Received: 9 August 2018 | Revised: 23 January 2019 | Accepted: 24 January 2019

DOI: 10.1111/epi.14673

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

Effects of an epilepsy-specific Internet intervention (Emyna) on depression: Results of the ENCODE randomized controlled trial

Björn Meyer[1,2] | **Mario Weiss**[1] | **Martin Holtkamp**[3] | **Stephan Arnold**[4] | **Katja Brückner**[5] | **Johanna Schröder**[6] | **Franziska Scheibe**[1] | **Yvonne Nestoriuc**[7]

[1]Research Department, Gaia Group, Hamburg, Germany

[2]Department of Psychology, City, University of London, London, UK

[3]Department of Neurology, Epilepsy Center Berlin-Brandenburg, Charité-Universitätsmedizin Berlin, Berlin, Germany

[4]Clinic for Epilepsy, Schön Clinic Vogtareuth, Vogtareuth, Germany

[5]Department of Neurology and Epileptology, Epilepsy Center Hamburg, Evangelical Hospital Alsterdorf, Hamburg, Germany

[6]Institute for Sex Research and Forensic Psychiatry, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[7]Department of Clinical Psychology, Helmut Schmidt University, Hamburg, Germany

Correspondence
Björn Meyer, Research Department, Gaia Group, Hamburg, Germany.
Emails: bjoern.meyer@gaia-group.com, bjorn.meyer.1@city.ac.uk

Funding information
Gaia Group, Germany

Summary

Objective: Depression and anxiety are highly prevalent among people with epilepsy (PwE) but often remain unrecognized and treated inadequately. Effective psychosocial treatments such as cognitive behavioral therapy (CBT) are rarely available to most PwE, which is one reason electronically delivered CBT (eCBT) is regarded as promising. This study examined an eCBT intervention, termed *Emyna*, that was tailored to suit the needs of PwE. It includes CBT-related content on depression, stress and anxiety, seizure triggers and auras, and lifestyle habits. The trial examined the efficacy of Emyna in reducing symptoms of depression (primary outcome) and anxiety as well as improving quality of life.

Methods: Participants (N = 200) with epilepsy, a diagnosis of a depressive disorder, and at least moderate depressive symptoms were randomized to Emyna or care as usual. At baseline and after 3, 6, and 9 months, participants were invited to complete online questionnaires. The primary outcome was improvement of depressive symptoms at 3 months.

Results: Relative to the control group, intervention group participants experienced significantly greater improvements in depression, anxiety, stress, social-occupational impairment, and epilepsy-related quality of life, in both intention-to-treat (ITT) and per-protocol analyses. In ITT analyses, effects of medium magnitude were observed, as measured by the Patient Health Questionnaire–9 items (Cohen $d = 0.54$, 95% confidence interval [CI] = 0.25-0.82, $P < 0.001$) and the Neurological Disorders Depression Inventory for Epilepsy ($d = 0.51$, 95% CI = 0.23-0.79, $P < 0.01$). At 3 months, intervention group participants also reported fewer illness-related days off work and fewer days hospitalized over the preceding months, compared to control group participants ($P \leq 0.05$), whereas no such differences were present at baseline ($P > 0.30$).

Significance: These findings showed that Emyna, used adjunctively to usual care, could help improve mental health, social-occupational functioning, and quality of life among PwE. The program provides an additional treatment option that could produce clinically relevant symptom reductions and reduce key cost drivers (ie, hospitalization rates and illness-related inability to work).

1 | INTRODUCTION

Among people with epilepsy (PwE), the prevalence of depression has been estimated at 18%-28% and of anxiety disorders at 15%-26%, according to recent meta-analytic findings.[1] These common comorbidities are associated with immense personal suffering, and they may contribute to reduced quality of life, higher health care costs, and increased suicide as well as mortality risk, pointing to the importance of early recognition and adequate treatment.[2]

Certain drugs are considered to be safe and effective for treating depression and anxiety in PwE, and cognitive behavioral therapy (CBT) can also be effective in this population, particularly when CBT techniques are tailored to match the needs of PwE.[3,4] However, a meta-analysis cautioned that CBT led to reliable depression improvement in only 30% of PwE.[5] A recent Cochrane review found only moderate evidence supporting the effectiveness of psychological interventions for PwE.[6]

Despite the availability of several potentially effective treatment options, depression and anxiety in PwE often remain underrecognized and undertreated. In particular, CBT is rarely available in epilepsy treatment settings. In a recent survey, epileptologists reported that lack of qualified psychotherapists and time pressure were major barriers to adequate mental health treatment provision.[7] Other barriers include low perceived need, preference to handle one's problems independently, negative attitudes toward mental health treatment, stigma concerns, high costs, inaccessibility of treatment, and mobility constraints.[8]

Electronically delivered CBT (eCBT) is often regarded as a potentially effective tool to overcome these barriers and improve quality of mental health care for PwE. Potential advantages include efficacy, low-threshold availability, flexibility, low cost, and low clinician burden. Meta-analyses have shown that eCBT Internet interventions for depression are effective in the general population, on average, and certain clinician-supported forms of eCBT have been shown to be as effective as face-to-face psychotherapy, which suggests that these interventions might be effective for PwE as well.[9,10]

Despite these advantages and encouraging findings, several limitations of eCBT must also be considered, including concerns about data security, incapacity to respond to crises, low adherence, and potential lack of safety and efficacy. For example, the effects of some fully automated eCBT interventions are only modest, although providing clinician support may improve adherence and outcomes.[11] Several direct comparisons between supported and fully automated eCBT interventions have yielded small or no differences, however, and some interventions failed to improve outcomes even when personal support was provided.[12–15] Thus, evidence is mixed, and more research is needed to evaluate the potential of eCBT interventions for PwE.

Key Points

- Randomized controlled trial of a novel Internet-based cognitive-behavioral therapy intervention to improve depression among people with epilepsy
- Over 3 months, use of the intervention adjunctively to usual care improved symptoms of depression, anxiety, and other aspects of mental health, with effect sizes that are above the threshold of clinical relevance ($d > 0.5$)
- Continued improvement of symptoms was observed at the 9-month time point, although access to the intervention expired after month 6 for the intervention group
- Decreases in illness-related days off work and hospitalization days were also observed

Thus far, only a few studies have examined eCBT in epilepsy. In one study, a CBT-based, distance-delivered intervention (Project UPLIFT) was effective in preventing new depressive episodes and reducing symptom severity.[16] This intervention was delivered by trained facilitators via telephone or a Web-based platform and included regular guided discussions. In another single-arm study, reductions in depressive symptoms and several secondary outcomes were observed in a sample of 27 PwE who used a clinician-supported Internet intervention.[17] However, this study did not include a control group, and both studies included clinician-support.

