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Blended Cognitive Behavioral Therapy versus Standard Cognitive Behavioral Therapy for Unipolar Depression: A Multicenter Randomized Controlled Trial

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Blended cognitive behavioral therapy · Digital intervention · Digital therapeutics · Depression

Abstract

Introduction: This study evaluated the effectiveness of blended cognitive behavioral therapy (bCBT) with a digital health application (elona therapy) compared to standard cognitive behavioral therapy (CBT) for unipolar depression in outpatient care. ***Methods:*** This multicenter, randomized, two-arm controlled trial recruited 283 adult patients with unipolar depression in Germany. Patients were randomized to receive either standard face-to-face CBT combined with the digital health application (bCBT group) or standard face-to-face CBT alone. Symptoms of depression and anxiety, along with other patient-related characteristics, were assessed at baseline (T0: week 0) and post-intervention (T1: week 12). ***Results:*** Patients in the bCBT group showed greater improvements in depressive symptoms (primary outcome: $d = 0.62$, $p < 0.001$), anxiety ($d = 0.61$, $p < 0.001$), quality of life ($d = 0.42$, $p < 0.001$), perceived self-efficacy ($d = 0.41$, $p = 0.003$), depression literacy ($d = 0.66$, $p < 0.001$) and overall disease severity outcomes ($d = 0.45–0.60$, $ps < 0.005$) compared with patients in the CBT group. ***Conclusion:*** This study provides evidence supporting the effectiveness of bCBT in patients diagnosed with unipolar depressive disorder across a broad range of clinically relevant outcomes. The discussion addresses important limitations of this trial.

Introduction

Depression is a widespread health disorder that profoundly impacts emotional well-being, social and occupational functioning, and quality of life and is among the leading causes of global disability [1, 2].

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Cognitive behavioral therapy (CBT) is a well-established and widely used evidence-based treatment for depression, endorsed by various studies and international guidelines for its effectiveness [3–5]. However, traditional CBT often struggles with limited accessibility, time constraints within sessions, and patient engagement with the therapeutic material between appointments [6, 7]. Moreover, traditional CBT is mostly conducted with low intensity, i.e., weekly or less frequent sessions. Although CBT is on average effective for depression, some patients experience only partial response or residual symptoms, indicating a need for complementary or augmented treatment strategies [8, 9]. Digital health applications offer a promising solution to these limitations by providing a structure, self-guided exercises, and psychoeducation outside the therapy room, enhancing engagement and extending therapy beyond face-to-face sessions [10, 11].

In the past decade, the use of digital health interventions, known as digital therapeutics, has increased in the treatment of mental health disorders. In particular, blended cognitive behavioral therapy (bCBT) has been introduced to address challenges in face-to-face CBT. The bCBT approach enhances face-to-face psychotherapy by providing patients with digital interventions through a smartphone or online app between sessions [11]. By encouraging adherence between sessions, bCBT aims to address the limitations of standard CBT, extending treatment beyond sessions and potentially enhancing its efficacy [12, 13]. bCBT can be understood as a multifaceted intervention that combines at least several interacting mechanisms: it aims to augment CBT treatment intensity and effectiveness by supporting the transfer of skills into daily life, to increase patient engagement and time spent with treatment content between sessions, and to modify the therapeutic process through structured digital modules [14–16].

While some studies have reported that bCBT yields superior outcomes in reducing depressive symptoms compared to CBT [13, 17], others have found the two modalities to be similarly effective [18, 19]. Evidence also suggested that bCBT may outperform standard CBT in enhancing quality of life [20], reducing anxiety symptoms [20], and improving mental health literacy [17]. However, these findings have not been consistently replicated, with several studies reporting no significant differences across these domains [18, 19]. Studies comparing the added benefits of bCBT to CBT remain scarce, and existing findings have not been consistently replicated, partly due to differences in digital programs and study designs. Furthermore, trial quality is often compromised due to high dropout rates and difficulties in recruiting the target sample size. Control conditions in blended care trials also vary widely in the earlier literature, from minimal personal contact with therapists to weekly full psychotherapy sessions, making it difficult to isolate the added value of digital components within real-world treatment contexts.

To address the limitations of previous research, a novel bCBT application was developed based on prior recommendations for developing bCBT applications (e.g., therapy congruence, fostering learning, guiding therapy, and connection building; [21]). The development of bCBT also integrated insights from qualitative studies that explored both patients' and therapists' expectations [22] and their experiences with bCBT [23].

This randomized controlled trial (RCT) examines the benefits of integrating a digital health application (elona therapy) into CBT for patients with depression, implemented under real-world clinical conditions. Preliminary evidence supporting this bCBT program builds upon a feasibility [24] and a pilot RCT [20]. The current, larger-scale trial aims to confirm and expand upon these prior findings.

