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A digital therapeutic for people with borderline personality disorder in Germany (EPADIP-BPD): a pragmatic, assessor-blind, parallel-group, randomised controlled trial



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Summary

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Background Fewer than 25% of patients with borderline personality disorder (BPD) receive guideline-adherent psychotherapy. Digital therapeutics can help reduce this gap. Therefore, we tested the effectiveness and safety of *priovi*, a digital therapeutic for BPD.

Methods We conducted a pragmatic, assessor-blind, parallel-group, randomised controlled trial, recruiting patients with BPD, according to DSM-5 classification, of at least moderate severity on the 23-item Borderline Symptom List (BSL-23) via online advertisements in Germany. Patients were aged 18 years or older, agreed on an emergency plan for suicidal crises, and gave informed consent to participate. Patients were excluded if they had a primary diagnosis of a substance use disorder or a diagnosis of a psychotic disorder. Simple computerised coin-toss randomisation (1:1) without stratification was used to assign patients to either the unguided digital therapeutic based on schema therapy together with treatment as usual (TAU; intervention group) or TAU alone (control group) and study investigators were masked to group assignment until after the analysis of the primary outcome and main safety outcome. All patients could use any form of usual care. The control group received freely available BPD-specific self-help material. The primary outcome was the time by treatment interaction in the intention-to-treat sample at 3 months measured by BSL-23 score. Safety was established via the number of serious adverse events (ie, suicide attempts, other life-threatening events, and hospitalisation), assessed via online questionnaire. Individuals with BPD were involved in the development of the digital therapeutic, but not in the design of this study. The trial was registered on German Clinical Trials Register (DRKS00028888) and is completed.

Findings Between May 3 and Oct 20, 2022, 1766 patients were screened for eligibility and 580 patients (520 [90%] women, 47 [8%] men, and 13 [2%] gender diverse) were randomly assigned to the intervention group (n=302) and control group (n=278). Ethnicity data were not recorded. At the primary timepoint of 3 months, 35 (12%) patients dropped out of the intervention group and 15 (5%) of the control group. The median age of patients was 29 years (IQR 24–37). Intention-to-treat analysis with linear mixed models showed a significant time by treatment interaction (p=0·0005) at 3 months in favour of the intervention group (d=0·24 [95% CI 0·07–0·42]). Regarding safety, there were significantly fewer suicide attempts in the intervention group (n=7) than in the control group (n=21; incidence rate ratio 0·34 [95% CI 0·14–0·79]; p=0·0081) and there were no differences regarding other serious adverse events.

Interpretation This trial provides tentative evidence of the effectiveness and absence of safety concerns of the digital therapeutic, *priovi*, in the treatment of individuals with BPD.

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Introduction

Borderline personality disorder (BPD) is a common and severe mental illness associated with substantial comorbidity, functional impairment,¹ and high societal costs.² There are several effective therapies available to treat patients with BPD and, in guidelines, BPD-specific psychotherapy is recommended as the first-line treatment,³ whereas treatment with medication is not evidence-based for patients with BPD and is only recommended in those with comorbidities.⁴ However, even in well developed health-care systems, fewer than

one in four patients receive access to BPD-specific psychotherapy.⁵ With such a large treatment gap, alternatives to face-to-face psychotherapy are needed for those who cannot find a specialised therapist. Digital therapeutics that are based on effective psychological treatments for BPD might contribute to improving mental health care for these patients.⁶

Meta-analyses have shown the effectiveness of digital therapeutics in reducing symptoms of numerous mental disorders, including depression and anxiety disorders.⁷ However, in the treatment of patients diagnosed with

Research in context

Evidence before this study

We based our research on a systematic review and meta-analysis previously published by Drews-Windeck and colleagues in 2023 who searched PsycINFO, PubMed, MEDLINE, Web of Science, and Cochrane Library using search terms under mental health terminology targeting borderline personality disorder (BPD), including research and practice-based terms “emotional intensity difficulties” or “borderline pattern” and typical symptoms (ie, difficulties with emotion regulation, impulsivity, identity disturbance, unstable relationships, emptiness, and fear of abandonment), mental health interventions (ie, treatment, mental health service, and psychoeducation), and information and communication technology (ie, computer, app, electronic health, mobile technology health, telehealth, and videoconference) for studies of digital interventions targeted at individuals with BPD, emotionally unstable personality disorder, and related symptoms published between database inception and September, 2022. This search yielded six randomised controlled trials that showed statistically significant, small to moderate effects on symptoms of BPD. The authors cautioned that the studies with the largest effect also had the highest risk

of bias (eg, due to high dropout rates), suggesting that more trials with lower risk of bias are needed.

Added value of this study

To our knowledge, the EPADIP-BPD study is the first randomised controlled trial to compare the digital therapeutic priovi with treatment as usual in a large sample of patients with BPD without mandatory concomitant therapy. Dropout rates were low for the intervention and control group. Analysis of the intention-to-treat population revealed that patients in the intervention group had greater reductions of BPD symptoms than those in the control groups. We also found favourable effects on some, but not all, secondary outcomes (anxiety and depression) and on one of the safety outcomes (suicide attempts). The effect sizes were small and the effects were stable at the 12-month follow-up.

Implications of all the available evidence

This trial provides tentative evidence of the effectiveness and absence of safety concerns for this digital therapeutic in the treatment of people with BPD, even if they are not currently treated by a psychiatrist or psychotherapist. It has the potential to become an additional option in the treatment of BPD and thus improve mental health care for individuals with BPD.

BPD, safety concerns have so far limited the use of digital therapeutics because of the high frequency of self-injurious and suicidal behaviours in this patient group. Consequently, studies involving digital interventions in this population have primarily been conducted under the premise that the utilised programmes are administered either as adjuncts to face-to-face therapy or, at the least, under the supervision of a psychotherapist or psychiatrist. These studies have shown that digital therapeutics can safely be used.⁶ As a next step, the effectiveness and safety of these interventions should be examined for patients who use them independently of a clinician.