A fully automated eCBT intervention we developed was shown to be effective in several randomized controlled trials (RCTs) in the general population and one RCT among PwE.[18–20] However, the effect size achieved in a trial with 76 PwE was small (Cohen $d = 0.22$ for the posttreatment group difference in depression severity), and participants noted that the intervention could have been better tailored to suit their illness-specific needs.[18,19] Based on these experiences, we developed a novel, epilepsy-focused Internet intervention, which was evaluated in this RCT.[21]

The primary hypothesis was that using this intervention adjunctively to care as usual (CAU) would result in greater depression reduction over 3 months than receiving only CAU. Secondarily, we hypothesized that intervention effects could be shown on several secondary outcomes, including anxiety, as detailed in the trial protocol and below.[21]

2 | MATERIALS AND METHODS

The trial was conducted in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines and its adaptation for Internet-based interventions.[22]

2.1 | Trial design

This was a parallel-group, pragmatic RCT that aimed to evaluate the effects of a novel Internet intervention for PwE, offered adjunctively to CAU. The outcome time point of primary interest was 3 months, and the CAU group was permitted to use the intervention after this time point. Online assessments were also conducted for both groups at 6 and 9 months postrandomization to examine the stability of symptom course and potential improvements beyond the 3-month time point.

2.2 | Trial setting and patient recruitment

PwE were recruited consecutively via outpatient clinics in epilepsy centers and other hospitals as well as Internet forums, social media (eg, Facebook), and health insurance brochures. PwE were invited to indicate their interest by entering their name and e-mail address at an online study website and were then contacted by a member of the research team with an invitation to complete the baseline online assessment. If the online assessment indicated a preliminary match with inclusion criteria, they were contacted for a telephone interview, which included a diagnostic interview. Participants were recruited between July 2016 and May 2017.

2.3 | Standard protocol approvals, registrations, and patient consents

The trial was entered into a trials registry prior to recruitment (ClinicalTrials.gov: NCT02791724) and approved by the local ethics committee of the Faculty of Psychology and Human Movement Science of the University of Hamburg, Germany (reference number: 30 2016). All study procedures involving human participants are in accordance with the ethical standards of the ethics committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Patients provided online consent to participate.

2.4 | Eligibility criteria

Eligibility criteria were (1) age of at least 18 years; (2) diagnosis of active epilepsy, as defined by having taken antiepileptic drugs within the past 5 years or having experienced seizures within the past 10 years[23]; (3) diagnosis of a current depressive disorder, confirmed by telephone-administered diagnostic interview (the Mini International Neuropsychiatric Interview[24]) administered by trained research associates; (4) at least moderate depression severity (Patient Health Questionnaire–9 items [PHQ-9] > 9); (5) ability to read and speak German; and (6) Internet access. Participants were not eligible if (1) antidepressant medication was newly prescribed or changed within 1 month prior to inclusion; (2) they were currently in psychotherapy; (3) they had been diagnosed with bipolar disorder, schizophrenia or another psychotic disorder, or borderline personality disorder; or (4) acute suicidality was confirmed in the telephone interview.

2.5 | Randomization and blinding

Randomization was performed by the principal investigator (PI; Y.N.) using a computer-generated sequence to generate the allocation sequence. The PI did not have knowledge of participant characteristics prior to performing the randomization, because participants were enrolled by trained research associates. Thus, concealed allocation was ensured. Participants were not blinded with regard to whether they were receiving the intervention.

2.6 | Intervention

The intervention (termed *Emyna*) is described in the trial protocol; further details are provided in the online Appendix S1.[21] The intervention name "Emyna" was inspired by the Greek word "amyna," which in English denotes "defense," alluding to the idea that the program might help PwE to defend themselves against some of the adverse emotional effects wrought by epilepsy. In brief, Emyna is a fully automatic Internet intervention that requires no clinician support. It conveys CBT techniques and exercises to PwE and can be accessed over a period of 180 days. We expected that reduction of depressive symptoms should be evident by 3 months, based on previous findings.[19] Program content is presented in interactive "simulated dialogues" in which patients navigate through the program by reading brief text passages or listening to audio recordings and then selecting one of several response options. The intervention can be accessed via a secure, password-protected website on any computer or smartphone with an Internet connection.

2.7 | Measures

Baseline data as well as 3-, 6-, and 9-month data were collected via a secure, encrypted online survey service, and participants were invited via e-mail to complete the assessments. Participants who did not respond were contacted with brief reminders up to five times.

2.7.1 | Primary outcome

Outcome measures are described in detail in the trial protocol.[21] The primary outcome was depressive symptom severity, assessed at the before and after time points with two self-report measures: (1) the PHQ-9 and (2) the Neurological Disorders Depression Inventory for Epilepsy (NDDIE). Whereas the PHQ-9 is a generic self-report measure of depression symptoms, the NDDIE was developed specifically for PwE.

2.7.2 | Secondary outcomes and additional measures

Secondary outcomes included (1) anxiety severity, measured with the Generalized Anxiety Disorder–7 items; (2) general distress (depression, stress, and anxiety), as assessed by the Depression Anxiety Stress Scales–21 items total score, which is more appropriate than subscale scores[25]; (3) depression-related social-occupational impairment, measured by the Work and Social Adjustment Scale (WSAS); and (4) health-related quality of life in PwE, measured with the Quality of Life in Epilepsy–10 items (QOLIE-10).[21] As described in the protocol, subjective usefulness of the intervention as well as seizure frequency was measured with individually designed items. For seizure frequency, the following item was used: "How many debilitating seizures did you experience in the past month? This refers to seizures that have impaired your ability to pursue your normal day-to-day activities." Response options included (1) none, (2) 1-5 seizures in the past month, (3) 6-10 seizures in the past month, and (4) more than 10 seizures in the past month. Other secondary outcomes included number of illness-related sick days off work and number of days hospitalized during the previous 3 months, as well as positive and negative/adverse events attributed to intervention, measured with the Inventory for the Assessment of Negative Effects of Psychotherapy, Modified for Online Interventions (INEP-ON).[26]

2.8 | Sample size

An a priori power analysis showed that a sample size of N = 200 would be required to attain 80% power to detect an anticipated effect size of $d = 0.5$ on the PHQ-9 at month 3, even if attrition was as much as 30%, as in a similar previous trial.[18]

2.9 | Statistical analyses

All outcomes were analyzed according to the intention-to-treat (ITT) principle. Per-protocol (PP) analyses included data only from intervention group participants who had registered to use the intervention. Missing data were imputed for ITT and PP analyses at the primary endpoint of 3 months with multiple imputation (100 imputations, 50 iterations) based on sociodemographic data and available outcomes, following current methodological recommendations.[27] The 100 imputation datasets were merged into one pooled dataset. Given that two time points were examined (baseline, 3 months), analyses of covariance (ANCOVA) were used, which are recommended for trials with before and after measurements.[28] In ITT and PP analyses, we examined the effects of group (intervention vs control) while controlling for the baseline levels of each respective variable. To examine the stability of effects, we examined observed means at all time points with *t* tests. To reduce familywise error due to multiple testing, we applied a *P* value of 0.01 for these analyses (two-sided). The groups were not expected to differ in outcomes at 6 and 9 months, because control group participants could access the intervention after 3 months.