Methods

Study Design and Hypotheses

This study was a two-arm, multicenter, pragmatic RCT designed to investigate additional benefits of a bCBT treatment program (face-to-face CBT supported by a digital health application) for patients with unipolar depression compared to standard CBT treatment. Participants were randomly assigned to either the intervention group (bCBT) or the control group (CBT). The intervention group was provided access to the depression module of the elona therapy application in addition to CBT, whereas the control group received standard CBT only over 12 weeks. Outcome assessments were conducted at baseline (T0) and after 12 weeks of treatment (T1). To minimize expectation bias, patients in both study groups were informed that they would receive an app to support their psychotherapy treatment at a random time within the 12-week study period (cover story). They were unaware that there were only two groups and that app access would be provided only at baseline or study end (for the control group). Therapists were aware of the study aim and allocated a treatment group of their patients. Control group patients could access the app after the study if desired. The full CONSORT checklist for this

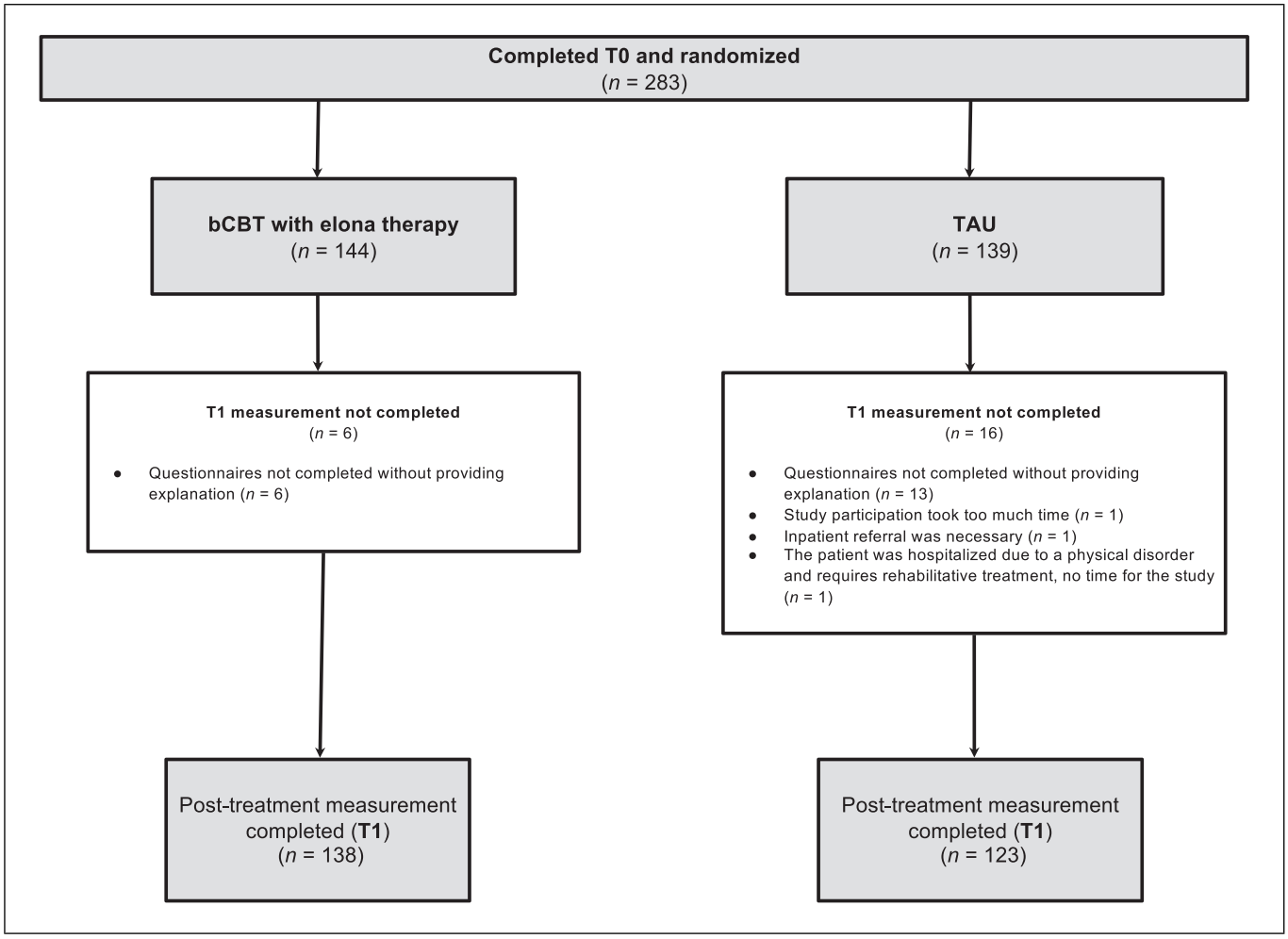

Fig. 1. Study flowchart. Two-hundred-eighty-three patients competed T0 and were randomized into two groups. bCBT consisted of 144 participants of which 138 completed T1. TAU consisted of 139 participants, of which 123 completed T1. TAU, treatment as usual.

study is available in the online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000550820).

Participants

A total of 283 patients were recruited between August 2023 and May 2024. Of these, 144 were randomized to the bCBT group and 139 to the CBT group. The study flowchart (Fig. 1) illustrates the enrollment process and participant dropouts throughout the trial. Table 1 shows baseline demographic characteristics of the two study groups.

There were no group differences in the baseline demographic characteristics, except for the employment status (p = 0.023; all other ps > 0.05). The sensitivity analysis reported in online supplementary A, therefore, includes employment status. A total of 224 patients were diagnosed through diagnostic or clinically structured interviews (e.g., Mini-DIPS; [25]). For the remaining 59 patients, the diagnosis was based on the therapist's clinical judgment or evaluated against the International Classification of Diseases version-10 (ICD-10, [26]) criteria, reflecting standard clinical practice.

