

Immediate and long-term effectiveness of adding an Internet intervention for depression to routine outpatient psychotherapy: Subgroup Analysis of the Evident Trial

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Public Health Significance Statement:

- Findings suggest that routine psychotherapy can be augmented by means of concomitant Internet treatment. Sustained gains were independent from therapeutic orientation of face-to-face psychotherapy, indicating general feasibility of adjunctive Internet treatment.

Running title: Combined Internet and face-to-face psychotherapy results in augmented effectiveness of routine outpatient psychotherapy

Highlights:

- This is the currently largest study on blended (face-to-face plus Internet-based) treatment for depression.
- Combined treatment resulted in augmented effectiveness of routine psychotherapy.
- Increases are comparable to those found in combined pharmaco- and psychotherapy studies.
- Treatment effects lasted over a 6-month follow-up period and were independent from therapeutic orientation of face-to-face psychotherapy.
- Limitations exist due to secondary data analysis and self-report assessment.

Objective: To examine immediate and long-term effectiveness of an adjunctive Internet intervention for depression in a large sample of patients undergoing routine psychotherapy.

Method: The current study evaluated a subgroup of patients from the Evident trial, a randomized investigation of a 12-week minimally guided Internet intervention (Deprexis) in the treatment of mild to moderate depression. 340 adults (mean age = 43.3 years; 71.7 % female) of the original sample received routine outpatient psychotherapy during the trial period, resulting in a standard psychotherapy group ($n = 174$) and an augmented therapy group ($n = 166$). Outcomes were assessed at baseline, post-treatment and 6-month follow-up.

Results: Intention-to-treat analyses indicated that combined treatment led to a greater reduction in symptoms of depression (effect size $d = 0.32$; $p = .002$), improved therapeutic progress ($d = 0.36$; $p = .003$), and higher mental health-related quality of life ($d = 0.34$; $p = .004$). There was no intervention effect on physical health-related quality of life. The same pattern was found at 6-month follow-up. Treatment success was independent from therapeutic orientation of combined face-to-face therapy. Median usage time of the adjunctive online intervention was 7.08 hours, indicating high patient engagement.

Conclusion: Results indicate that the adjunctive use of the investigated intervention can produce additional and lasting effects in routine outpatient psychotherapy for mild to moderate levels of depression. The study adds to the ongoing literature on augmented effects of blended treatment. Future studies should investigate different types of blends in diverse populations by means of change-sensitive assessment strategies.

1 Introduction

2 Over the last two decades, the evidence base for Internet interventions has grown steadily and
3 first routine online clinics have emerged (Hedman et al., 2014; El Alaoui et al., 2015; Titov et
4 al., 2018; Wells et al., 2018). While unguided Internet interventions provide wide reach at
5 potentially low cost (Karyotaki et al., 2017), programs that include guidance have been shown
6 to be associated with higher effectiveness and adherence rates (Baumeister, Reichler,
7 Munzinger & Lin; 2014; Wells et al., 2018). For this reason, many Internet interventions
8 entail some form of written guidance, or they are blended with occasional personal sessions
9 (e.g. diagnostic assessment, or treatment introduction).

10 Recent research has shown that Internet interventions might also help to improve face-to-face
11 therapy. In a first review on so-called blended cognitive behavioural therapy (bCBT), Erbe
12 and colleagues (2017) identified 44 studies on blended treatment. Since then additional high
13 quality studies have been carried out (Kleiboer et al., 2016; Thase et al., 2017; Vernmark et
14 al., 2018), and several of the above mentioned online clinics offer routine blended care (Titov
15 et al., 2018).

16 The term “blended therapy” usually refers to face-to-face treatment augmented with one or
17 more digital intervention elements (e.g. Internet-, app-, or VR-based interventions). Erbe and
18 colleagues (2017) distinguish between integrated and sequential interventions, with the latter
19 including Internet-based aftercare. Within integrated formats, in which Internet interventions
20 and face-to-face therapy are applied simultaneously, a further distinction can be made
21 between adjunctive (Berger et al., 2018; Zwerenz et al., 2017) and highly integrated
22 interventions. In many adjunctive treatments, both treatment strands (face-to-face and digital
23 elements) remain largely independent. Highly integrated treatments, by contrast, are designed
24 as new treatment rationales (cf. Kooistra et al., 2016; Schuster et al., 2019) or as a repository
25 of applications to be selected according to the individual course of face-to-face therapy

26 (Månsson, Ruiz, Gervind, Dahlin, & Andersson, 2013; Månsson, Klintmalm, Nordqvist, &
27 Andersson, 2017). Furthermore, it is likely that digital assessment and digital treatment will
28 merge into new approaches (e.g. EMI, ecological momentary intervention). A short overview
29 of empiric formats is provided in *Figure 1*.