For the primary outcome measure (PHQ-9), we examined clinical significance following established algorithms.[29] Specifically, participants who improved by at least five points between baseline and 3 months and scored below 10 at 3 months were classified as clinically significantly improved. For descriptive purposes, we also computed the proportion of participants whose PHQ-9 scores at 3 months indicated minimal or no (0-4), mild (5-9), moderate (10-14), or severe (≥15) symptoms, and we applied the clinical significance approach of Jacobson and Truax.[30]

3 | RESULTS

3.1 | Description of trial participants

Demographic and clinical characteristics are presented in Table 1. The mean PHQ-9 for the total sample at baseline was 15.01 (SD = 3.18), indicating moderate to moderately severe depression. There were no baseline group differences in demographic or clinical characteristics, indicating successful randomization (Table 1 in Appendix S1).

3.2 | Intervention delivery and usage, and participant retention

A total of 200 participants were randomized (Figure 1). Most participants (52.0%) reported having learned about the study via an Internet forum or Facebook post. Other entry points included the following: information provided by a clinic or hospital (14.5%), recommendation by a doctor or therapist (5.5%), flyer or newsletter (8.5%), informed by friends (8.5%), or "other" sources (2.0%). Of the randomized participants, 154 (77.0%) completed primary outcome measures at 3 months; the dropout rate was,

TABLE 1 Participant demographics and clinical characteristics

	Intervention, n = 100	Control, n = 100	Total sample, N = 200	Statistics
Gender, M/F	35/65	38/62	73/127	χ^2 (1) = 0.19, P = 0.66
Age, y, mean (SD)	40.53 (12.90)	40.07 (13.40)	40.30 (13.12)	t_{198} = −0.25, P = 0.81
Education				χ^2 (6) = 7.54, P = 0.27
Did not finish school	8	9	17	
Basic-level high school (Hauptschule)	1	2	3	
Medium-level high school (Realschule)	9	15	24	
Higher-level high school (Fachhochschulreife)	37	22	59	
Highest-level high school (Abitur)	12	19	31	
University degree	15	13	28	
Other educational qualification	18	20	38	
Employment status				χ^2 (3) = 2.03, P = 0.57
Working full-time	20	18	38	
Working part-time	28	31	59	
Not working	14	20	34	
Other (eg, volunteering)	38	31	69	
Debilitating seizures in past month				χ^2 (3) = 2.34, P = 0.51
None	43	40	83	
1-5	39	34	73	
6-10	10	15	25	
>10	7	11	18	
Anticonvulsant use and adherence				χ^2 (4) = 1.21, P = 0.88
Not taking any anticonvulsants	7	4	11	
Miss about once per week	7	6	13	
Miss about once per month	9	11	20	
Miss less than once per month	30	29	59	
Never miss a dose	46	49	95	
Characterization of depression				
Age at depression onset, y, mean (SD)	24.40 (10.87)	25.20 (14.02)	24.80 (12.52)	t_{198} = 0.45, P = 0.65
Years lived with depression, mean (SD)	16.13 (12.93)	14.87 (12.48)	15.50 (12.69)	t_{198} = 0.70, P = 0.48
Previous episodes, mean (SD)	7.77 (7.67)	8.08 (7.25)	7.92 (7.45)	t_{198} = 0.29, P = 0.77
Chronic depression, no/maybe/yes	35/44/21	23/58/19	58/102/40	χ^2 (2) = 4.50, P = 0.11

F, female; M, male.

therefore, 23.0%. With respect to demographic variables, only gender was associated with a higher dropout risk, as 31.5% of men but only 19.7% of women dropped out by month 3, χ^2 (1) = 3.55, P = 0.06.

Of the 100 participants randomized to the intervention, 18 were excluded from the PP analysis because they did not register to use the intervention. Among the 82 participants who registered, mean usage duration over the first 3 months was 355.06 minutes (SD = 357.59). Average session duration was 25.84 minutes (SD = 13.91).

3.3 | Adverse events, and negative and positive reported consequences

Negative or positive effects were assessed with the INEP-ON among the 135 participants who used the intervention immediately (intervention group) or after a 3-month delay (control group). Items cover content such as improvements or deterioration in relationships, a sense of dependency on the program, and emerging suicidal thoughts. Of the 135 intervention users, 74 reported at least one positive or