Study Procedure

Recruitment and Randomization

Potential participants were recruited at psychotherapy clinics affiliated with training institutes for CBT therapists in several large cities in Germany as part of routine care. Therapists who took part in the trial were licensed psychotherapists or psychotherapists in training under clinical supervision at a 1:4 ratio. Recruitment for the

Table 1. Mean values (standard deviations) or frequencies of the demographic characteristics of the bCBT group and the CBT group

	bCBT group (n = 144)	CBT group (n = 139)	p value
Age, years			0.611[1]
Mean value (standard deviation)	37.52 (10.90)	38.18 (10.86)	
Range	19–63	18–64	
Gender, n (%)			0.525[2]
Female	108 (75)	102 (73)	
Male	36 (25)	35 (25)	
Diverse	0 (0)	2 (1.4)	
Diagnoses, n (%)			0.867[3]
Mild depressive episode (F32.0)	22 (15)	23 (17)	
Moderate depressive episode (F32.1)	33 (23)	28 (20)	
Severe depressive episode without psychotic symptoms (F32.2)	12 (8.3)	11 (7.9)	
Recurrent depressive disorder, current episode mild (F33.0)	16 (11)	15 (11)	
Recurrent depressive disorder, current episode moderate (F33.1)	38 (26)	45 (32)	
Recurrent depressive disorder, current episode severe without psychotic symptoms (F33.2)	15 (10)	9 (6.5)	
Dysthymia (F34.1)	8 (5.6)	8 (5.8)	
Psychopharmacological medication, n (%)			0.053[3]
Yes	22 (15)	34 (24)	
No	122 (85)	105 (76)	
Highest secondary education qualification, n (%)			0.090[2]
Completion of polytechnic secondary school, intermediate school leaving certificate, secondary school certificate	21 (15)	20 (14)	
Advanced technical college or university entrance qualification	122 (85)	111 (80)	
Secondary school leaving certificate	1 (0.7)	7 (5)	
Still in school education	0 (0)	1 (0.7)	
Education level, n (%)			0.425[2]
Apprenticeship or vocational training technical college degree	46 (32)	44 (32)	
Bachelor	24 (17)	33 (24)	
Master	47 (33)	36 (26)	
Doctorate	4 (2.8)	6 (4.3)	
Currently in (bachelor) studies	15 (10)	9 (6.5)	
Without a vocational qualification	8 (5.6)	10 (7.2)	
Employment status, n (%)			0.023[4]
Self-employed, freelance work	7 (4.9)	4 (2.9)	
Student	23 (16)	11 (7.9)	
Employed full-time	60 (42)	59 (42)	
Employed part-time	28 (19)	21 (15)	
Currently on sick leave	7 (4.9)	13 (9.4)	
Currently on parental leave	1 (0.7)	4 (2.9)	
Seeking employment	13 (9)	10 (7.2)	
Other	3 (2.1)	14 (10)	
Relationship status, n (%)			0.217[3]
Single	60 (42)	48 (35)	
In a relationship	84 (58)	91 (65)	

bCBT, blended cognitive behavioral therapy; CBT, cognitive behavioral therapy. [1]Independent samples t test. [2]Fisher's exact test. [3]Pearson's chi-squared test. [4]Fisher's test with simulated p value.

study was offered to potential participants during consultation or probationary sessions if the therapist deemed an appropriate diagnosis for study participation. Diagnostic assessment followed routine care procedures. Therapists were free to use structured clinical interviews and/or any other tool to support the diagnosis (e.g., standardized questionnaires, ICD-10 criteria). After providing informed consent, participants were registered in the electronic data capture (EDC) system and randomly assigned to one of the study groups (bCBT, CBT). Randomization used a 1:1 allocation ratio, stratified by depressive symptom severity (mild/moderate/severe depression/dysthymia) into four groups: Group 1 (F32.0, F33.0), Group 2 (F32.1, F33.1), Group 3 (F32.2, F33.2), and Group 4 (F34.1). The random allocation sequence was centrally generated by the study coordinator using computer software and was stratified according to each severity group. Randomization was completed by therapists through the EDC, where the therapists reached spreadsheets that stored the random allocation sequence. By selecting the next available participant ID on the spreadsheet, the study group for the respective patient was assigned. Group allocation remained concealed until completion via the EDC system, with no visibility of other assignments. Recruitment was concluded as scheduled when the planned study end date was reached.

After recruitment and randomization, participants received baseline (T0) and demographics questionnaires via e-mail through the EDC system. Twelve weeks later, they received the post-treatment questionnaires (T1) via the system. At each measurement point, they had up to 14 days to complete the questionnaires, after which the questionnaires expired. Responses were confidential and not accessible to therapists, as communicated to participants. If a patient dropped out of the study, or an adverse event (AE) or a serious adverse event (SAE) occurred at any time during the study, therapists were instructed to record the relevant information in the EDC system. AEs were defined as any undesirable medical occurrence, and SAEs as life-threatening events, hospitalizations, or persistent disability, regardless of their relation to the study or intervention, and whether it was expected or unanticipated. Therapists monitored and reported AEs and SAEs during sessions or when communicated by patients.