30 ***** Figure 1 about here *****

31 Usually blended interventions are based on cognitive-behavioural therapy (CBT). Postulated
32 advantages are, for example, the improved self-management of patients, beneficial effects on
33 treatment transfer, repetition of CBT materials, or reduced travel times (Titzler, Saruhanjan,
34 Berking, Riper, & Ebert, 2018; Urech et al., 2018; van der Vaart et al., 2014), as well as
35 comparably high acceptance amongst stakeholders (Topooco et al., 2017; Schuster, Topooco,
36 Keller, Radvogin, & Laireiter, 2020). Risks and limitations can exist with regard to possible
37 over-structuring of therapy (Schuster, Sigl, Berger, & Laireiter, 2018), problems with non-
38 verbal communication (van der Vaart et al., 2014), or additional workload for therapists
39 (Titzler et al., 2018).

40 Blended treatments aim at increasing efficiency in terms of reduced therapist time, or in terms
41 of enhanced treatment effects. *Non-inferiority studies* consistently found comparable
42 outcomes in time-reduced treatments (Marks, Kenwright, McDonough, Whittaker, & Mataix-
43 Cols, 2004; Wright et al., 2005). Most recent studies support these findings. For example,
44 Thase and colleagues (2017) found comparable outcomes for a treatment in which face-to-
45 face sessions were reduced by two thirds. The study included 154 medication-free patients
46 suffering from major depression (MDD). In addition, a large European multicentre study on
47 depression (eCompared, www.ecompared.eu) is currently investigating the cost-effectiveness
48 of time-reduced bCBT over standard CBT (Kleiboer et al., 2016). Preliminary results of a
49 pilot study ($N = 102$) indicate potential savings on provider- but not on societal-level
50 (Kooistra et al., 2019). As an efficient alternative to individual therapy, blending might also

51 improve the delivery of group treatments, which have been tested for depression (Schuster et
52 al., 2018; Schuster et al., 2019), anxiety (Gruber, Moran, Roth, & Taylor, 2001; Newman,
53 Przeworski, Consoli, & Taylor, 2014), or hoarding (Fitzpatrick et al., 2018; Ivanov et al.,
54 2018).

55 With regard to *enhanced treatment effects*, several superiority studies with different
56 intervention designs have been carried out in the past. A relatively large number of studies
57 investigated sequential aftercare programs, which frequently led to enhanced effects (Bauer,
58 Wolf, Haug, & Kordy, 2011; Ebert, Tarnowski, Gollwitzer, Sieland, & Berking, 2013;
59 Hennemann, Farnsteiner, & Sander, 2018). For simultaneous bCBT (with digital support
60 during face-to-face therapy), Carroll and colleagues (2009; 2014) published a series of
61 articles, indicating that relapse rates and abstinence times for substance-related addictions
62 could persistently be improved by the use of individual- and group-based bCBT. This finding
63 is supported by comparable studies (cf. Christensen et al., 2014). For depression, however,
64 only few studies exist (cf. Berger, Krieger, Sude, Meyer, & Maercker, 2018; Sethi, Campbell,
65 & Ellis, 2010; Zwerenz et al., 2017). Berger and colleagues (2018) investigated the effects of
66 outpatient psychotherapy supplemented with an adjunctive Internet program ($N = 98$).
67 Enhanced effects ($d = 0.51$) were observed immediately after treatment, but during follow up
68 ($N = 44$) these effects diminished ($d = 0.28$) and failed to reach statistical significance. In a
69 second study, Zwerenz and colleagues (2017) found comparable results using the same
70 intervention in addition to routine inpatient treatment ($N = 229$). Compared to the active
71 control group (computer-assisted psychoeducation over 12 weeks) the combined treatment
72 again resulted in enhanced effects ($d = 0.44$). The corresponding follow-up results have been
73 published recently (Zwerenz et al., 2019).