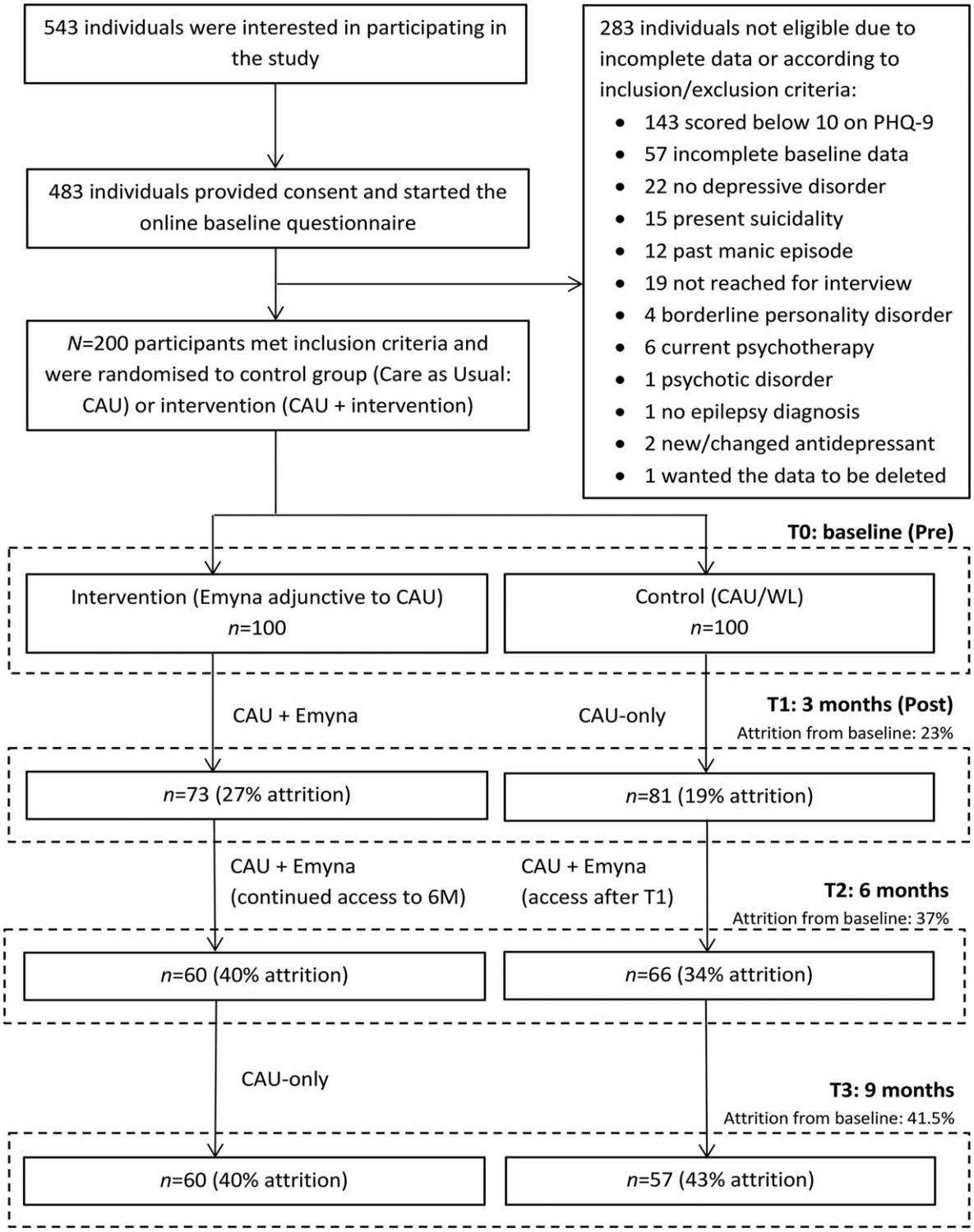

FIGURE 1 Participant flow. PHQ-9, Patient Health Questionnaire–9 items; WL, waitlist control

negative effect. Sixteen of these 135 participants never registered to activate the program but nevertheless reported effects due to the intervention; their responses were therefore excluded.

Across the 10 items that measure positive or negative intervention effects, six participants (4.44%) reported at least one negative effect, whereas 73 (54.07%) reported at least one positive effect. The most common negative effect was reduced psychotherapy motivation (2.96%). However, 26.67% reported feeling more motivated to start psychotherapy after using Emyna. Additional positive effects attributed to Emyna included improvements

in thinking/reasoning (47.41%), reduced rumination (31.11%), improved well-being (30.37%), and reduced loneliness (28.89%). Across the 13 items that measure only negative intervention effects, 51 participants (37.78%) reported at least one mild (n = 44), moderate (n = 10), or severe (n = 2) effect. The two participants who reported severe negative effects expressed feeling worried about data protection or feeling pressured by the program to comply with therapeutic exercises. No participant reported increased drug use or emerging suicidality due to Emyna (see Figure 1 in Appendix S1).

3.4 | Study outcomes

3.4.1 | Primary outcome: depression

The ITT analysis showed significant effects of the intervention on depression at 3 months, on both the PHQ-9 and the NDDIE (Cohen $d = 0.54$ and 0.51, respectively; Table 2 and Figure 2). Participants in the control group also experienced depression reduction, but improvement rates were exceeded significantly by participants in the intervention group. These effects were confirmed and slightly larger in PP analyses (Table 3).

Clinically significant improvement was observed in 29% of intervention group participants compared to 15% in the control group, χ^2 (1) = 5.71, $P = 0.02$. At month 3, 8% of intervention group participants scored in the no or minimal depression range (0-4), 40% in the mild range (5-9), 37% in the moderate range (10-14), and 15% in the severe range (≥15). Among control group participants, 2% scored in the no or minimal range, 19% mild, 42% moderate, and 37% severe. These proportions differed significantly, χ^2 (3) = 20.70, $P < 0.001$. There were no group differences in depression severity category at baseline; overall, 47% scored in the moderate range and 53% in the severe range, χ^2 (1) = 0.72, $P = 0.40$.

Applying the Jacobson and Truax[30] methods to estimate clinical significance, recovery criteria were achieved by 25% of intervention versus 11% of control group participants, reliable improvement without fulfilling recovery criteria was achieved by 8% of participants in both groups, no reliable change occurred in 66% of intervention versus 79% of control group participants, and deterioration was observed in 1% of intervention versus 2% of control group participants. Further details on these analyses are provided in Appendix S1.

3.4.2 | Secondary outcomes

Significant intervention effects were observed on all outcome measures at 3 months (Table 2, Figure 2). Intervention group participants reported greater improvements in anxiety, stress, and depressive symptoms, social-occupational impairment, and epilepsy-related quality of life. All effects were significant in ITT and PP analyses (Tables 2 and 3). Whereas ITT analyses yielded medium effect sizes, PP effect sizes were slightly larger. Effects on quality of life were slightly smaller than those observed for symptom changes.

3.4.3 | Stability of effects

Observed means at all assessment points are presented in Table 2 in Appendix S1. At month 3, intervention group participants differed on all but one measure from control group participants, $P < 0.05$. The exception was that a P value of 0.06 was observed at 3 months for the QOLIE-10. However, the ANCOVA, which takes baseline group differences into account, showed significant intervention effects for the QOLIE-10 at 3 months in both ITT and PP analyses. The group differences at month 6 tended to be smaller than those at month 3 and, as expected, were not significant with the adjusted P value of 0.01. At month 9, there were no group differences. Control group participants experienced improvements on most measures from baseline to month 3 as well as month 3 to month 6 (they were permitted to access the intervention after month 3), but no further changes from month 6 to month 9. Intervention group participants reported substantial improvements on all measures between baseline and month 3. Improvements thereafter attained significance on two occasions (PHQ-9 from month 6 to month 9 and WSAS from month 3 to month 6; see Table 3 in Appendix S1).

3.4.4 | Dose-response relationships

We examined correlations between usage intensity (minutes engaged with the intervention) and baseline to month 3 PHQ-9 change. However, usage intensity did not correlate with depression reduction as measured either by point reduction or percentage reduction, $p > 0.43$.

3.4.5 | Subsidiary analyses

At posttreatment, participants in the intervention group reported fewer hospitalization days in the preceding 3 months (mean = 1.67, SD = 4.75) than control group participants (mean = 3.88, SD = 7.37), $t_{151} = 2.18$, $P = 0.031$, whereas there was no difference in the 3 months prior to study entry ($t_{198} = 0.35$, $P = 0.73$). Similarly, at posttreatment, intervention participants reported fewer sick days over the previous 3 months (mean = 8.56, SD = 18.31) than control group participants (mean = 16.02, SD = 25.28), $t_{151} = 2.07$, $P = 0.040$, whereas there was no difference at baseline ($t_{198} = 0.99$, $P = 0.32$).