Inclusion and Exclusion Criteria

Participants had to: (i) meet the diagnostic criteria for a depressive episode (F32.0, F32.1, F32.2), recurrent depressive disorder (F33.0, F33.1, F33.2), or dysthymia (F34.1) according to the ICD-10; (ii) be between 18 and 65 years old; (iii) have sufficient German language proficiency to participate in psychotherapy and use the digital health application; (iv) own a smartphone (iOS or Android) with internet access, and (v) provide signed and dated informed consent and agree to adhere to the study protocol.

The following criteria for exclusion were applied: Participants were excluded if they: (i) exhibited acute suicidality (assessed by the clinical judgment of the therapist); (ii) met the diagnostic criteria for comorbid organic mental disorders (F0–F09), substance use disorders (F10–F19, except F17), disorders with psychotic symptoms (F2–F29, F30, F32.3, F33.3), or bipolar disorder (F31). Participants who were currently enrolled in a potentially confounding drug or device trial or those who plan to change the dose of their current psychiatric medication or start a new one during the study period were excluded (a stable dose of psychiatric medication was allowed). Inclusion and exclusion criteria were assessed at baseline by the therapist.

Intervention and Control Groups

Patients in the intervention group received access to the digital health application elona therapy in addition to standard face-to-face CBT for 12 weeks with weekly CBT sessions. The digital health app comprises two integrated interfaces: A smartphone application for patients and a web-based platform for therapists. The therapist platform enables therapists to create individualized treatment plans by assigning digital content personally for each patient – including psychoeducational materials, therapeutic techniques, and exercises – selected from a structured library of interventions and monitor patient progress. The available content of the application is based on evidence-based CBT methods and includes a collection of over 400 available resources in the digital library. An overview of digital content available in the elona therapy is provided in online supplementary B. Therapists were encouraged to use their professional judgment when choosing digital content suited to each patient's individual symptoms, therapeutic needs, and current treatment focus. Patients had access to the assigned digital interventions at any time via their smartphones throughout the treatment period. In addition to the therapeutic interventions, the bCBT application included features such as daily mood tracking, visual progress feedback, session reflections, and a digital therapy schedule. Participants were able to set reminders and notifications for their preferred features. In addition to the interventions assigned by therapists, the digital application automatically provides relevant content that

is accessible to each participant. These core modules are recommended by the system alongside therapist-assigned interventions and topics such as emotional awareness and goal setting, foundational knowledge about depression, the psychotherapy process, and various therapeutic approaches. Integration between patient and therapist interfaces ensured continuous oversight, allowing timely intervention in case of symptom deterioration. The primary difference between the intervention and control groups was the use of the bCBT application. Therapists received specific instructions on the study procedures and an information session on the use of the digital health application provided by the study team.

The control group received standard CBT for 12 weeks. CBT was delivered according to each therapist's usual clinical practice, thereby reflecting routine care. Weekly CBT sessions were scheduled over the 12-week study period, with no specific instructions provided. Therapists in the control group exercised their discretion to assign homework to assign homework aligned with CBT guidelines. In both study groups, the study period was 12 weeks, but continuation of the therapy was possible as part of routine care if deemed necessary based on therapist-patient agreement and individual treatment needs.

Outcome Measures

The primary outcome was the severity of symptoms of depression measured by the Patient Health Questionnaire-9 (PHQ-9; [27]; German version: [28]) using nine items rated on a scale from 0 to 3. The reliability and validity of the German PHQ-9 have been demonstrated [29].

Secondary outcome measures included generalized anxiety symptoms, psychological quality of life, and overall well-being. Generalized anxiety symptoms were assessed using the Generalized Anxiety Disorder-7 (GAD-7; [30]; German version: [31]), which consists of seven items rated from 0 to 3. The German version has demonstrated robust psychometric properties [31]. Patients' quality of life was measured using the psychological health subscale of the WHOQOL-BREF, which includes six items rated from 1 to 5. The WHOQOL-BREF has demonstrated strong reliability and validity [32, 33]. Patients' perceived self-efficacy was measured by the General Self-Efficacy Scale (GSE; [34]) through ten items rated from 1 to 4. Previous work has demonstrated the reliability and validity of the GSE [35, 36]. Depression-related health literacy was measured using the Depression Literacy Questionnaire (D-Lit), which includes 22 items with a three-option response format ("true," "false," "don't know"). A technical issue resulted in the omission of one item in our EDC system, resulting in a 21-item version. As the items are independent, this omission did not compromise the validity of the scale. The German version of the D-Lit scale has satisfactory psychometric properties [37]. Patient adherence to therapy content between sessions was assessed using brief questionnaires developed by the study team, grounded in prior literature [38–40]. Patients and therapists each responded to four items, rated from 1 to 4, reflecting their respective perspectives. The full item set is available in online supplementary C. Finally, overall disorder severity and improvement from baseline were measured using the Clinical Global Impression-Severity (CGI-S; [41]; German version: [35]) and the Clinical Global Impression-Improvement (CGI-I; [41, 42]), respectively. Both are rated on 7-point scales (1–7), with higher scores indicating greater severity (CGI-S) or less improvement (CGI-I). All outcome measures were administered at baseline (T0) and post-treatment (T1), except for adherence and CGI-I, which were assessed only at T1.