We conducted the Effectiveness of Priovi, a Digital Self-Management Intervention, in Patients with Borderline Personality Disorder (EPADIP-BPD) study, a large confirmatory trial testing the effectiveness and safety of the digital therapeutic priovi (hereafter referred to as the digital therapeutic) added to treatment as usual (TAU). The digital therapeutic was specifically designed for patients with BPD and is based on schema therapy, a BPD-specific cognitive behavioural therapy (CBT). We tested the primary hypothesis that the use of the digital therapeutic in addition to TAU would be more effective than TAU alone in the reduction of BPD symptoms after 3 months.

Methods

Study design and patients

The EPADIP-BPD study is a pragmatic, randomised, parallel-group, assessor-blind clinical trial. Patients were recruited via online advertisement in Germany. The study was reviewed and approved by the ethics committee

of University of Lübeck (reference number 22-012). This study report adheres to CONSORT guidelines and methodology. The trial was registered on the German Clinical Trials Register (DRKS00028888). The conduct of the trial and the statistical analyses followed a predefined clinical investigation plan that is available online.⁸

Patients were eligible when they: (1) were at least aged 18 years, (2) were diagnosed with BPD by a structured clinical interview for the DSM-5 (SCID-5-PD), (3) had at least moderate severity of BPD symptoms (23-item Borderline Symptom List [BSL-23] mean score ≥ 1.07),⁹ (4) agreed on an emergency plan for suicidal crises, and (5) gave informed written consent to participate. Exclusion criteria were: (1) a primary diagnosis of a substance use disorder, and (2) a diagnosis of a psychotic disorder (patients with transitory paranoid ideas related to the BPD and mostly intact reality testing ability were not excluded). Sex and gender were self-reported with the options male and female for biological sex, and the options male, female, and gender diverse for the gender to which they feel they belong. Individuals with BPD were systematically involved in the development of the digital therapeutic, but not in the design or conduct of this study. Another group of 20 people participated in two previous qualitative interview studies^{10,11} and the digital therapeutic was adapted based on their results.

Randomisation and masking

Patients were randomly assigned to receive either the digital therapeutic together with TAU or TAU alone, with no blocked randomisation and no stratification at a 1:1

See Online for appendix

allocation ratio, automatically performed by an external computerised tool simulating a digital coin toss. For each participant, this digital coin toss took place after enrolment, thus ensuring allocation concealment. Patients were not masked to group assignment because it is not possible for a psychological online intervention. Study investigators were masked to group assignment until the end of the analysis of the primary outcome and main safety outcome.

Procedures

Patients were recruited for this online study through a targeted Google Ads campaign, which directed potential patients to a dedicated information website. Here, interested individuals could contact the study team to express their interest in participation. The enrolment process began with an initial screening through an online survey, electronic informed consent, and the collection of baseline data. This stage was followed by a telephone call to perform the SCID-5-PD and to develop an individual emergency plan for suicidal crises. These interviews were carried out by trained clinical psychologists under the supervision of a licensed psychotherapist. After enrolment and subsequent randomisation to the study groups, patients were informed of the randomisation result via email.

All patients in this trial were free to use any form of care, including pharmacological and psychological treatment (including BPD-specific psychotherapy), reflecting the current reality of care. This care was not influenced by the study team and was referred to as TAU.

Patients in the intervention group received access to the digital therapeutic *priovi* in addition to TAU. The digital therapeutic has been developed specifically for patients with BPD and is based on schema therapy, an evidence-based BPD-specific treatment¹² that applies the schema-mode model for BPD (modes are specific emotional-cognitive-behavioural states). Users are guided through the programme with simulated dialogues. The digital therapeutic starts with psychoeducation on BPD symptoms, basic human needs, and emotions as well as BPD-specific modes. The second phase includes exercises (imagery, cognitive restructuring, behavioural homework assignments, etc) tailored to the user. Users are advised to use the digital therapeutic twice a week for 30 min; this frequency reflects common recommendations for the treatment of BPD¹² and has been shown to be feasible for the use of therapeutic online programmes in different disorders.¹³ If users do so, they need about 3–4 months to complete all dialogues. Additional resources, such as media and exercises, can be used for a year. The intervention itself is unguided, but users can contact technical support by telephone or email. This support was exclusively for solving technical problems and not for psychological support. After an initial randomised controlled trial of *priovi*,¹⁴ the intervention was revised substantially and we conducted

this trial with the improved version. A detailed description of the digital therapeutic can be found in the appendix (pp 2–4).

Patients in the control group were provided with information on freely available self-help online material in addition to TAU. The control group was granted access to the digital therapeutic after 6 months.

Safety was assessed with a questionnaire recording the occurrence of the following serious adverse events within the previous 3 months: suicide attempts, other life-threatening events (eg, non-suicidal self-injury, drug intoxication, and accidents), and hospitalisations, as per the methods of the original randomised controlled trial.¹⁴

Outcomes

Outcome data were assessed via online questionnaires after 3 months (the primary timepoint for evaluation of effectiveness) and 6 months. Up to three reminder emails were sent if patients missed an assessment.

The primary outcome was the change over time of the severity of borderline symptoms at 3 months measured with the BSL-23.⁹ The BSL-23 is a BPD-specific self-rating instrument with good psychometric properties that was optimised to reflect both clinical and lived experience and to discriminate between degrees of severity of BPD symptomatology.⁹ It is freely available, has been translated into at least 18 languages,⁹ takes about 3–4 min to complete, and is widely used in clinical and research settings.¹⁵ The 3-month assessment was chosen as the primary endpoint because earlier studies on this digital therapeutic had shown that the intensity of usage steadily declined to less than once per week over the first 3 months.¹⁴

Secondary outcomes to support the primary outcome included BSL-23 at 6 months and response and remission based on borderline symptom severity on the BSL-23 at 3 months and 6 months. Response was defined by both reaching the psychometric criterion of a reliable change index¹⁶ and having a change in the total score of BSL-23 towards a less severe grade from baseline. People with deteriorating symptoms were defined accordingly by both reaching a reliable change index and having a change of BSL-23 total score towards a more severe grade from baseline. People without responsive symptoms were defined as having no change in the borderline symptom severity grade, even if the reliable change index was reached. Remission of borderline symptoms was defined as reaching a BSL-23 mean score of less than 0.28 (corresponding to the none or low category of BPD severity).⁹