74 To sum up, the evidence base for Internet interventions is growing rapidly, and the developed
75 interventions might also serve to enhance face-to-face therapy. Apart from considerable

76 evidence for sequential bCBT (e.g. in aftercare), the concomitant treatment of depression by
77 face-to-face therapy together with Internet interventions remains rarely investigated. At this
78 point, ongoing evidence indicates that such interventions could actually lead to augmented
79 effects in the treatment of depression, but more evidence building on preferably larger sample
80 sizes is required.

81 The purpose of the present study is to investigate the effects of an adjunctive treatment for
82 mild to moderate depression in routine care. It therefore reports on re-analyses of a
83 sufficiently large subsample ($N = 340$) of the Evident trial ($N = 1013$; Klein et al., 2016),
84 which received outpatient psychotherapy during the trial period. According to existing
85 literature, we hypothesized that combined treatment would result in enhanced immediate
86 effects, and that those effects would be maintained during the follow-up period. Furthermore,
87 we were interested in potential predictors of therapy success and intervention usage. A
88 considerable number of studies on Internet interventions tested relevant predictors, such as
89 age, attitudes towards digital treatment, or initial depression level (cf. Beintner et al., 2019).
90 Regarding simultaneous bCBT for depression, evidence is clearly limited by the small number
91 of conducted studies. However, two previous studies investigated potential predictors of
92 treatment utilization and effects in the context of the Evident study (Fuhr et al., 2018;
93 Schneider et al., 2018). Findings revealed, for example, a positive relation between higher age
94 or higher depressive symptoms and use of the intervention. Relations with treatment outcome,
95 however, were less clear (cf. Schneider et al., 2018; Fuhr et al., 2018). We therefore
96 investigated if those variables would exhibit a comparable pattern in the selected subsample
97 of the Evident trial, which received the Internet intervention as an adjunct to routine
98 psychotherapy.

99

100 Method

101 Study design

102 This study analysed a subsample which was taken from the EVIDENT trial ($N = 1013$; Klein
103 et al., 2016). Adhering to the CONSORT and the CONSORT-EHEALTH statement, this large
104 randomized multicentre study investigated the effectiveness of the Internet intervention
105 *Deprexis*. The trial was conducted at five sites in Germany after ethical approval by the Ethics
106 Committee of the German Psychological Association (SM042012), and after registration at
107 ClinicalTrials.gov (NCT01636752). In the principal study, participants were either
108 randomised to care as usual (CAU) or to CAU plus *Deprexis*. CAU of the original trial
109 comprised any form of treatment participants actively sought, including antidepressant
110 medication (50.2 %), and/or psychotherapy (33.6 %), and/or outpatient psychiatric treatment
111 (27.1 %), and/or treatment by general practitioner, or no formal treatment.

112 The present subsample ($N = 340$), however, received concomitant routine psychotherapy
113 during the trial period. Selection of the subsample was based on patients indicating to having
114 undergone routine psychotherapy at post-assessment of the EVIDENT trial. Of these patients,
115 $n = 174$ (17.2 % of the original sample) received psychotherapy and $n = 166$ (16.4 %)
116 received psychotherapy plus the adjunctive Internet intervention *Deprexis*. Thus, the first
117 group constituted the control condition, while the latter constituted the blended treatment
118 condition of the present study. Due to secondary data analysis, the exact onset of
119 psychotherapy did not coincide with time of randomization to both groups.

120

121 Participants

122 Recruitment of the original study began in 2012 and ended in 2015 (see the CONSORT flow
123 chart in Klein et al. 2016, p. 222). The current sub-sample included all patients undergoing
124 psychotherapeutic treatment at the time of the study ($N = 340$). Patients of the original study

125 were either recruited via outpatient medical or psychological clinics, or via a multimodal
126 recruitment strategy, including health insurance companies and public media (e.g. newspaper
127 or radio). The main inclusion criterion was presence of self-reported mild to moderate levels
128 of depression, defined as a score of 5 to 14 scale points on the Patient Health Questionnaire
129 (PHQ-9; Kroenke, Spitzer, & Williams, 2001). Eligible patients were able to communicate in
130 German, and their age ranged from 18 to 65 years. Acute suicidality, or a lifetime diagnosis of
131 schizophrenia or bipolar disorder constituted further exclusion criteria. Written informed
132 consent was obtained online prior to baseline assessment. Psychiatric diagnoses were based
133 on the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), and acute
134 suicidality was assessed by status of current suicidal ideation together with past suicide
135 attempts.

