present-state cognitions in episodic depression, which might require more present-state interventions such as CBT. Further, it can be speculated that the simpler rationale of activation-oriented CBT interventions is easier to transfer to the everyday life of depressive patients than the more complex rationales of the other interventions. However, in light of the positive results in favor of CBASP versus mindfulness interventions in the study of Michalak et al. [12] for depression expert ratings (yet not self-ratings) in chronic depression, and considering the specific advantage of CBASP versus supportive therapy in the study of Schramm et al. [11] which selected only patients fulfilling the specific target criteria (early-onset, chronic depression), CBASP certainly has potential for offering significant help in particular for the original target group [10]. However, a more critical interpretation is in line with the small effect sizes in meta-analyses mentioned above or only moderate effects found for CBASP in this and another study with chronically depressed patients [52], with only significant advantages compared to a care as usual arm at week 52, but not at weeks 8, 16, and 32.

In our study, we wanted to use treatments with an economic format of 16 weekly sessions that seems acceptable in many health care systems, and therefore we used a CBASP version that was shorter than in some other trials [11]. Indeed, in the study of Schramm et al. [11], the first significant advantages for CBASP compared to supportive therapy occurred after 20 weeks of treatment. However, the relation between treatment duration and outcome for CBASP seems to be inconsistent: the initial CBASP study [50] used 16 sessions as in our trial, other successful CBASP trials used fewer sessions [12, 53], while Schramm et al. [11] and Wiersma et al. [52] used 22–25 sessions [39]. Despite longer treatments with CBASP, the Wiersma study did not find significant pre-post improvements. Treatment responses for CBASP in the Schramm study were similar to ours (38.7 vs. 34%), and remission rates of 25.7% in the study of Michalak et al. [12] using a CBASP group format also seem to be in a similar range. Another study suffering from a one-arm design and large dropout rates (38%) reported positive follow-up effects, using 20 sessions [54]. Still, it is possible that in particular chronically depressive patients require longer treatment durations.

The group of patients with chronic, early-onset depression was reported to have specific features that distinguished it from other forms of depression [55]. Klein and Kotov [56] confirmed that this group is characterized by more early childhood adversity, more personality disorders, more comorbidity with other mental disorders, and more frequent suicide attempts. Moreover, early childhood adversities are associated with certain personality characteristics in adulthood, such as lower agreeableness, higher anger/aggression and extrinsic focus [57]. These findings could contribute to a poorer prognosis for this subgroup compared to more episodic forms of depression. However, CBT seems to still be one of the first-line treatments even for these more complex versions.

It comes with some surprise that the most traditional CBT approach with a special focus on the increase in physical activity shows the best treatment results. However, on the other hand, also in the meta-analysis from Cuijpers et al. [43] the behavioral activation intervention performed the best, and the major reason not to confirm treatment differences in their meta-analyses was small numbers of studies for other interventions (and corresponding large confidence intervals for the other treatments). Our findings of large effect sizes for differences

in BDI-II scores between CBT arms and the WL group are also comparable to findings from another meta-analysis which reports large effect sizes for comparisons between CBT and control conditions for BDI (g = 0.79) and BDI-II (g = 0.72) [58]. A closer inspection of online supplementary Figure 2 reveals that our CBT approach shows strong effects in episodic depression, while CBT effects in chronic depression were only moderate. Just recently, Collado et al. [59] confirmed an advantage of behavioral activation above supportive counseling in a small sample of Hispanic patients. In their meta-analysis adjusting for publication bias, Schuch et al. [60] concluded that the positive effect of exercise-oriented interventions has been underestimated due to publication bias, and exercise has a large and significant effect on depression. This effect is also modulated by a dose response [61], while Cochrane analyses confirmed a moderate effect of exercise [62]. In contrast to other CBT approaches, behavioral activation in conjunction with exercise may have the potential to reverse, in part, immunological alterations in major depression [21]. Even short-term trainings of therapists in behavioral activation lead to effective outcome in patients, and this recommends behavioral activation as an easy to deliver but effective intervention [63]. Therefore our results are a strong argument to compare innovative psychological treatments with well-established therapies before far-reaching interpretations about a potential advantage of the new intervention can be drawn.

Researcher allegiance shows close associations with reported treatment outcomes, and therefore requires transparency [64, 65]. While 2 authors (W.R., F.E.) have a major training in CBT and sympathies for the CBASP concepts, the other coauthors represent therapists/supervisors with a full training in CBASP, and they were mostly involved in another multicenter CBASP study [11]. However, all CBASP therapists had a former training in CBT as well, and we can only speculate whether this had an influence.

A major shortcoming of our trial is the lack of a standardized follow-up period with a low frequency of interfering treatments. The German health care system allows free access to treatments that are even longer than our treatments, and therefore a significant amount of patients requested continuation (mostly of the same treatment), which hindered a systematic evaluation of long-term effects. Second, as primary outcome we chose the BDI-II as a self-rating scale, because expert ratings notoriously reveal overestimations of effects (also in the placebo groups [2, 28]); however, additional expert ratings would further strengthen the interpretability. Third, any subgroup analyses of our trial should be considered as tentative, because sample sizes substantially decreased within the subgroups. Moreover, in contrast to our analysis of the primary outcome, secondary outcome analyses and moderator analyses were exploratory, and not corrected for multiple testing. Finally, treatment fidelity was only ensured via personal supervision (every 4th session). All therapists brought at least 1 session video per patient to supervision sessions, and more metric assessment of treatment fidelity would be advisable. And finally, while we controlled for different moderators separately, CBASP could be mainly efficient only for the selected subgroup fulfilling all 3 criteria of chronicity, early onset, and early adverse events.

Despite these shortcomings, this is the first study directly comparing CBASP with the most frequently evaluated treatment CBT. A broad heterogeneity of depressive patients and a large number of involved therapists underline the external validity of our results. While positive and early-response effects could be confirmed for CBT, our results also include a plea that sufficiently powered head-to-head trials against the well-evaluated CBT approach are urgently needed if new or other treatments are tested, with an adequate and comparable implementation of CBT. We found no evidence that CBASP can compete with the success of CBT interventions in the case of general depression, although similarity of success of CBASP versus CBT in some subgroups of depression is still an option. CBASP can still offer a specific treatment alternative and might be further empowered with future inventions. To summarize, our study confirms the need to continue to improve depression-specific psychotherapy and to find replicable moderators.

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Disclosure Statement

The authors declare no specific conflict of interest that could have influenced treatment results or the content of this paper. Dr. Rief is the head of a licensed postgraduate training program for psychologists with a focus on CBT, but which also offers CBASP workshops; he was not an active therapist of this study, while all other coauthors were. W.R. received honoraria from pharmacological enterprises for talks on placebo and nocebo effects (Heel; Berlin Chemie; Bayer). G.B. and K.W. received honoraria for offering CBASP workshops.

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