Further secondary outcomes, measured after 3 months and 6 months, were mental health-related quality of life, assessed with the 12-item Short Form questionnaire (SF-12; sum score of mental health domain); depression, assessed via the nine-item Patient Health Questionnaire (PHQ-9); anxiety, assessed with the seven-item

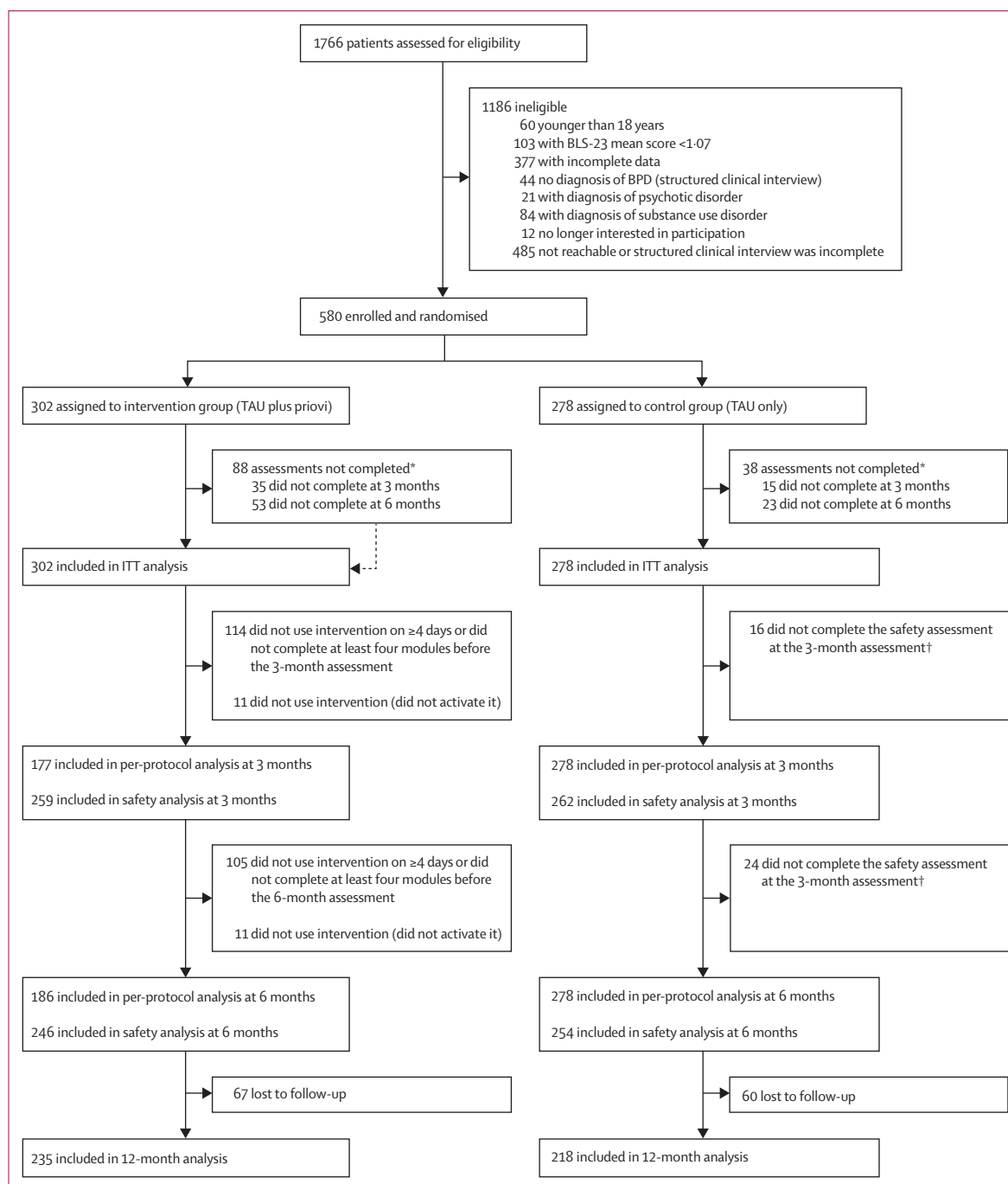


Figure: Trial profile

BPD=borderline personality disorder. BLS-23=23-item Borderline Symptom List. ITT=intention-to-treat. TAU=treatment as usual. Some patients completed an assessment at 3 months but not at 6 months and vice versa, and more patients fulfilled the per-protocol criteria at 6 months than at 3 months. *Reasons not recorded due to automated online assessments. †One patient had incomplete data.

Generalised Anxiety Disorder (GAD-7) assessment; and social and work-related functioning, assessed with the Work and Social Adjustment Scale (WSAS). Exploratory endpoints included all secondary outcomes after 6 months. Furthermore, patients were contacted again after 12 months to explore whether the improvement in

the intervention group was stable and whether patients in the control group also had improvement after receiving access to the digital therapeutic. Safety was established via the number of serious adverse events.

Regarding the usage of the digital therapeutic, the parameters collected were the number of modules