136 Interventions

137 Patients in both groups received full routine outpatient psychotherapy in Germany.
138 Psychotherapy in Germany is part of public health care, and, therefore, widely accessible and
139 free of charge. All included patients of both study conditions underwent routine
140 psychotherapy by trained psychotherapists from a low number of officially recognized
141 therapeutic orientations. The assignment of therapeutic orientation was based on self-report,
142 and half of the sample received one of the two common forms of psychotherapy (CBT: 23.7
143 %; or psychodynamic therapy (PDT): 22.5 %). A minor proportion of 2.7 % received
144 systemic therapy. The remaining patients either indicated to have received talk therapy or
145 client-centred therapy (20.1 %), or were not able to specify the respective treatment
146 orientation (26.0 %).

147 Patients in the bCBT study condition ($n = 166$) additionally received Deprexis as adjunctive
148 Internet intervention together with the above described forms of routine psychotherapy.
149 Deprexis is a 12-week CBT-based online programme which has been evaluated for mild to

150 moderate levels of depression (Berger, Hämmerli, Gubser, Andersson, & Caspar, 2011;
151 Meyer et al., 2009), as well as for severe depression (Meyer et al., 2015). A comprehensive
152 overview of studies is presented by Twomey, O'Reilly, & Meyer (2017). The programme
153 consists of ten modules (e.g. cognitive restructuring, behavioural activation, acceptance and
154 mindfulness, problem solving) and a summary module, presented by an algorithm to increase
155 tailoring of text- or audio-based elements (including automatized shifts between modules).
156 Automatized daily messages, delivered either by SMS or e-mail, supported the programme,
157 and all patients with moderate depressive symptoms (PHQ-9 > 9 scale points; $n = 109$)
158 received weekly asynchronous feedback by a trained, remotely operating supporter. The
159 generic feedback was restricted in time (approximately 5 minutes per message) and did not
160 apply specific therapeutic techniques, but was rather aimed to motivate patients to engage
161 with the provided online modules. Further information on the intervention and the provided
162 guidance is presented in the study protocol of the original trial (Klein et al., 2013).

163 Measures

164 The primary outcome was the digitalized version (Erbe, Eichert, Rietz, & Ebert, 2016) of the
165 9 item form of the Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001), a common
166 scale to assess severity of self-rated depression on a 4 step Likert-scale. The observed internal
167 consistency of the PHQ-9 can be classified as good (Cronbach's alpha = .821). According to
168 the authors, mild depression severity can be classified by scorings of 5 to 9 scale points,
169 whereas moderate depression severity is represented by scorings between 10 to 14 scale
170 points (Kroenke et al., 2001).

171 Furthermore, a measure of health-related quality of life (Short-Form Health Survey, SF12;
172 Ware, Kosinski, & Keller, 1996), and a measure for the Evaluation of Psychotherapeutic
173 Progress (Lutz et al., 2009) were employed in the study. The FEP-2 is a generic process
174 questionnaire with four latent factors (symptom severity, interpersonal problems,

175 psychological incongruence, and personal wellbeing). With Cronbach's alpha = .901 internal
176 consistency can be classified as excellent. The SF-12 is composed of the subscales mental
177 health (MH), and physical health (PH). As the scale includes three different types of Likert-
178 scales we did not calculate internal consistency. All measures were administrated online and
179 took place at pre-, post-, and 6-month follow-up.