Statistical Analyses

We tested the efficacy hypotheses of the study using a fixed-sequence (hierarchical) testing approach to control the type I error rate across multiple outcomes. The hierarchical testing approach tests the hypotheses in the pre-defined order until the first nonsignificant result [43]. The order starts with the primary hypothesis and continues with the secondary hypotheses in the order that secondary endpoints are listed below. The primary effectiveness hypothesis posited that patients receiving bCBT would experience stronger improvements in symptoms of depression than patients receiving standard CBT. Then, we tested the following secondary efficacy hypotheses: Patients receiving bCBT would experience stronger improvements in generalized anxiety symptoms, psychological health-related quality of life, perceived self-efficacy, depression literacy, and patient- and therapist-rated adherence (both subsections needed to be significant for hypothesis confirmation). Later, we tested the hypothesis that the proportion of patients showing clinically significant improvement (i.e., ≥50% symptom reduction on the PHQ-9; [44–46]) would be larger for patients receiving bCBT compared to patients receiving CBT. Finally, therapist-rated overall symptom severity and improvement level were hypothesized to be larger in the bCBT group than in patients receiving CBT. The safety hypothesis was that patients in the bCBT group would not experience more AEs or SAEs than those in

the CBT group. The safety hypothesis was isolated and not part of the hierarchical testing.

An a priori sample size calculation using G*Power 3.1 [47], employing the independent *t* test option as an approximation to our planned analytic approach, indicated that 260 participants (130 per group) were required to detect a post-treatment between-group effect of d = 0.35 with 80% power at α = 0.05. Allowing for an anticipated 20% attrition rate [48], the target sample size was set at 312 participants (156 per group).

The study analyses were based on the intention-to-treat sample, including all randomized participants. Missing values at T1 were imputed using reference-based multiple imputation (jump to reference; [49]). For the hypothesis concerning minimally clinically relevant improvement in the PHQ-9, missing values were imputed by assuming non-response for that patient, i.e., not having achieved at least 50% improvement. Within the multiple imputation (MI) approach, ten datasets were generated. Statistical analyses were conducted separately on each dataset and then pooled using Rubin's rules [50] to give a single MI estimate for inference.

The MI model included the following variables: study arm, baseline score, the diagnostic subgroup, age, gender, and the patient's educational level. For the efficacy hypotheses comparing score improvement, a linear mixed model with random intercept was specified. Change from baseline served as the dependent variable. Fixed effects included the baseline measurement, study group (bCBT, CBT), diagnostic subgroup (stratification variable), age, gender, and the patient's educational level. Therapists were included as a random effect to account for individual treatment variations. To account for multiple imputation, the models were fitted separately to each imputed dataset, and results were combined using Rubin's rules.

Statistical significance was defined as $p \leq 0.05$. To test the hypothesis of minimally clinically relevant improvement, the proportion of patients achieving clinically meaningful improvement on the PHQ-9 was compared between study groups using the Cochran-Mantel-Haenszel test, applied to the imputed dataset under the non-response assumption. An independent samples *t* test was used to compare adherence levels and CGI-I scores at T1 between study groups. The proportion of patients who experienced AEs or SAEs was compared between study groups using Pearson's chi-squared test. Reliabilities of the outcome measures (Cronbach's α) were calculated based on the observed data before imputation for all outcome measures except for the D-Lit, CGI-S, and CGI-I for feasibility reasons.

Potential group differences in baseline values in outcome measures and demographic characteristics were tested using independent samples *t* tests or χ^2 tests. A Pearson's chi-squared test was used to compare the proportion of patients who dropped out over the study period between the study groups.

Results

Descriptive statistics for outcome measures at T0 and T1 are presented in Table 2. Average PHQ-9 ($p = 0.010$) and GAD-7 ($p = 0.041$) scores at baseline were higher for the bCBT compared to CBT group. Baseline scores on the other outcome measures did not differ between study groups (all $p > 0.05$). A sensitivity analysis adjusting for differing baseline scores was conducted and reported in online supplementary A. The bCBT group attended a higher number of weekly sessions (M = 10.95, SD = 1.38) over the 12-week intervention period than the CBT group (M = 10.10, SD = 2.19), $t(262) = 3.79$, $p < 0.001$, $d = 0.47$. Frequency distribution of the single item CGI-I scores is separately depicted in Table 3 for the bCBT and the CBT groups. The rate of patients who dropped out in the CBT group (11.51%) was significantly higher than the rate of patients who dropped out in the bCBT group (4.17%), χ^2 (1, $N = 283$) = 5.32, $p = 0.021$.

Primary Effectiveness Hypothesis

Results of the primary effectiveness hypothesis are presented in Table 4 together with the results of the secondary efficacy hypotheses. Patients in the bCBT group showed greater improvement in the PHQ-9 scores than the CBT group, $d = 0.62$, $p < 0.001$; between-group difference 95% CI [1.19, 3.29]. Cronbach's α for the PHQ-9 was 0.68 at T0 and 0.83 at T1.