	Total (N=580)	Intervention group (n=302)	Control group (n=278)
Age, years	29 (24-37)	29 (24-36)	30 (25-38)
Sex			
Female	530 (91%)	273 (90%)	257 (92%)
Male	50 (9%)	29 (10%)	21 (8%)
Gender			
Women	520 (90%)	268 (89%)	252 (91%)
Men	47 (8%)	26 (9%)	21 (8%)
Diverse	13 (2%)	8 (3%)	5 (2%)
Relationship status			
Divorced or registered partnership annulled	32 (6%)	21 (7%)	11 (4%)
Living in partnership >2 years	138 (24%)	66 (22%)	72 (26%)
Living in partnership <2 years	132 (23%)	68 (23%)	64 (23%)
Married or registered civil partnership	84 (14%)	42 (14%)	42 (15%)
Single	192 (33%)	105 (35%)	87 (31%)
Widowed or registered partner deceased	2 (<1%)	0	2 (1%)
Education			
No or primary education	8 (1%)	3 (1%)	5 (2%)
Lower secondary education	33 (6%)	21 (7%)	12 (4%)
Intermediate secondary education	98 (17%)	57 (19%)	41 (15%)
Upper secondary education	45 (8%)	25 (8%)	20 (7%)
Highest secondary education	88 (15%)	43 (14%)	45 (16%)
Completed vocational training	141 (24%)	63 (21%)	78 (28%)
Completed university studies	147 (25%)	74 (25%)	73 (26%)
Other education	20 (3%)	16 (5%)	4 (1%)
Employment			
Unemployed	185 (32%)	100 (33%)	85 (31%)
Marginal employment (maximum €556/month*)	29 (5%)	14 (5%)	15 (5%)
Employed part-time	108 (19%)	55 (18%)	53 (19%)
Employed full-time	176 (30%)	87 (29%)	89 (32%)
Other form of employment	82 (14%)	46 (15%)	36 (13%)
Psychiatric history			
Ever had psychotherapy	552 (95%)	285 (94%)	267 (96%)
Currently in psychotherapy	263 (45%)	138 (46%)	125 (45%)
Currently taking any psychotropic medication	297 (51%)	157 (52%)	140 (50%)
Regular medication (multiple answers possible)			
Antidepressants	259 (45%)	131 (43%)	128 (46%)
Antipsychotics	77 (13%)	36 (12%)	41 (15%)
Sedatives	22 (4%)	16 (5%)	6 (2%)
Psychostimulants	20 (3%)	9 (3%)	11 (4%)
Antiepileptics	14 (2%)	10 (3%)	4 (1%)
Anxiolytics	12 (2%)	6 (2%)	6 (2%)
Medication as needed (multiple answers possible)			
Antipsychotics	37 (6%)	15 (5%)	22 (8%)
Sedatives	33 (6%)	20 (7%)	13 (5%)
Anxiolytics	27 (5%)	17 (6%)	10 (4%)
Antidepressants	12 (2%)	5 (2%)	7 (3%)

(Table 1 continues on next page)

completed, the number of days active, and the time spent in the programme. These data reflect only measurable engagement with the digital therapeutic itself and do not capture how long a person has engaged with its content outside the digital therapeutic (eg, short text messages sent by the digital therapeutic or PDF file materials printed from the digital therapeutic).

Statistical analysis

The target difference for the sample size calculation was based on the available evidence for a realistic and important effect.¹⁷ Specifically, a previous smaller randomised controlled trial of the same digital therapeutic established an effect size of Cohen’s *d*=0.27 on symptoms of BPD.¹⁴ Furthermore, a systematic assessment of a minimally clinically important difference (MCID) estimated that, from a patient perspective, the MCID cutoff for BPD might be *d*=0.21.^{18,19} As described in more detail in the appendix (p 4), this estimate is based on research assessing meaningful changes in health states from the viewpoint of the patient and then converting these changes into effect sizes. Based on an estimated effect size of Cohen’s *d* of 0.28 after 3 months, a power of 0.80, an α level of 0.05, and an expected dropout rate of 30%,¹⁴ 290 patients were required in each condition, resulting in a target sample size of 580.

The intention-to-treat (ITT) sample included all patients who were randomly assigned. The per-protocol sample included all patients from the control group and only those from the intervention group who used the intervention on at least 4 days and used a total of at least four modules. The primary outcome was assessed in the ITT sample. The safety analysis was conducted on the safety population (ie, all patients from the control group and only those from the intervention group who used the intervention at least once).

Missing values for continuous outcomes were substituted with multiple imputations (appendix pp 4–5). For the primary, secondary, and safety outcomes, mixed-model analyses were implemented with the package lme4 in R (version 4.3.0), which uses an unstructured covariance matrix by default to model within-participant errors. Analyses included a random intercept for each participant to account for interindividual differences and the fixed effects of time, group, and time by group. Starting from baseline, all timepoints were included and time was modelled as a natural log of time from baseline in months plus 1.

The total score of the primary outcome (BSL-23) was analysed with a linear mixed model suitable for repeated measures with restricted maximum likelihood. The primary study hypothesis was tested on the slope difference between groups (ie, time×group interaction); the primary comparison was the contrast between groups at 3 months. The significance test was based on estimated marginal means using a two-sided α of 0.05 (two-sided

95% CIs). The same analytical strategy was used for a secondary analysis of the primary outcome, the per-protocol analysis, and most of the secondary outcomes. Rates of response, remission, and deterioration were analysed by χ^2 tests. Secondary outcomes were chosen to support findings from the primary outcome; therefore no adjustment for multiple testing was made and p values are reported for descriptive purposes and not significance testing.

Safety outcomes were count data analysed with a generalised linear mixed model with maximum likelihood estimation, a Poisson distribution, and a log link function. Exploratory subgroup analyses were conducted on the ITT dataset with the baseline variables of BPD severity (ie, moderate, high, very high, and extremely high),⁹ sex, psychotherapy status, and medication status. Furthermore, we exploratorily tested the moderating effect of physical health-related quality of life (sum score of physical health subscale of SF-12), baseline symptom severity, and psychotherapy status by rerunning the primary analysis and testing the interaction effect of time by group by putative moderator variable.

For the primary endpoint, we also conducted a reference-based sensitivity analysis to assess the effect of missing values on our outcome estimation.²⁰ Reference-based sensitivity analyses address different missing-not-at-random scenarios. In the analysis we have chosen, the jump-to-reference analysis, patients dropping out of the intervention group are treated as if they no longer use the intervention and only have treatment similar to that of patients in the control group after dropout. Their outcome after dropout is assumed to be the same as that of those in the control group. Therefore, for each participant dropping out in the intervention group, the joint distribution of this individual's observed and missing outcome data is formed as a multivariate normal distribution with a mean and covariance matrix from the intervention group before dropout and from the control group after dropout.

Role of the funding source

Researchers from the funder collaborated with the other authors in the study design, drafting of the study protocol and its amendments, data collection, data analysis, data interpretation, and review of the manuscript. The main results were analysed independently of the funder.