180

181 Statistical analyses

182 Statistical analyses were based on the intent-to-treat principle (ITT), which included all
183 randomized patients of the selected subsample. The analyses were performed using SPSS 25,
184 and linear mixed models (LMM) were applied to test treatment by time interactions of the 2 x
185 3 factorial design. Under the assumption of random missing data, LMM yields the advantage
186 of providing unbiased estimates of treatment effects (Bell, Fiero, Horton, & Hsu, 2014). In
187 order to account for dependence of repeated measures, restricted maximum likelihood
188 estimation (REML) with compound symmetry (CS) was chosen in the model specifications.
189 To optimize statistical power, baseline assessments entered the analysis as covariates (van
190 Breukelen, 2006). Rates of clinically significant improvement for PHQ-9 were defined as less
191 than nine scale points during post-assessment (McMillan, Gilbody, & Richards, 2010),
192 combined with a 50 % symptom reduction. We used 50 % change from baseline as this
193 criterion classifies cases independently from their baseline level of depression (Karin, Dear,
194 Heller, Gandy, & Titov, 2018). For reliable deterioration (RD) two criteria were defined. The
195 standard RD criterion was defined as a 50 % increase from baseline. As this criterion should
196 identify a low number of subjects (in our case 7 % of the sample), statistical power to detect
197 differences in deterioration rates between groups is low. We therefore defined suboptimal to
198 reliably deteriorated cases as any deterioration above 25 % increase from pre- to post-
199 assessment, resulting in 12.6 % of critical cases in the sample.

200 Depending on their distribution, demographic variables of conditions were tested with *t* tests
201 for independent samples or with corresponding chi-squared tests to estimate success of
202 randomisation. Potential predictors of overall therapy success and of adherence with the
203 online part of the intervention were investigated by means of multiple linear regression, in
204 which baseline severity entered as independent predictor variable. Further predictor variables
205 from previous Deprexis studies (Fuhr et al., 2018; Schneider et al., 2018) constituted
206 demographic variables (age, gender, education, and relation status), as well as important
207 clinical variables (therapeutic orientation of concomitant psychotherapy, attitudes towards
208 Internet interventions, medication status, and level of baseline depression). Additionally, we
209 tested if adherence with the Internet intervention (e.g. time spent on platform) influenced
210 treatment success in a meaningful way. Adherence was assessed objectively by tracking
211 number of chats and minutes spent with the intervention.

212 All presented effect sizes were calculated according to Cohens' *d* (Cohen, 1988), by
213 subtracting the estimated mean of the experimental group from the mean of the control group.
214 Power calculation was based on G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) and
215 revealed statistical power of 80 % to detect between group differences in a factorial study
216 design with a treatment effect of $d = 0.25$, and correlation of repeated measures of $r = 0.3$.
217 Note that the baseline covariate is not implemented into the analysis and we do not report the
218 interaction term here, making the power calculation a conservative estimate.

219

220 Results

221 Patient characteristics

222 There were neither significant differences in baseline characteristics (*Table 1*), nor in
223 psychotherapeutic orientation of face-to-face treatment between both groups ($p = .119$ –

224 .996), and the study exhibited excellent retention of 88.8 % for the follow-up period. If not
225 corrected for alpha inflation, however, marital status ($\chi^2 = 2.32, p = .021$) and number of
226 depressed episodes ($\chi^2 = 2.05, p = .040$) would have deviated significantly. Overall, women
227 constituted the majority of the sample (71 %) and level of education can be considered
228 representative for Germany (54 % high school graduate or higher). Participants' age ranged
229 from 19 to 65 years ($M = 43.3, SD = 10.9$). About 84 % of the sub-sample fulfilled the criteria
230 for full MDD with a high number of self-reported recurring depressive episodes. Regarding
231 time of randomization, patients on average received 12 therapy sessions ($SD = 7.6$) before
232 pre-assessment, resulting in expectably smaller pre-to-post treatment effects for the present
233 subgroup analysis. A higher number of sessions was received by psychodynamic patients (M
234 $= 18, SD = 17$) and a lower number by patients undergoing systemic therapy ($M = 6.1, SD =$
235 1.4) Details on both groups' demographic and clinical characteristics are presented in *Table 1*.

236 ***** Table 1 about here *****

237

238 Intervention usage

239 A total of 166 participants was randomized to the 12 week blended format, with a small
240 fraction not using the program (0.9 % less than two sessions or 60 minutes). A somewhat
241 larger fraction only exhibited moderate program usage (4.1 % less than four sessions or 120
242 minutes). The median usage time was 425 minutes ($Q_{25-75} = 288 - 600$ minutes) or 7.08 hours.
243 The median number of therapist messages was 9 ($Q_{25-75} = 6 - 11$).