Secondary Effectiveness Hypotheses

Patients in the bCBT group showed significantly greater improvements across several clinical and psychological outcomes compared to those in the CBT group (Table 4). Specifically, bCBT participants reported greater reductions in generalized anxiety symptoms (GAD-7, $d = 0.61$, $p < 0.001$), higher psychological quality of life (WHOQOL-Psychological Health, $d = 0.42$, $p < 0.001$), enhanced perceived self-efficacy (GSE, $d = 0.41$, $p = 0.003$), and greater mental health literacy (D-Lit, $d = 0.66$, $p < 0.001$). Internal consistency for these measures was acceptable to good, with Cronbach's α reported at T0 and T1 as follows: 0.79

Table 2. Sample size, means, and standard deviations for the bCBT group and the CBT group

Outcome	T0		*p* value (baseline comparisons)	T1	
	bCBT (*n* = 144)	CBT (*n* = 139)		bCBT (*n* = 144)	CBT (*n* = 139)
PHQ-9	16.38 (3.86)	15.17 (3.90)	0.010	9.14 (4.20)	10.72 (5.38)
GAD-7	12.86 (4.05)	11.88 (4.02)	0.041	7.15 (4.01)	8.58 (4.64)
WHOQOL-BREF-Psychological	14.56 (2.75)	14.62 (2.89)	0.867	18.30 (3.87)	16.84 (4.15)
GSE	22.86 (5.06)	23.65 (4.36)	0.160	26.23 (5.11)	25.62 (4.80)
D-Lit	12.76 (3.41)	13.02 (3.51)	0.520	14.77 (2.76)	13.56 (3.32)
Adherence to treatment					
Patient-rated	–	–		12.72 (1.86)	12.11 (2.62)
Therapist-rated	–	–		12.48 (2.67)	11.31 (3.11)
CGI-S	4.42 (0.73)	4.24 (0.94)	0.065	3.59 (1.11)	3.91 (1.10)
CGI-I	–	–		2.41 (0.77)	2.89 (0.85)

Means (and standard deviation) for both groups (in the imputed data set). bCBT, blended cognitive behavioral therapy; CBT, cognitive behavioral therapy; PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalized Anxiety Disorder-7; WHOQOL-BREF-Psychological, World Health Organization Brief Quality of life Scale-Psychological Health; GSE, General Self Efficacy Scale; D-Lit, Depression Literacy Scale; CGI-S, Clinical Global Impression-Severity; CGI-I, Clinical Global Impression-Improvement. There was a technical error in the presented D-Lit questionnaire in this trial, resulting in one question missing (21 total questions instead of 22 presented).

Table 3. Frequency distribution of the CGI-I scores for the bCBT and the CBT groups

CGI-I categories	bCBT	CBT
Completion rate (*n*, %)	(138, %96)	(126, %91)
1 – Very much improved	12	6
2 – Much improved	68	31
3 – Minimally improved	53	62
4 – No change	3	24
5 – Minimally worse	2	3
6 – Much worse	0	0
7 – Very much worse	0	0
Median (IQR)	2 (2–3)	3 (2–3)
Responder rate (≤2)	80 (%58)	37 (%29)

IQR, interquartile range.

and 0.85 for the GAD-7, 0.63 and 0.83 for the WHOQOL-Psychological Health subscale, and 0.85 and 0.90 for the GSE.

Adherence to treatment was higher in the bCBT group, both by patient self-report ($d = 0.27$, $p = 0.034$) and therapist ratings ($d = 0.41$, $p = 0.002$). Cronbach's α for the patient-rated adherence scale was 0.66, and the therapist-rated adherence scale was 0.85.

Clinician-rated overall symptom improvement also favored the bCBT group. Improvements on the CGI-S were significantly greater ($d = 0.45$, $p = 0.004$), as were changes to the CGI-I ($d = 0.60$, $p < 0.001$).

Finally, the proportion of patients achieving a clinically significant treatment response – defined as a 50% reduction in PHQ-9 scores – was higher in the bCBT group (40.28%, 58 of 144) than in the CBT group (25.90%, 36 of 139). This corresponds to an odds ratio of 1.89 (95% CI [1.14, 3.13], $p = 0.012$), indicating a statistically significant advantage for bCBT in reducing depressive symptoms.

Safety Outcomes

In the bCBT group, one patient experienced symptom worsening due to external stressors (e.g., examination phase) and one patient had suicidal ideation. In the CBT group, one patient discontinued treatment due to the need for psychiatric inpatient treatment. There was no indication that any AE observed was associated with the use of the additional app or the provided psychotherapy. The proportion of AEs reported in the bCBT group (2 of 144) and the CBT group (1 of 139) did not differ significantly, χ^2 (1, $N = 283$) = 0.30, $p = 0.583$.

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Table 4. Between-group differences in study groups