Results

Between May 3, 2022, and Oct 20, 2022, 1766 patients were screened for eligibility, of whom 580 were enrolled and randomly assigned and included in the ITT analysis. 302 were assigned to the intervention group and 278 to the control group (figure). The differences observed are within the expected range of the binomial distribution and are due to the digital coin tossing used for randomisation. Attrition rates at 3 months were 12% (n=35) for the intervention group and 5% (n=15) for the control group.

	Total (N=580)	Intervention group (n=302)	Control group (n=278)
(Continued from previous page)			
Clinical characteristics			
BSL-23	2.3 (0.6)	2.3 (0.6)	2.3 (0.6)
SF-12 mental health subscale	12.0 (2.6)	12.0 (2.7)	11.9 (2.5)
PHQ-9	17.3 (4.7)	17.3 (4.7)	17.4 (4.6)
GAD-7	14.9 (3.8)	14.7 (3.7)	15.0 (3.8)
WSAS	23.5 (7.9)	23.4 (8.0)	23.5 (7.7)
Data are median (IQR), mean (SD), or n (%). BSL-23=23-item Borderline Symptom List. SF-12=12-item Short Form. PHQ-9=nine-item Patient Health Questionnaire. GAD-7=seven-item Generalised Anxiety Disorder assessment. WSAS=Work and Social Assessment Scale. *As of Jan 1, 2025.			
Table 1: Descriptive baseline characteristics of the intention-to-treat sample			

Patients who dropped out of the study for any reason before 3 months were significantly more likely to be men ($p=0.013$) and have more severe BPD ($p=0.025$; appendix p 6). Because it was an online study, no reasons for dropout could be assessed. The last follow-up assessment was conducted on May 3, 2023.

Patients were mostly women (520 [90%] vs 47 [8%] men and 13 [2%] gender diverse) and the median age was 29 years (IQR 24–37). The majority (354 [61%]) reported being in a relationship and 185 (32%) were not employed. Almost half the cohort was in psychotherapy at baseline (263 [45%]), taking psychotropic medication (297 [51%]), or both. Nearly all patients (552 [95%]) had been in psychotherapy previously (table 1).

In the intervention group, 291 (96%) patients activated their voucher for the digital therapeutic. The mean use of the digital therapeutic in the intervention group was 16 active days (SD 16) at 3 months, which increased to 20 days (26) at 6 months. The mean number of modules completed was 4.5 (3.1) at 3 months and 5.0 (3.2) at 6 months. Patients were active in the programme for a mean of 4.6 h (4.4) until 3 months and 5.2 h (5.2) until 6 months. Technical support was contacted six times by five (2%) different patients (eg, because of problems with programme registration).

For the primary outcome (ie, BSL-23 at 3 months), the linear mixed model showed a significant time by treatment interaction ($p=0.0005$) with a small between-group effect size ($d=0.24$ [95% CI 0.07 to 0.42]) in favour of the intervention group (table 2). This effect remained significant at the 6-month follow-up ($p=0.011$; $d=0.15$ [−0.03 to 0.32]; appendix p 7). Findings were similar for the reference-based sensitivity analysis at 3 months ($p=0.0006$; $d=0.21$ [0.05 to 0.36]) and 6 months ($p=0.0068$; $d=0.12$ [−0.03 to 0.27]). Results at the 12-month follow-up assessment suggest that the improvement was stable in the intervention group and that patients in the control group also improved after receiving access to the digital therapeutic (appendix p 8).

An overview of response, remission, and deterioration rates of the BPD symptoms (BSL-23), odds ratios (ORs),

	Control group	Intervention group	Linear mixed model		Between-group effect size
	Mean (SD)	Mean (SD)	Treatment effect (95% CI)*	p value	d (95% CI)†
BSL-23					
3 months	1.9 (0.8)	1.7 (0.8)	-0.19 (-0.3 to -0.09)	0.0005	0.24 (0.07 to 0.42)
6 months	1.8 (0.9)	1.6 (0.8)	-0.09 (-0.15 to -0.02)	0.011	0.15 (-0.03 to 0.32)
SF-12 mental health subscale					
3 months	13.0 (3.4)	13.6 (3.4)	0.4 (-0.1 to 0.9)	0.065	0.18 (0.01 to 0.34)
6 months	13.5 (3.6)	13.8 (3.6)	0.2 (-0.1 to 0.4)	0.28	0.10 (-0.07 to 0.27)
PHQ-9					
3 months	15.5 (5.4)	14.4 (5.5)	-1.0 (-1.8 to -0.3)	0.0087	0.21 (0.04 to 0.38)
6 months	14.6 (5.5)	13.7 (5.5)	-0.5 (-0.9 to -0.1)	0.025	0.16 (-0.01 to 0.33)
GAD-7					
3 months	13.2 (4.7)	12.1 (4.6)	-0.7 (-1.4 to -0.1)	0.030	0.23 (0.06 to 0.41)
6 months	12.8 (4.8)	11.7 (4.8)	-0.5 (-0.9 to -0.1)	0.025	0.24 (0.06 to 0.42)
WSAS					
3 months	21.8 (8.9)	20.7 (9.2)	-0.9 (-2.0 to 0.2)	0.11	0.12 (-0.05 to 0.30)
6 months	21.1 (9.4)	20.3 (9.5)	-0.4 (-1.1 to 0.2)	0.22	0.08 (-0.09 to 0.25)

BSL-23=23-item Borderline Symptom List. SF-12=12-item Short Form. PHQ-9=nine-item Patient Health Questionnaire. GAD-7=seven-item Generalised Anxiety Disorder assessment. WSAS=Work and Social Assessment Scale. *Group × time interaction effect on original scale 3 or 6 months after baseline. †Cohen's d based on unadjusted means from the multiple imputation for each assessment and their pooled SD; positive values show effects in favour of the intervention group.