244

245 Main outcome

246 Based on hierarchical analyses (LMM) of the intention-to-treat sample, bCBT resulted in
247 higher treatment effects on the primary study outcome (PHQ-9: $F_{(2, 646.56)} = 6.21, p = .002; d$

248 = 0.32) compared to psychotherapy alone. Those differences remained stable at 6-month
249 follow-up (PHQ-9: $F_{(1, 342.86)} = 7.67, p = .006, d = 0.31$). Detailed information on estimated
250 scale means, standard deviations and effect sizes is provided in *Table 2*. Clinically significant
251 improvement was observed in 20.7 % of cases in the standard condition and 30.1 % in the
252 augmented group, indicating more clinically significant improvement for the latter ($\chi^2 = 1.99,$
253 $p = .046$). Rates of reliable deterioration (> 50 % from baseline) were 8 % for the standard
254 group and 6 % for the augmented group, indicating no significant differences ($\chi^2 = 0.73, p =$
255 $.468$). Finally, rates for suboptimal to reliable deterioration (deteriorations > 25 %) were 15 %
256 in the standard group and 10.2 % in the augmented group, indicating significant differences in
257 favour of the augmented treatment ($\chi^2 = 2.40, p = .017$).

258

259 Secondary outcomes

260 Most self-rated secondary outcomes indicated superior effects at termination of treatment.

261 While both psychological constructs, the SF-12 for mental health related quality of life ($F_{(2,$
262 $610.83)} = 5.63, p = .004, d = 0.34$), and the FEP-2 for overall therapy progress ($F_{(2, 635.89)} = 5.85,$
263 $p = .003, d = 0.36$), indicated augmented effects, no increases have been found for physical
264 health-related quality of life (SF-12 PH: $F_{(2, 606.28)} = 0.72, p = .488; d = 0.11$).

265 Regarding stability of secondary outcomes, a consistent pattern emerged. Together with the
266 primary outcome, overall therapy progress (FEP-2: $F_{(1, 315.53)} = 7.42, p = .007, d = 0.35$), as
267 well as mental health related quality of life (SF-12 MH: $F_{(1, 307.85)} = 3.59, p = .033, d = 0.22$)
268 indicated superiority of bCBT. Again, physical health-related quality of life was comparable
269 in both groups (SF-12 PH: $F_{(1, 295.42)} = 0.38, p = .536, d = -0.05$). Detailed information on scale
270 means, standard deviations and effect sizes is presented in *Table 2*.

271 ***** Table 2 about here *****

272

273 Predictors of therapy success and intervention usage

274 Depression severity at post-treatment was neither predicted by demographic variables (age,
275 gender, level of education, or relation status) nor by parameters of program utilization.

276 Neither of the z standardized utilization variables predicted the primary outcome PHQ-9 at
277 post-treatment ($p = .101 - .901$), nor at 6-month follow-up ($p = .027 - .910$), after Bonferroni
278 adjustment for alpha inflation had been applied. It was only predicted by baseline depression
279 severity ($\beta = .268, p = .002$). Regarding prediction of intervention usage, baseline depression
280 severity again emerged as clear predictor ($\beta = .221, p = .004$), indicating a positive relation
281 between severity of depression and utilization of the Internet intervention. Age was also
282 positively related to increased usage time ($\beta = .208, p = .008$). As a last aspect, therapeutic
283 orientation influenced intervention usage negatively ($\beta = -.280, p = .002$) if patients indicated
284 to have undergone client-centred or talk therapy.

285 ***** Table 3 about here *****

286

287 Discussion

288 This study analysed the effects of combined Internet-based and face-to-face treatment for
289 mild to moderate depression. In a subsample ($N = 340$) of the Evident trial (Klein et al., 2016)
290 the Internet intervention Deprexis was randomly added to outpatient psychotherapy, making
291 the study the presently largest investigation on long-term effects of bCBT. We found that
292 combined treatment was associated with immediate and long-term benefits for all assessed
293 psychological parameters (depression, mental health, and therapeutic progress), but not for
294 physical-health related quality of life (SF-12 PH). During 6-month follow-up those increases
295 remained stable, even though mental-health related quality of life diminished slightly ($d_{diff} =$

296 0.12). Thus, the present results indicate that the effectiveness of routine psychotherapy can be
297 augmented by adjunctive Internet treatment.