TABLE 2 Intention-to-treat analyses

	Pre/baseline, mean (SD)	Post/3 mo, mean (SD)	WG effect size, pre-post within-group change, Cohen *d* (95% CI)	BG effect size, post between-group difference, Cohen *d* (95% CI)	*F*, ANCOVA; DV, post; IV, group; cov, pre	*t* tests, independent groups, between-group comparisons at pre and post time points
Primary outcome [depression symptoms]						
PHQ-9 [depression symptoms, generic measure]						
Intervention	14.74 (3.00)	10.42 (4.38)	1.15 (0.84 to 1.45)	0.54 (0.25 to 0.82)	$F_{1,197} = 13.23$, $P < 0.001$	Pre: $t_{198} = 1.18$, $P = 0.24$; post: $t_{198} = 3.81$, $P < 0.001$
Control	15.27 (3.35)	12.73 (4.19)	0.67 (0.38 to 0.95)			
NDDIE [depression symptoms, epilepsy-specific measure]						
Intervention	17.01 (3.03)	14.35 (3.40)	0.83 (0.53 to 1.11)	0.51 (0.23 to 0.79)	$F_{1,197} = 13.50$, $P < 0.001$	Pre: $t_{198} = 0.71$, $P = 0.48$; post: $t_{198} = 3.61$, $P < 0.001$
Control	17.30 (2.84)	16.02 (3.15)	0.43 (0.14 to 0.71)			
Secondary outcomes						
GAD-7 [anxiety symptoms]						
Intervention	10.33 (4.39)	7.74 (4.30)	0.60 (0.31 to 0.88)	0.51 (0.22 to 0.79)	$F_{1,197} = 8.03$, $P < 0.01$	Pre: $t_{198} = 2.13$, $P = 0.04$; post: $t_{198} = 3.57$, $P < 0.001$
Control	11.62 (4.19)	9.82 (3.91)	0.44 (0.16 to 0.72)			
DASS-21 [depression and anxiety scales]						
Intervention	29.22 (11.56)	19.09 (9.64)	0.95 (0.66 to 1.25)	0.53 (0.24 to 0.81)	$F_{1,197} = 20.70$, $P < 0.001$	Pre: $t_{198} = -0.25$, $P = 0.80$; post: $t_{198} = 3.74$, $P < 0.001$
Control	28.84 (9.32)	23.90 (8.52)	0.55 (0.27 to 0.83)			
WSAS [social-occupational impairment caused by depression]						
Intervention	20.06 (7.68)	14.87 (7.92)	0.67 (0.38 to 0.95)	0.52 (0.23 to 0.80)	$F_{1,197} = 21.25$, $P < 0.001$	Pre: $t_{198} = -0.25$, $P = 0.80$; post: $t_{198} = 3.74$, $P < 0.001$
Control	20.14 (6.58)	18.70 (6.83)	0.21 (−0.06 to 0.49)			
QOLIE-10						
Intervention	30.44 (5.93)	32.50 (5.12)	0.37 (0.09 to 0.65)	0.31 (0.03 to 0.59)	$F_{1,197} = 6.90$, $P < 0.01$	Pre: $t_{198} = -0.41$, $P = 0.69$; post: $t_{198} = -2.22$, $P < 0.03$
Control	30.11 (5.24)	30.91 (5.05)	0.16 (−0.12 to 0.43)			

All randomized participants were included. Missing data at post were replaced by multiple imputation; N = 200; n = 100 in intervention group and n = 100 in control group. ANCOVA, analysis of covariance; BG, between-groups; CI, confidence interval; cov, covariate; DASS-21, Depression Anxiety Stress Scales–21 items; DV = dependent variable; GAD-7, Generalized Anxiety Disorder–7 items; IV = independent variable; NDDIE, Neurological Disorders Depression Inventory for Epilepsy; PHQ-9, Patient Health Questionnaire–9 items; post, posttreatment; pre, pretreatment; QOLIE-10, Quality of Life in Epilepsy–10 items; WG, within group; WSAS, Work and Social Adjustment Scale.

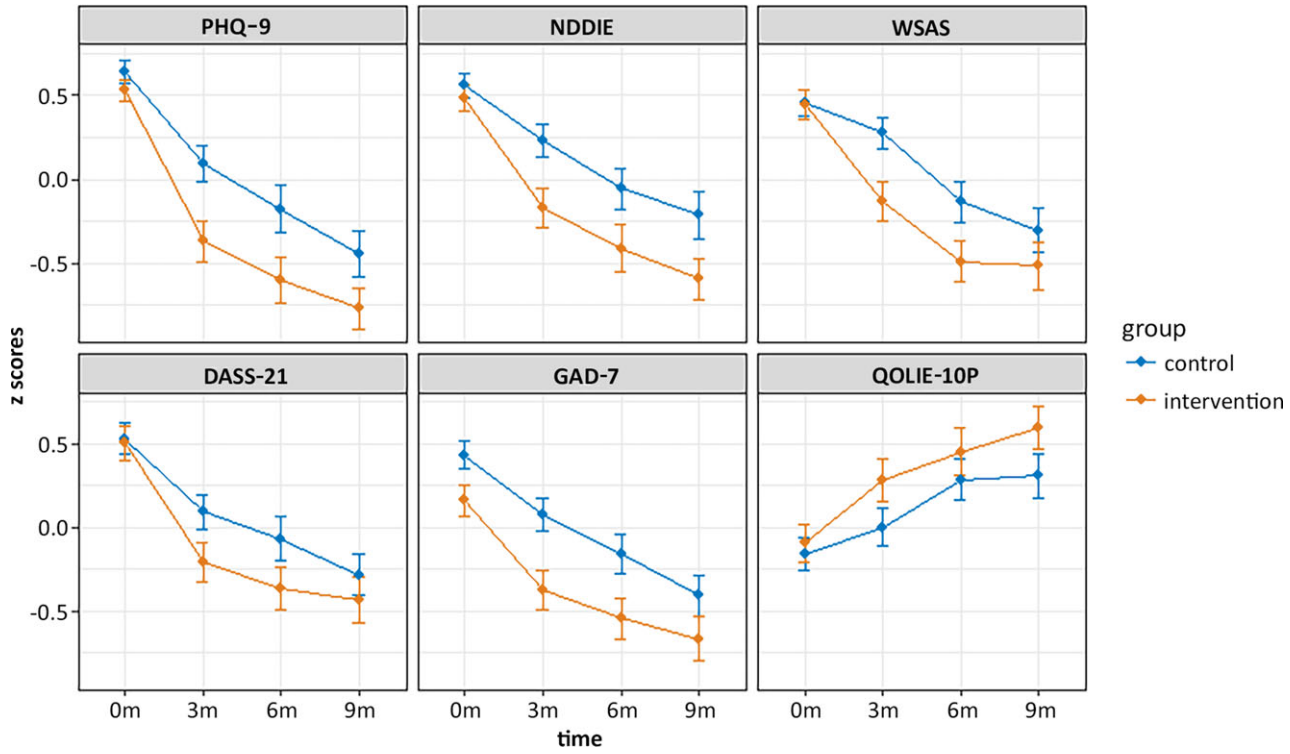

FIGURE 2 Symptom course on primary and secondary outcomes (means and standard errors), intention-to-treat analyses (missing data replaced by multiple imputation). DASS-21, Depression Anxiety Stress Scales–21 items; GAD-7, Generalized Anxiety Disorder–7 items; NDDIE, Neurological Disorders Depression Inventory for Epilepsy; PHQ-9, Patient Health Questionnaire–9 items; QOLIE-10P, Quality of Life in Epilepsy–10 items, patient weighted; WSAS, Work and Social Adjustment Scale

Seizure frequency did not differ between groups at baseline or 3 months (see Table 1), χ^2 (3) = 1.21, $P = 0.75$.