Table 2: Estimated means, treatment effect, and effect size for the primary and secondary outcomes in the linear mixed model based on the intention-to-treat sample

	Control group	Intervention group	OR (95% CI)*	p value
3 months				
Responsive symptoms	41/263 (16%)	64/267 (24%)	1.71 (1.10–2.64)	0.016
Deteriorating symptoms	3/263 (1%)	5/267 (2%)	1.65 (0.39–6.99)	0.74
Remission	1/263 (<1%)	2/267 (1%)	1.98 (0.18–21.94)	1.00
6 months				
Responsive symptoms	58/255 (23%)	75/249 (30%)	1.46 (0.98–2.18)	0.60
Deteriorating symptoms	1/255 (<1%)	4/249 (2%)	4.15 (0.46–37.40)	0.36
Remission	7/255 (3%)	6/249 (2%)	0.87 (0.29–2.64)	1.00

Data are n (%) unless otherwise indicated. Modified intention-to-treat sample sizes represent the number of participants who completed the assessments at each timepoint. Significant at p<0.05. BSL-23=23-item Borderline Symptom List. OR=odds ratio. *Calculated with unconditional maximum likelihood estimation (Wald test). An OR >1.00 signifies a higher likelihood of the event occurring in the intervention group, whereas an OR <1.00 signifies a lower likelihood in the intervention group.

Table 3: Responsive symptoms and remission analysis of the BSL-23 at 3 months and 6 months in the modified intention-to-treat sample

and test statistics are provided in table 3. Significantly more patients in the intervention group were classified as having responsive symptoms at 3 months than in the control group (p=0.016; OR 1.71 [95% CI 1.10–2.64]). There was no significant difference in the proportion of patients experiencing a deterioration of BPD symptoms (p=0.74; 1.65 [0.39–6.99]) or remission (p=1.00; 1.98 [0.18–21.94]) between the intervention group and the control group at 3 months. At 6 months, there was no significant difference between the intervention group and the control group regarding response (p=0.60; 1.46 [0.98–2.18]), deterioration (p=0.36; 4.15 [0.46–37.40]), and remission (p=1.00; 0.87 [0.29–2.64]; table 3).

Regarding the secondary outcomes, for depressive symptoms (PHQ-9) and anxiety (GAD-7), the time by treatment interaction was significant at 3 months (p=0.0087 for PHQ-9, p=0.030 for GAD-7) and 6 months (p=0.025 for PHQ-9, p=0.025 for GAD-7), with lower mean scores in the intervention group (table 2). In contrast, the interaction was not significant for mental health-related quality of life (SF-12 mental health subscale; p=0.28 at 3 months, p=0.065 at 6 months) and social and work-related functioning (WSAS; p=0.11 at 3 months, p=0.22 at 6 months; table 2). The effect size for the secondary outcomes ranged between d=0.08 (95% CI -0.09 to 0.25) for the WSAS at 6 months and d=0.24 (0.06 to 0.42) for the GAD-7 at 6 months, all in favour of the intervention group.

For the safety outcomes, the Poisson mixed model showed a significant time by treatment interaction at 3 months (p=0.0081) and 6 months (p=0.0002) for suicide attempts in the intervention group (with fewer attempts), but not for hospitalisation (p=0.79 at 3 months, p=0.15 at 6 months) and life-threatening events (p=0.99 at 3 months, p=0.70 at 6 months; table 4). Similar results were seen in the per-protocol sample: the Poisson mixed model showed a significant time by treatment interaction at 3 months (p=0.0056) and 6 months (p<0.0001) in favour of the intervention group for suicide attempts, but not for hospitalisation (p=0.49 at 3 months, p=0.36 at 6 months) and life-threatening events (p=0.083 at 3 months, p=0.10 at 6 months). A breakdown of serious adverse events by sex in the safety population is reported in the appendix (p 13).

	Control group		Intervention group		Poisson mixed model		Between-group effect size
	n	Events	n	Events	Treatment effect (95% CI)*	p value	Incidence rate ratio (95% CI)†
Safety sample							
Suicide attempts							
3 months	262	21 (8%)	259	7 (3%)	-0.99 (-1.73 to -0.26)	0.0081	0.34 (0.14 to 0.79)
6 months	254	29 (11%)	246	10 (4%)	-0.87 (-1.32 to -0.41)	0.0002	0.36 (0.17 to 0.73)
Hospitalisations							
3 months	262	54 (21%)	259	72 (28%)	0.05 (-0.31 to 0.41)	0.79	1.35 (0.95 to 1.92)
6 months	254	26 (10%)	246	47 (19%)	0.20 (-0.07 to 0.46)	0.15	1.87 (1.16 to 3.01)
Life-threatening events							
3 months	262	310 (118%)	259	254 (98%)	0.00 (-0.16 to 0.16)	0.99	0.83 (0.70 to 0.98)
6 months	254	135 (53%)	246	113 (46%)	-0.02 (-0.14 to 0.10)	0.70	0.86 (0.67 to 1.11)
Per-protocol sample							
Suicide attempts							
3 months	262	21 (8%)	171	3 (2%)	-1.37 (-2.35 to -0.40)	0.0056	0.22 (0.07 to 0.73)
6 months	254	29 (11%)	165	5 (3%)	-1.12 (-1.68 to -0.56)	<0.0001	0.27 (0.10 to 0.69)
Hospitalisations							
3 months	262	54 (21%)	171	39 (23%)	-0.14 (-0.55 to 0.26)	0.49	1.11 (0.73 to 1.67)
6 months	254	26 (10%)	165	30 (18%)	0.14 (-0.16 to 0.44)	0.36	1.78 (1.05 to 3.00)
Life-threatening events							
3 months	262	310 (118%)	171	119 (70%)	-0.17 (-0.37 to 0.02)	0.083	0.59 (0.48 to 0.73)
6 months	254	135 (53%)	165	61 (37%)	-0.12 (-0.27 to 0.03)	0.10	0.70 (0.51 to 0.94)

Suicide attempts, hospitalisations, and life-threatening events within the previous 3 months of the assessment timepoint. *Group × time interaction effect 3 or 6 months after baseline. †Calculated with unconditional maximum likelihood estimation (Wald test).