298 As Berger and colleagues (2018) suggest, a simple explanation for this effect is the additional
299 time patients invested in the treatment. The median patient spent about 7 hours with the
300 minimally supported intervention, which can be considered a reasonable amount of extra
301 therapy time. The argument of treatment intensification seems particularly plausible, as the
302 number of weekly sessions predicted the outcome of psychotherapy for depression in previous
303 studies (Cuijpers et al., 2013). Furthermore, homework engagement generally relates to
304 success of CBT (Conklin & Strunk, 2015; Kazantzis, Whittington, & Dattilio, 2010), and
305 bCBT has been described as treatment facilitator, fostering the reconsolidation of CBT
306 materials, as well as the transfer into daily life (Eitzelmueller, Radkovsky, Hannig, Berking, &
307 Ebert, 2018; Schuster et al., 2018; Urech et al., 2018). However, the assumption that more
308 online activity (e.g. time spend with the intervention, or number of logins) would result in
309 pronounced decreases of depression was not supported by the present study ($Beta = 0.018$ to -
310 0.043) - even though tracked usage patterns exhibited sufficient variability, and results from
311 the principal study indicated a weak but statistically significant relation (Klein et al., 2016).
312 Two possible explanations are that the relation between intervention usage and therapy
313 outcome might be more complex, or that intervention usage (formalized by online log files) is
314 not synonymous with effective engagement or actual therapy adherence in blended
315 interventions (Sieverink, Kelders, & van Gemert-Pijnen, 2017; Yardley et al., 2016).

316 Regarding immediate effectiveness, reported findings are in line with results from first bCBT
317 trials on depression (Berger et al., 2018; Sethi et al., 2010; Zwerenz et al., 2017). At this,
318 present effects appear a bit smaller ($d_{diff} = 0.1$) than in two current studies (Berger et al., 2018;
319 Zwerenz et al., 2017). While the use of different questionnaires for assessing depression
320 symptoms limits the interpretability of these marginal differences, smaller effects might also

321 relate to differences in sampling. Both studies included patients with severe levels of
322 depression (rather than mild to moderate levels), and meta-analyses suggest greater symptom
323 reductions with increased levels of depression (Bower et al., 2013). Moreover, the delayed
324 onset of face-to-face psychotherapy could have limited observable effects. On average, 12
325 therapy sessions were consumed before start of face-to-face treatment. To provide a reference,
326 German psychotherapy is free of charge and the average treatment (across therapeutic
327 orientations) endures 49.8 sessions (Rabe-Menssen et al., 2011). It is therefore probable, that
328 carefully designed studies in unrestricted samples would result in even higher gains in routine
329 care. Still, even the comparably moderate effects of the present study should be considered as
330 meaningful as they approach effects from combined antidepressant and psychotherapy
331 treatment (Cuijpers et al., 2014; Hedge's $g = 0.43$). As a last aspect, clinically significant
332 improvement was significantly higher in the blended treatment group, with comparable
333 proportions as reported in the German outpatient study by Berger and Colleagues (2018).
334 Regarding reliable deterioration, present findings suggest no significant difference between
335 standard and augmented treatment. As reliable deteriorations typically constitute comparably
336 rare events our study was underpowered to detect potential deviations, limiting interpretability
337 of present findings. When cases of mild deterioration are added ($> 25\%$ from baseline),
338 however, the augmented treatment resulted in improved outcomes. This pattern also fits the
339 reported improvements of therapeutic progress (assessed by FEP-2). Taken together, results
340 indicate that adding an adjunctive Internet intervention can lead to statistically and clinically
341 relevant improvements of routine psychotherapy for depression. Furthermore, the blended
342 format could contribute to reductions of undesired effects, at least when clinically mild
343 deteriorations are included.

344 Concerning long-term effectiveness of bCBT, the magnitude of observed improvement ($d =$
345 0.22 to 0.35) is consistent with first findings from one comparable study ($N = 98$) (Berger et

346 al., 2018). Due to the considerably larger sample size, the present study possessed statistical
347 power to detect the effect of adjunctive treatment more reliably. Supporting evidence can be
348 found for other mental disorders, such as substance-related addictions (Carroll et al., 2009;
349 Carroll et al., 2014), as well as for sequential bCBT in aftercare (Bauer et al., 2011; Ebert et
350 al., 2013; Hennemann et al., 2018), and the wider field of Internet interventions (Andersson,
351 Rozental, Shafran, & Carlbring, 2018). As potential improvement, long-term depression was
352 only assessed by means of self-report questionnaires. Future studies should therefore include
353 clinician ratings over a follow-up period of one year, which is in accordance with current
354 mental health research priorities (Wykes et al., 2015). Taken together, the present study can
355 be regarded as ongoing evidence for augmented and enduring effects of combined Internet-
356 based and face-to-face depression treatment.