Additional analyses explored whether concurrent depression treatment might account for observed effects. At 3 months, 19.4% of intervention group participants and 30.9% of control group participants reported being in psychotherapy, which was not a significant difference, χ^2 (1) = 2.62, $P = 0.11$. Moreover, 29.2% of intervention group participants and 29.6% of control group participants reported taking antidepressant medication at posttreatment, which was not significantly different, χ^2 (1) = 0.0039, $P = 0.95$. We also examined whether psychotherapy or antidepressant use moderated intervention effects. Factorial analyses of variance with group and treatment status as independent variables and PHQ-9 change (baseline to 3 months) as dependent variable did not yield significant effects for the interactions between treatment modality and group (intervention, control), $P > 0.25$. Thus, symptom reduction rates were not differentially affected by concurrent depression treatment.

3.4.6 | User satisfaction

Detailed analyses of treatment satisfaction are provided in Table 4 in Appendix S1. In brief, most participants (82.26%) were satisfied with the program; 16.13% were slightly dissatisfied, and 1.61% were very dissatisfied. Similarly, 85.25% judged intervention quality as good (59.02%) or excellent (26.23%), and none appraised it as poor. No participant reported feeling worse after using the intervention. Satisfaction ratings correlated moderately with usage intensity (average correlation between usage and the 10 items presented in Table 4 in Appendix S1: $r = 0.32$). As expected, participants who were more satisfied tended to use the intervention for longer durations.

4 | DISCUSSION

4.1 | Summary of findings

This RCT provided evidence for the efficacy of Emyna, a novel eCBT intervention to help PwE cope with depression, anxiety, stress, and other aspects of their illness. Over 3 months, the intervention produced clinically meaningful effects on improvements in depression, anxiety, stress, social-occupational impairment, and illness-related quality of life, which exceeded improvements observed among control group participants who received only usual care. On the primary outcome, effect sizes at 3 months of above $d = 0.50$ were observed, which is well above the threshold

TABLE 3 Per-protocol analyses

	Pre/baseline, mean (SD)	Post/3 mo, mean (SD)	WG effect size, pre-post within-group change, Cohen *d* (95% CI)	BG effect size, post between-group difference, Cohen *d* (95% CI)	*F*, ANCOVA; DV, post; IV, group; cov, pre	*t* tests, independent groups, between-group comparisons at pre and post time points
Primary outcome [depression symptoms]						
PHQ-9 [depression symptoms, generic measure]						
Intervention, n = 82	14.51 (2.89)	10.04 (4.13)	1.25 (0.91 to 1.58)	0.65 (0.34 to 0.94)	$F_{1,179} = 15.85$, $P < 0.001$	Pre: $t_{180} = 1.62$, $P = 0.11$; post: $t_{180} = -4.33$, $P < 0.001$
Control, n = 100	15.27 (3.35)	12.73 (4.19)	0.67 (0.38 to 0.95)			
NDDIE [depression symptoms, epilepsy-specific measure]						
Intervention, n = 82	16.90 (2.91)	14.13 (3.21)	0.90 (0.58 to 1.22)	0.59 (0.29 to 0.89)	$F_{1,179} = 15.51$, $P < 0.001$	Pre: $t_{180} = 0.94$, $P = 0.35$; post: $t_{180} = -4.00$, $P < 0.001$
Control, n = 100	17.30 (2.84)	16.02 (3.15)	0.43 (0.14 to 0.71)			
Secondary outcomes						
GAD-7 [anxiety symptoms]						
Intervention, n = 82	10.18 (4.44)	7.38 (4.10)	0.66 (0.34 to 0.97)	0.61 (0.31 to 0.91)	$F_{1,179} = 11.37$, $P < 0.001$	Pre: $t_{180} = 2.24$, $P = 0.03$; post: $t_{180} = -4.10$, $P < 0.001$
Control, n = 100	11.62 (4.19)	9.82 (3.91)	0.44 (0.16 to 0.72)			
DASS-21 [depression and anxiety scales]						
Intervention, n = 82	28.20 (11.06)	18.08 (9.40)	0.99 (0.66 to 1.31)	0.65 (0.35 to 0.95)	$F_{1,179} = 22.78$, $P < 0.001$	Pre: $t_{180} = 0.43$, $P = 0.67$; post: $t_{180} = -4.37$, $P < 0.001$
Control, n = 100	28.85 (9.32)	23.90 (8.52)	0.55 (0.27 to 0.83)			
WSAS [social-occupational impairment caused by depression]						
Intervention, n = 82	19.54 (7.33)	14.22 (7.75)	0.71 (0.39 to 1.02)	0.62 (0.32 to 0.91)	$F_{1,179} = 23.09$, $P < 0.001$	Pre: $t_{180} = 0.58$, $P = 0.56$; post: $t_{180} = -4.15$, $P < 0.001$
Control, n = 100	20.14 (6.58)	18.70 (6.83)	0.21 (−0.06 to 0.49)			
QOLIE-10						
Intervention, n = 82	31.11 (5.68)	33.28 (4.75)	0.41 (0.10 to 0.78)	0.48 (0.18 to 0.78)	$F_{1,179} = 10.22$, $P < 0.01$	Pre: $t_{180} = -1.23$, $P = 0.22$; post: $t_{180} = -3.25$, $P = 0.001$
Control, n = 100	30.11 (5.24)	30.91 (5.05)	0.16 (−0.12 to 0.43)			

All control group participants plus intervention participants who registered were included. Missing data at post were replaced by multiple imputation; n = 182. ANCOVA, analysis of covariance; BG, between-groups; CI, confidence interval; cov, covariate; DASS-21, Depression Anxiety Stress Scales–21 items; DV = dependent variable; GAD-7, Generalized Anxiety Disorder–7 items; IV = independent variable; NDDIE, Neurological Disorders Depression Inventory for Epilepsy; PHQ-9, Patient Health Questionnaire–9 items; post, posttreatment; pre, pretreatment; QOLIE-10, Quality of Life in Epilepsy–10 items; WG, within group; WSAS, Work and Social Adjustment Scale.

of clinical relevance ($d = 0.24$).[31] Clinically significant depression improvement was observed among 29% of intervention group participants compared to 15% in the control group. At 3 months, intervention group participants also reported fewer sick days and fewer days hospitalized, although no differences in seizure frequency were reported.