Table 4: Analyses of safety outcomes at 3 months and 6 months in the safety and per-protocol samples

Of those who successfully redeemed their voucher in the intervention group, 177 (61%) met criteria for sufficient usage time up to 3 months and 186 (64%) up to 6 months (ie, completed at least four modules on ≥ 4 days) and were thus included in the per-protocol analysis. All 278 patients from the control group were included in this analysis. The descriptive baseline characteristics of the per-protocol sample are presented in the appendix (pp 9–10). Here, the time by treatment interaction for the BSL-23 at 3 months was significant ($p < 0.0001$; $d = 0.40$ [95% CI 0.20–0.59]; appendix p 11), with a larger effect size than in the ITT sample. The results of the primary and secondary outcomes for the per-protocol sample are presented in the appendix (pp 11–12).

The results of the exploratory subgroup and moderator analyses are reported in the appendix (pp 14, 16). No significant differences were found in the comparison of TAU during the study between the intervention group and the control group (appendix p 15).

Discussion

In the EPADIP-BPD study, we investigated the effectiveness and safety of the digital therapeutic privio, provided in addition to TAU. To the best of our knowledge, this trial is the largest of a psychological intervention that has been conducted in patients with BPD to date. We found that the digital therapeutic was effective in reducing BPD symptoms, with a between-group effect of $d = 0.24$

after 3 months. The improvement in the intervention group was stable at the 12-month follow-up assessment. Secondary outcomes support the primary findings with respect to response and other mental illness symptoms, such as depression and anxiety, but not with respect to remission, mental health-related quality of life, and functioning. The safety analysis showed significantly fewer suicide attempts in the intervention group; there were no significant differences regarding hospitalisations and life-threatening events.

The between-group effect for the primary outcome was similar to the anticipated effect and within the range of effects found in two meta-analyses of randomised controlled trials of digital interventions targeted at symptoms of BPD ($d = 0.16$ – 0.37).^{6,21} For dialectical behavioural therapy, the most commonly studied BPD-specific face-to-face psychotherapy, the meta-analytic effect sizes range from $d = 0.36$ to 0.60 in reducing BPD symptoms when compared with TAU.^{15,22,23} Non-specific psychotherapies, including CBT, tend to have a smaller effect in the treatment of BPD ($d = 0.24$).²⁴

A systematic review by Storebø and colleagues¹⁵ suggested that the MCID in the treatment of BPD is $d = 0.44$. This suggestion is based on a randomised controlled trial that showed that an intervention that has an effect of this magnitude on a symptom scale is also associated with an outcome that is clinically meaningful (ie, fewer emergency room visits).²⁵ In the treatment of

depression, an effect size of $d=0.50$ was long considered the cutoff for MCID until a more systematic assessment concluded that, from a patient perspective, an effect size of $d=0.24$ might be meaningful.¹⁹ When adapting this method to BPD, the MCID is $d=0.21$.¹⁸ The effect size observed in our study ($d=0.24$) exceeds this threshold. Given that there is a small association between adherence and outcome in digital interventions, the effect of the digital therapeutic might have been greater if patients had used the intervention more.²⁶

Furthermore, effect sizes should be viewed in the context of outcome relevance and the burden the intervention places on a patient. We showed an effect on a clinically relevant outcome, namely suicide attempts (66% lower incidence in the intervention group), and compared with the time demands of long-term psychotherapy, the digital therapeutic had these effects with less time investment (approximately 4–5 h over 3 months). Therefore, we tentatively conclude that the effect of this digital therapeutic could be clinically meaningful. In addition, the effect might be meaningful from a societal perspective because this digital therapeutic can be scaled easily to reach those individuals with BPD who currently do not have access to treatment.

However, no significant effects were found on mental health-related quality of life and social and work-related functioning, indicating that although the digital therapeutic might alleviate symptoms of BPD as well as anxiety and depression, it does not necessarily translate into an improvement in wellbeing and functioning. This finding is in line with results from psychotherapy studies, which found that the effect of BPD treatment on wellbeing and functioning is much smaller than the effect on BPD symptoms.^{3,12,27} The effects of the intervention also need to be weighed against its potential adverse effects. We observed fewer suicide attempts in those treated with the digital therapeutic than in those who received TAU alone. Similarly, in a previous study, adverse events were less severe in those who received the digital therapeutic than in those who received TAU alone.¹⁴ In a separate qualitative study, some patients have expressed that they felt safe from devaluation because they interacted with a digital therapeutic instead of a psychotherapist.¹¹

This trial has several limitations that should be considered. One limitation to the internal validity of this study is that although dropout rates were remarkably low, they differed between the intervention group (12%) and the control group (5%). Furthermore, dropout rates were higher among men and patients with more severe symptoms of BPD, but the sensitivity analysis yielded results consistent with the primary analysis, suggesting that our findings are robust. Furthermore, the fact that the TAU administered in our study was of low intensity might have inflated the effect size²⁸ and we did not predefine a superiority margin. From a superiority margin perspective, our results would likely be regarded as

inconclusive.²⁹ As with most studies of digital therapeutics, the outcome assessment was only based on self-ratings.

Regarding external validity, only a third of all patients who were screened for the study could be included. However, most patients who did not participate in the study were not excluded due to exclusion criteria, but due to not completing the screening assessment, suggesting that many patients who wanted to participate in the study could have done so. The fact that we did not record the ethnicity of the patients and that we did not involve individuals with lived experience in the design of the study also limits its external validity. Most patients in this study were women (90%) and all were recruited online. The high percentage of women is in line with other studies on psychotherapy for BPD.^{12,27} In fact, few BPD studies have included as many men ($n=47$) and gender diverse ($n=13$) patients in absolute numbers as our study. Previous studies have shown that participants recruited over the internet share most clinical and demographic characteristics with participants recruited in clinical settings and intervention effectiveness was not affected by the recruitment setting.³⁰

The factors of education level, employment status, relationship status, baseline symptom severity, and frequency of previous psychotherapy in our sample differ only slightly from individuals recruited in specialised mental health centres.^{12,27} These findings suggest that this digital therapeutic might be effective even in more severely affected individuals.

To conclude, this trial provides tentative evidence of the effectiveness and absence of safety concerns for the digital therapeutic prior to the treatment of BPD. This digital therapeutic has the potential to become an additional option in the treatment of BPD, particularly for patients who do not use any of the more effective treatments.