	bCBT (n = 144)			CBT (n = 139)			Between-group difference (CBT-bCBT)						
Drop-out rates, n (%)	6 (4.17%)			16 (11.51%)									
Outcome	LS mean	SE	95% CI	LS mean	SE	95% CI	LS mean	SE	95% CI	p value	d	Lower 95% CI	Upper 95% CI
PHQ-9	−6.96	0.36	[−7.67, −6.24]	−4.72	0.40	[−5.50, −3.93]	2.24	0.54	[1.19, 3.29]	<0.001	**0.62**	0.37	0.86
GAD-7	−5.49	0.32	[−6.12, −4.86]	−3.40	0.36	[−4.11, −2.69]	2.09	0.48	[1.14, 3.04]	<0.001	**0.61**	0.36	0.86
WHOQOL-BREF-Psychological	3.78	0.29	[3.21, 4.34]	2.37	0.32	[1.74, 3.00]	−1.41	0.42	[−2.24, −0.58]	<0.001	**0.42**	0.17	0.67
GSE	3.35	0.35	[2.68, 4.03]	1.87	0.38	[1.12, 2.61]	−1.49	0.50	[−2.46, −0.51]	0.003	**0.41**	0.17	0.66
D-Lit	1.99	0.19	[1.62, 2.35]	0.43	0.21	[0.01, 0.85]	−1.56	0.28	[−2.11, −1.01]	<0.001	**0.66**	0.41	0.92
Adherence (patient-rated)	12.72	0.16	[12.40, 13.05]	12.11	0.24	[11.63, 12.59]	−0.61	0.29	[−1.17, −0.05]	0.034	**0.27**	0.02	0.51
Adherence (therapist-rated)	12.48	0.23	[12.04, 12.93]	11.30	0.29	[10.73, 11.88]	−1.17	0.37	[−1.90, −0.45]	0.002	**0.41**	0.15	0.66
CGI-S	−0.77	0.10	[−0.96, −0.57]	−0.35	0.10	[-0.56, −0.15]	0.39	0.14	[0.13, 0.66]	0.004	**0.45**	0.19	0.70
CGI-I	2.41	0.06	[2.28, 2.53]	2.89	0.08	[2.73–3.05]	0.48	0.10	[0.28, 0.69]	<0.001	**0.60**	0.34	0.86

95% CI, 95% confidence interval. LS, least squares (parameter estimation) (model-based estimates); SE, standard error; d, standardized between-group difference in study groups. All effect sizes are baseline-adjusted, accounting for pre-treatment scores, and are not directly comparable to unadjusted reference values; bCBT, blended cognitive behavioral therapy; CBT, cognitive behavioral therapy; PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalized Anxiety Disorder-7; WHOQOL-BREF, World Health Organization Brief Quality of life; GSE, General Self-Efficacy Scale; D-Lit, Depression Literacy Scale; CGI-S, Clinical Global Impression-Severity; CGI-I, Clinical Global Impression-Improvement.

Discussion

In this RCT, bCBT was compared to standard CBT in a routine outpatient setting. The results indicate that bCBT led to greater improvements in depressive and anxiety symptoms, quality of life, perceived self-efficacy, depression literacy, treatment adherence, and overall symptom severity across the 12-week treatment period.

A significantly higher rate of patients in the bCBT group achieved clinically relevant improvement in their symptoms of depression compared with the CBT group. These findings provide support for our primary and secondary hypotheses. The between-group effect size for the PHQ-9 (d = 0.62), including its 90% CI, exceeded the established threshold for clinical significance in depression intervention studies (d = 0.24) [51]. This suggests a robust and meaningful therapeutic advantage of the bCBT intervention evaluated in this study. The effects of bCBT were further supported by lower dropout rates and higher session attendance in the bCBT group. This finding is in line with prior research suggesting that digital tools can enhance adherence to standard treatments, mainly demonstrated in earlier studies addressing physical health appointments or medication adherence [52, 53]. Our results suggest that these adherence-enhancing effects may also apply to psychotherapy. The overall dropout rate in the study (7.77%) was low, indicating patients' high compliance with the study protocol and general acceptance of bCBT. The bCBT group did not report more AEs than the CBT group. Overall, these findings suggest that bCBT is a safe and potentially more effective approach to treating depression in routine care settings.

Comparable RCTs evaluating bCBT versus standard CBT with an equal number of face-to-face sessions are rare (e.g., [19, 20]), and those that exist have not demonstrated any significant advantage of bCBT over standard CBT in reducing depressive symptoms. By contrast, the present study demonstrated a larger between-group effect size for the primary outcome, indicating a stronger treatment effect. While some studies reported greater improvements in anxiety and quality of [20] with bCBT, others found no significant differences between bCBT and CBT in these domains [19]. Our study identified consistent improvements across multiple domains, suggesting a broader pattern of benefits than previously reported. In addition, previous bCBT studies involving patients with depression have been limited by smaller sample sizes than this one. To our knowledge, this represents the largest RCT to date examining the added benefits of a bCBT program.

The between-group effect sizes observed in our trial are larger than those reported in prior bCBT trials (e.g., [13, 17, 20]). It appears plausible that the comparatively stronger effects in this study may result from the close and regular integration of the digital application into ongoing CBT, where therapists tailored digital exercises to each patient to enhance engagement and adherence, a level of individualization that is uncommon in previous trials. Moreover, the digital application used in this study was developed to be integrated directly into therapy rather than as a standalone app, providing high-quality content and a user-friendly design [23, 24], which may have enhanced its practical impact compared with previous bCBT apps.

Limitations

This trial has several limitations that warrant consideration. Although the results provide robust evidence that the addition of the digital health app to CBT improves the efficacy of CBT for depression, it is unclear which specific features of the app contribute most to this improvement. Our study design did not permit an exploration of these mechanisms. To address this, future qualitative studies focusing on patients' and therapists' experiences with the bCBT program could provide valuable insights. In addition, future studies should consider incorporating objective process data from within the app, such as assignment completion rates, time spent on tasks, homework frequency, and the most frequently accessed digital therapeutic materials, which were beyond the scope of the present study. Investigating these detailed processes would further deepen our understanding of the mechanisms underpinning blended therapy. Additionally, our findings are specific to the bCBT application used in this study and may not generalize to other bCBT treatments. Comparative studies evaluating different digital applications within bCBT frameworks are needed to better understand the processes behind treatment outcomes and to guide the development of digital tools tailored to the needs of patients with depression.