4.2 | Strengths

Strengths of the trial included adequate power, use of validated outcome measures, follow-up assessment points up to 9 months after randomization (that is, 3 months after discontinuation of intervention access for those in the intervention group), pragmatic design that may represent the heterogeneity of routine care conditions, and differentiated assessment of perceived negative effects attributable to the intervention.

4.3 | Limitations

Several limitations have to be acknowledged. First, the dropout rate was 23%, which is less than in a previous similar study but above the target of maximally 20%.[18] Of note, dropout is often even higher with medication or other self-guided interventions.[32–34] Adherence could potentially be improved by providing personal support, but combining eCBT and support in one study arm makes it impossible to disentangle which element drove the effect.[35] Other limitations of this trial concern reliance on self-report measures as well as lack of comparison against an active control or a placebo intervention. Such comparisons are rare in studies of psychological interventions and fraught with conceptual problems, because the placebo concept can be applied more easily to drug research.[36,37]

Another limitation concerns the 9-month assessment taking place only 3 months after program access had expired for the intervention group. Thus, research is needed to examine the long-term stability of effects after program discontinuation. Another limitation concerns intervention developer involvement, as previous research has shown that developer allegiance effects can sometimes bias findings.[38] However, steps were taken to ensure transparency and objectivity, as described in the trial protocol, and a meta-analysis of trials of another Internet intervention developed by this group showed no developer bias.[19,21] Additional limitations were that epilepsy diagnoses were not verified independently, that interrater reliability for the diagnostic interviews was not examined, that data on past psychological and pharmacological interventions for depression were not collected, and that participants in this study might have been more Internet-savvy and motivated than the average PwE, which introduces potential selection bias. Therefore, the findings might generalize not to all PwE but only to those PwE who are able and motivated to use Internet programs such as Emyna.

4.4 | Interpretation

This trial demonstrated that the Internet intervention Emyna produced clinically meaningful effects on depression, anxiety, and other secondary outcomes, which were stronger than those observed for an eCBT intervention that was not tailored for PwE.[18,19] Symptomatic improvements persisted at 6 and 9 months, although comparisons with a control group unexposed to the intervention were not possible beyond 3 months. Although some participants started antidepressant medication or psychotherapy after the trial had commenced, there was no evidence that intervention effects were confounded by differential treatment utilization.

These effects are encouraging in the context of other self-guided depression interventions, where meta-analyses have yielded an average effect size of $g = 0.27$, and in the context of psychotherapy efficacy, where meta-analyses have yielded an average effect size of $d = 0.42$ after correcting for publication bias ($d = 0.67$ without correction).[10,39] Effects can be regarded as clinically relevant when they exceed $d = 0.24$, and more stringent guidelines suggest that they should exceed $d = 0.50$ (corresponding to number needed to treat [NNT] = 3.6).[31] For antidepressants, systematic reviews in primary care have shown NNTs of 6-8.5.[40] Effects observed for Emyna meet and exceed these thresholds, suggesting that they are clinically meaningful and comparable to established depression treatments.

Of note, participants also reported positive intervention effects far more frequently than negative effects. Reports of negative effects, such as concerns about data protection, feeling pressured to undertake therapeutic exercises, or feeling anxious about becoming too dependent on the program, could be addressed in future refinements.

4.5 | Implications for research and health care

The present study showed that Emyna, used as an adjunctive treatment tool, could help improve mental health, social-occupational functioning, and quality of life among PwE. Future research could clarify who benefits most and by which mechanisms these effects unfold. Furthermore, there is a need to evaluate the cost-effectiveness and dissemination of Emyna into routine care. Given its convenient accessibility and cost-saving potential, this intervention could augment health care providers' treatment repertoire, and it might offer payer organizations the opportunity to increase quality of care while reducing costs.

ACKNOWLEDGMENTS

We acknowledge the contributions of the multidisciplinary development team at Gaia, which designed and produced the Internet intervention examined in this study, as well as the contributions of the patients, relatives of patients, and treatment providers who provided feedback and valuable suggestions in the intervention development process. We also thank Tobias Arthen, who supported the statistical analyses. This research was funded by Gaia, Germany, a research-focused small-to-medium enterprise that specializes in e-health interventions and regularly participates in publicly funded research. There was no external funding.

DISCLOSURE OF CONFLICT OF INTEREST

B.M., M.W., and F.S. are affiliated with Gaia, the company that funded this trial and that developed, owns, and operates the Internet intervention evaluated in it. B.M. is employed full-time as Chief Scientific Office, M.W. is Chief Executive Officer and founder of Gaia, and F.S. is employed full-time as a research associate. None of the authors who are not employed by Gaia (M.H., S.A., K.B., J.S., Y.N.) has received any remuneration from Gaia. M.H. has received speaker honoraria and/or consultancy fees from Bial, Desitin, Eisai, LivaNova, Novartis, Shire, and UCB within the past 3 years. S.A. has received speaker honoraria and/or consultancy fees from Bial, Desitin, Eisai, LivaNova, and UCB within the past 3 years. The other authors (K.B., J.S., Y.N.) declare that they have no competing interests. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Björn Meyer https://orcid.org/0000-0003-1100-0260
Martin Holtkamp https://orcid.org/0000-0003-2258-1670