Contributors

GJ and JPK designed the study with substantial input from LB, EF, and TZ. LB, GJ, and TZ collected the data. JPK and TZ analysed the data and verified the underlying data with substantial input from LB. NA and JPK interpreted the data and wrote the manuscript with substantial input from all the authors. All authors had full access to all the data in the study. All authors commented on the manuscript and approved the final version. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

AA reported receiving grants from the Netherlands Organisation for Health Research and Development and the Netherlands Foundation for Mental Health, and receiving other grants outside the submitted work from Netherlands Organisation for Scientific Research, Netherlands Organisation for Health Research and Development, Stichting Achmea Gezondheidszorg, CZ Fonds, Stichting Volksbond Rotterdam, and Stichting tot Steun Vereniging voor Christelijke Verzorging van Geestes-en Zenuwzieken; receiving royalties (paid to the university) from Academic Press, American Psychological Association Press, Beltz, Bohn Stafleu van Loghum, Boom Uitgevers, Cambridge University Press, Context Press, Guilford, De Tijdstroom, Oxford University Press, SAGE Publications, Uitgeverij Nieuwezijds, and Wiley; providing workshops and lectures on CBT, imagery rescripting, personality disorders, schema therapy, and small-scale research in clinical practice (remuneration to the

university) for the British Association for Behavioural and Cognitive Psychotherapies, Bulgarian Association for CBT, Clinical Academic Group for Psychotherapy Denmark, Danish Competence Centre for Psychotherapy, European Association for Behavioural and Cognitive Therapies, European College of Neuropsychopharmacology, European Society for the Study of Personality Disorders, Estonian CBT Association, German Psychosomatic Congress, Geestelijke Gezondheidszorg inGeest, Greek CBT Association, ICCP, Institut für Schematherapie Frankfurt, International Science Council, International Society for the Study of Personality Disorders, International Society of Schema Therapy, Jellinek, Kenniscentrum Persoonlijheidsstoornissen, Leiden University Medical Center, Lemion, Moroccan Association of CBT, Norwegian Psychological Association, Parnassia/PsyQ, Polish Association for Cognitive and Behavioral Therapies, Portuguese Association of Behaviour Therapy, Psyflix, SCEM, Scuole APC-SPC-SICC-IGB-AIPC, Tunisian Association of CBT, Turkish Association for Cognitive and Behavioural Psychotherapies, Ukraine Association for CBT, Ukraine Institute for CBT, University of Bordeaux, Vereniging voor Gedrags- en Cognitieve Therapieën, VST, and World Confederation of Cognitive and Behavioural Therapies; supervising research at the mental health institute PsyQ (remuneration to the University of Amsterdam); and being Chair of the board of the PDO foundation, north Holland postgraduate training institute (unpaid). NA provided workshops on schema therapy to the Institut für Schematherapie Hamburg and Ausbildungsinstitut für Verhaltenstherapie und Verhaltensmedizin Hannover; and received personal fees from supervision in schema therapy and received grants from University of Lübeck for an observational study and for open access publication fees (both outside the submitted work). TB reported receiving grants from the Swiss National Science Foundation, the Swiss Red Cross, the Swiss Cancer League, the German Ministry of Health, and the European Commission; received payments for books and book chapters from Hogrefe and Elsevier; and received payments for presentations and workshops on internet interventions, case conceptualisations in psychotherapy, and the therapeutic relationship in psychotherapy training programmes and conferences. LB is an employee of GAIA (Hamburg, Germany), which owns and runs the digital therapeutic in this trial. EF received grants outside the submitted work from the Else Kröner-Fresenius-Stiftung, the University of Lübeck, and Addisca; royalties from Beltz Verlag and Elsevier Books; personal fees for supervision, workshops, and presentations on CBT, imagery rescripting, personality disorders, schema therapy, and behavioural activation from Ausbildungsinstitut für Verhaltenstherapie und Verhaltensmedizin Hannover, Arbeitsgemeinschaft Wissenschaftliche Psychotherapie Berlin, German Association for Psychiatry and Psychotherapy, Institut für Psychotherapieausbildung Marburg, Institut für Therapie und Gesundheitsforschung gemeinnützige Kiel, Institut für Psychologische Psychotherapieausbildung Halle, Institut für Schematherapie Hamburg, Institut für Schematherapie Köln, Online Akademie für Psychotherapie, Institut für Schematherapie Berlin, Oberberg Kliniken, Sophie-Hufeland-Kliniken Weimar; is co-chair of the Deutscher Fachverband für Verhaltenstherapie eV (unpaid); and received payments from GAIA for presentations on schema therapy and consulting activities for designing digital therapeutics for patients with BPD. GJ is an employee of GAIA and has received payments for training from Training Institutes for Schema Therapy in Hamburg, Freiburg, Berlin, Cologne, Nuremberg, Stuttgart, and Bolzano, and published books and DVDs on schema therapy and treatment of BPD from Hogrefe and Beltz Publishing Group. JPK received funding for clinical trials from the German Federal Ministry of Health and Servier; payments for presentations on internet interventions from GAIA, Oberberg, Servier, and Stillachhaus; consulting fees from developers and distributors of internet interventions from All About Me, Ethypharm, and GAIA; payments for workshops and books on psychotherapy for chronic depression and psychiatric emergencies from Beltz, Elsevier, Hogrefe, and Springer; and serves as vice chairman of the chapter Digital Psychiatry of the German Psychiatric Association. AS received funding from University of Lübeck (Habilitationförderung für Wissenschaftlerinnen); personal fees for giving supervision in schema therapy and imagery rescripting; payments for manuscripts from Theme and workshops on schema therapy and imagery rescripting for ISST Hamburg; support for attending meetings or travel from Gesellschaft zur Erforschung und Therapie von Persönlichkeitsstörungen (Hamburger

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Data sharing

Data are available upon reasonable request. Individual participant data that underlie the results reported in this Article can be shared with researchers who provide a methodologically sound proposal to JPK (philip.klein@uksh.de). Proposals can be submitted up to 36 months after publication of this Article.

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