A noteworthy limitation is that therapists in the blended therapy group had access to additional structured digital resources and support, which may have shaped how they provided the treatment. Hence, the integration of digital elements likely provided a greater sense of structure, continuity, and support for patients between sessions, potentially influencing perceived treatment intensity and satisfaction. These perceived differences in structure and support may have contributed to the observed effects and cannot be fully disentangled from the benefits of the digital component itself. However, this limitation is inherent to the very concept of blended care,

which is designed to augment ongoing psychotherapy rather than replace it. In fact, the added structure and integration into therapy represent how blended interventions are intended to be used in real-world practice. Moreover, therapist involvement beyond standard CBT was largely confined to selecting and activating digital content, representing only a minor addition to the total treatment time, indicating that the digital component itself likely played a key role in the observed effects.

In this study, we did not require following a specific treatment manual; therapists were instructed to provide treatment consistent with general CBT guidelines. While this is a strength, as it reflects a routine clinical setting and demonstrates the efficacy and feasibility of the bCBT application in real-world conditions, it also limits the comparability of standard CBT between the intervention and control groups and reduces the replicability of the study. Similarly, therapists used a range of diagnostic approaches, from structured clinical interviews to less structured multi-method assessments, to reflect a realistic setting for participant selection. While this variability may have introduced heterogeneity in baseline clinical profiles, randomization likely minimized systematic imbalances. Moreover, a certain degree of self-selection bias cannot be entirely ruled out as patients with a more positive attitude toward digital tools may have been more inclined to participate after receiving information about the study [54, 55]. Nevertheless, this factor is likely of limited impact, given that Germany ranks among the countries with the highest smartphone penetration worldwide [56], and familiarity with digital tools is widespread, particularly in the urban populations where this study was conducted.

Additionally, each patient was diagnosed by a single therapist. While this approach reflects real-world clinical practice (e.g., [57]), it represents a limitation due to potential inconsistencies in diagnostic procedures across participants.

The adherence instruments used in this trial were developed by experts specifically for this study and, therefore, lack established validity. In addition, the reliability of the patient-rated adherence scale was relatively low. As a result, findings related to adherence should be interpreted with some caution. Future studies should prioritize the development and use of validated instruments or undertake systematic development and validation of new adherence measures to ensure robust assessment. Despite these limitations, the instruments provided practical and context-sensitive insights into adherence patterns within this trial.

A limitation of this trial was the inability to collect data on the reasons for exclusion among patients who were screened but not recruited. This was primarily due to feasibility constraints and data protection considerations. Screening at the participating study centers was part of routine clinical practice, and therapists approached potential participants as they became eligible. Since patients were not attending screenings for research purposes, collecting exclusion data without explicit informed consent was considered ethically inappropriate.

Finally, the absence of longer term follow-up precludes conclusions about the durability of treatment effects. Future studies should investigate whether the benefits of bCBT are maintained over time and whether digital components influence relapse rates or long-term adherence. Follow-up assessments at three- or six-month post-treatment could help clarify the long-term sustainability of the benefits of the bCBT application. Moreover, including qualitative follow-up interviews in future studies could provide valuable insight into the mechanisms underlying bCBT. Interviews with therapists could help identify specific strategies used to integrate face-to-face sessions with digital components, while interviews with patients could offer a deeper understanding of how the bCBT influences adherence, motivation and therapeutic change processes.

Conclusion

This RCT provides evidence that bCBT yields greater improvements than standard CBT across multiple outcomes, including symptoms of depression and anxiety, quality of life, self-efficacy, and treatment adherence over a 12-week period. The intervention was also well tolerated, with no indication of increased AEs. Compared to previous trials, this research offers stronger evidence, reflected by larger effect sizes and a broader range of positive outcomes. These findings support the potential of bCBT as a safe, acceptable, and clinically effective treatment for depression in routine care.

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Statement of Ethics

Ethical approval for this study was obtained from the Ethics Committee of the Medical Faculty of the Heinrich Heine University of Düsseldorf (Approval No. 2022-2183). The study was registered in the ISRCTN registry under ISRCTN-ID 11129335, with no important changes. Participants received both written

and oral information about the trial and subsequently provided written informed consent. All procedures were conducted in accordance with the Declaration of Helsinki and the International Standard ISO 14155 for Good Clinical Practice in clinical investigations of medical devices involving human subjects.

Conflict of Interest Statement

E.A. is a part-time employee at Elona Health alongside her academic responsibilities. J.S. and A.P. have worked as consultants for Elona Health. M.S. and P.N. are shareholders of Elona Health. J.K., P.H., J.H., and R.P. did not have any conflict of interest.

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Author Contributions

J.K.: conceptualization, data curation, resources, investigation, methodology, project administration and execution, writing – original draft, and validation. E.A.: methodology and writing – original draft. J.S.: conceptualization and writing – review and editing. M.S.: conceptualization and funding acquisition. P.N.: resources and validation. P.A. and J.H.: resources. A.P.: supervision, validation, and writing – review and editing. R.P.: supervision, validation, ethical approval, and writing – review and editing.

Data Availability Statement

The data supporting the results of this study are not publicly available as they contain information that could compromise patient privacy, but are available from the corresponding author on reasonable request.

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