REFERENCES

1. Scott AJ, Sharpe L, Hunt C, et al. Anxiety and depressive disorders in people with epilepsy: a meta-analysis. Epilepsia. 2017;58:973–82.
2. Keezer MR, Sisodiya SM, Sander JW. Comorbidities of epilepsy: current concepts and future perspectives. Lancet Neurol. 2016;15:106–15.
3. Gandy M, Sharpe L, Perry KN. Cognitive behavior therapy for depression in people with epilepsy: a systematic review. Epilepsia. 2013;54:1725–34.
4. Mula M. Epilepsy and psychiatric comorbidities: drug selection. Curr Treat Options Neurol. 2017;19:44.
5. Noble AJ, Reilly J, Temple J, et al. Cognitive-behavioural therapy does not meaningfully reduce depression in most people with epilepsy: a systematic review of clinically reliable improvement. J Neurol Neurosurg Psychiatry. 2018;89:1129–37.
6. Michaelis R, Tang V, Wagner JL, et al. Psychological treatments for people with epilepsy. Cochrane Database Syst Rev. 2017;10: CD012081.
7. Bermeo-Ovalle A. Psychiatric comorbidities in epilepsy: we learned to recognize them; it is time to start treating them. Epilepsy Curr. 2016;16:270–2.
8. Andrade LH, Alonso J, Mneimneh Z, et al. Barriers to mental health treatment: results from the WHO World Mental Health surveys. Psychol Med. 2014;44:1303–17.
9. Karyotaki E, Ebert DD, Donkin L, et al. Do guided Internet-based interventions result in clinically relevant changes for patients with depression? An individual participant data meta-analysis. Clin Psychol Rev. 2018;63:80–92.
10. Karyotaki E, Riper H, Twisk J, et al. Efficacy of self-guided Internet-based cognitive behavioral therapy in the treatment of depressive symptoms: a meta-analysis of individual participant data. JAMA Psychiatry. 2017;74:351–9.
11. Baumeister H, Reichler L, Munzinger M, et al. The impact of guidance on Internet-based mental health interventions—a systematic review. Internet Interv. 2014;1:205–15.
12. Gilbody S, Littlewood E, Hewitt C, et al. Computerised cognitive behaviour therapy (cCBT) as treatment for depression in primary care (REEACT trial): large scale pragmatic randomised controlled trial. BMJ. 2015;351:h5627.
13. Titov N, Dear BF, Staples LG, et al. Disorder-specific versus transdiagnostic and clinician-guided versus self-guided treatment for major depressive disorder and comorbid anxiety disorders: a randomized controlled trial. J Anxiety Disord. 2015;35:88–102.
14. Twomey C, O'Reilly G. Effectiveness of a freely available computerised cognitive behavioural therapy programme (MoodGYM) for depression: meta-analysis. Aust N Z J Psychiatry. 2017;51:260–9.
15. Berger T, Hammerli K, Gubser N, et al. Internet-based treatment of depression: a randomized controlled trial comparing guided with unguided self-help. Cogn Behav Ther. 2011;40:251–66.
16. Thompson NJ, Patel AH, Selwa LM, et al. Expanding the efficacy of Project UPLIFT: distance delivery of mindfulness-based depression prevention to people with epilepsy. J Consult Clin Psychol. 2015;83:304–13.
17. Gandy M, Karin E, Fogliati VJ, et al. A feasibility trial of an Internet-delivered and transdiagnostic cognitive behavioral therapy treatment program for anxiety, depression, and disability among adults with epilepsy. Epilepsia. 2016;57:1887–96.
18. Schroder J, Bruckner K, Fischer A, et al. Efficacy of a psychological online intervention for depression in people with epilepsy: a randomized controlled trial. Epilepsia. 2014;55:2069–76.
19. Twomey C, O'Reilly G, Meyer B. Effectiveness of an individually-tailored computerised CBT programme (Deprexis) for depression: a meta-analysis. Psychiatry Res. 2017;256:371–7.
20. Zwerenz R, Becker J, Knickenberg RJ, et al. Online self-help as an add-on to inpatient psychotherapy: efficacy of a new blended treatment approach. Psychother Psychosom. 2017;86:341–50.
21. Meyer B, Weiss M, Holtkamp M, et al. Protocol for the ENCODE trial: evaluating a novel online depression intervention for persons with epilepsy. BMC Psychiatry. 2017;17:55.
22. Eysenbach G. CONSORT-EHEALTH: improving and standardizing evaluation reports of Web-based and mobile health interventions. J Med Internet Res. 2011;13:e126.

23. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55:475–82.
24. Sheehan D, Lecrubier Y, Sheehan KH, et al. The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. Eur Psychiatry. 1997;12:232–41.
25. Osman A, Wong JL, Bagge CL, et al. The Depression Anxiety Stress Scales-21 (DASS-21): further examination of dimensions, scale reliability, and correlates. J Clin Psychol. 2012;68:1322–38.
26. Ladwig I, Rief W, Nestoriuc Y. Welche risiken und nebenwirkungen hat psychotherapie? Entwicklung des inventars zur Erfassung Negativer Effekte von Psychotherapie (INEP). Verhaltenstherapie. 2014;24:252–63.
27. Jakobsen JC, Gluud C, Wetterslev J, et al. When and how should multiple imputation be used for handling missing data in randomised clinical trials—a practical guide with flowcharts. BMC Med Res Methodol. 2017;17:162.
28. O'Connell N, Dai L, Jiang Y, et al. Methods for analysis of pre-post data in clinical research: a comparison of five common methods. J Biom Biostat. 2017;8:2.
29. McMillan D. Defining successful treatment outcome in depression using the PHQ-9: a comparison of methods. J Affect Disord. 2010;127:122–9.
30. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol. 1991;59:12–9.
31. Cuijpers P, Turner EH, Koole SL, et al. What is the threshold for a clinically relevant effect? The case of major depressive disorders. Depress Anxiety. 2014;31:374–8.
32. Arnberg FK, Linton SJ, Hultcrantz M, et al. Internet-delivered psychological treatments for mood and anxiety disorders: a systematic review of their efficacy, safety, and cost-effectiveness. PLoS One. 2014;9:e98118.
33. Karyotaki E, Kleiboer A, Smit F, et al. Predictors of treatment dropout in self-guided Web-based interventions for depression: an 'individual patient data' meta-analysis. Psychol Med. 2015;45:2717–26.
34. Vermeire E, Hearnshaw H, Van Royen P, et al. Patient adherence to treatment: three decades of research. A comprehensive review. J Clin Pharm Ther. 2001;26:331–42.
35. Schueller SM, Tomasino KN, Mohr DC. Integrating human support into behavioral intervention technologies: the efficiency model of support. Clin Psychol Sci Pract. 2017;24:27–45.
36. Kirsch I, Wampold B, Kelley JM. Controlling for the placebo effect in psychotherapy: noble quest or tilting at windmills? Psychol Conscious: Theory Res Pract. 2016;3:121.
37. Evers AWM, Colloca L, Blease C, et al. Implications of placebo and nocebo effects for clinical practice: expert consensus. Psychother Psychosom. 2018;87:204–10.
38. Dragioti E, Dimoliatis I, Fountoulakis KN, et al. A systematic appraisal of allegiance effect in randomized controlled trials of psychotherapy. Ann Gen Psychiatry. 2015;14:25.
39. Cuijpers P, Smit F, Bohlmeijer E, et al. Efficacy of cognitive-behavioural therapy and other psychological treatments for adult depression: meta-analytic study of publication bias. Br J Psychiatry. 2010;196:173–8.
40. Arroll B, Chin WY, Martis W, et al. Antidepressants for treatment of depression in primary care: a systematic review and meta-analysis. J Prim Health Care. 2016;8:325–34.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Meyer B, Weiss M, Holtkamp M, et al. Effects of an epilepsy-specific Internet intervention (Emyna) on depression: Results of the ENCODE randomized controlled trial. *Epilepsia*. 2019;60:656–668. https://doi.org/10.1111/epi.14673