357 Further strategies to optimize statistical power and to reduce required sample size are
358 advisable for future trials, as the improvement of current gold-standard treatments probably
359 will lead to moderate effects and conducting sufficiently large RCTs will impose high
360 financial costs. In this context, digital psychiatry could facilitate the implementation of
361 intense assessment, for example by weekly assessment or by short pre-post ecological
362 momentary assessment (EMA). The magnitude of expectable gains in statistical power is
363 considerable and could help to mitigate the current situation without necessarily increasing
364 sample sizes. For example, a hypothetical RCT with point assessments of psychopathology
365 (pre-post assessment by questionnaire) would need 90 patients, but 8 (bi-) weekly assessments
366 during the active trial phase reduce the required sample size to 42 - 50 patients. Additionally,
367 short EMA has previously been tested to substitute point assessments of psychopathology in
368 randomized controlled trials (Moore, Depp, Wetherell, & Lenze, 2016; Vork et al., 2019;
369 Schuster et al., 2020). As app-based assessments can easily be implemented into bCBT
370 (Newman et al., 2014; Kleiboer et al., 2016; van de Ven et al., 2017; Colombo et al., 2018),

371 digital mental health interventions could facilitate both, the provision and evaluation of
372 psychological treatments.

373 As a last aspect, we investigated potential predictors of bCBT. At this, baseline depression
374 severity emerged as the only significant predictor, suggesting effectiveness of bCBT
375 independently from basic patient characteristics. The present study also explored the impact
376 of therapeutic orientation on combined therapy, with results indicating that adjunctive online
377 treatment can improve face-to-face psychotherapy regardless of its orientation. This finding
378 fits both previous bCBT superiority trials, as one was conducted in a psychodynamic inpatient
379 setting (Zwerenz et al., 2017), while the other investigated outpatient CBT (Berger et al.,
380 2018). Regarding utilization of the Internet intervention, engagement was higher in more
381 depressed individuals and it was positively related to age. This result is in accordance with
382 prior findings (Fuhr et al., 2018; Schneider et al., 2018), and may be related to increased
383 motivation or conscientiousness of those groups. Furthermore, patients indicating to have
384 participated in client-centred (CP) or talk therapy exhibited less compliance with tracked
385 online tasks. This result, however, needs to be interpreted with caution as therapy orientation
386 was based on self-report, and client-centred and (more general) talk therapy can be
387 confounded due to similarity in German language. Taken together, the present findings
388 suggest no relation between demographic characteristics or type of face-to-face treatment and
389 effectiveness of bCBT. Additionally, some predictors of intervention usage have been found,
390 but the literature in the field for now remains inconclusive (Beatty & Binnion, 2016).

391 This study has noteworthy strengths and limitations. Amongst its most important strengths,
392 the principal study (Klein et al., 2016) was based on a multiple recruitment strategy and those
393 involved in the current study received publicly funded high quality routine psychotherapy
394 from several different clinics, settings, and therapeutic orientations in Germany. Furthermore,
395 the adjunctive use of the Internet intervention reduced potential interferences with the

396 respective routine treatment. Regarding its evaluation, the study was based on assessments of
397 psychopathology, therapeutic progress and mental health. During the evaluation, a consistent
398 pattern of improvements in psychological but not in physical scales emerged, indicating low
399 risk of overall response bias. As a last aspect, the study exhibited very low attrition during the
400 follow-up period.

401 Regarding the study limitations, issues of intervention and trial design need to be considered
402 when interpreting its findings. Firstly, due to secondary data analysis the onset of
403 psychotherapy did not coincide with the time of randomization to the study groups. Instead,
404 randomization to the actual trial frequently lagged behind the onset of psychotherapy.
405 Therefore, the reported pre-to-post effects could underestimate the true impact of routine
406 psychotherapy, while the influence on reported between-group effect sizes appears less
407 impactful (cf. paragraph three of the discussion section). Secondly, the investigated blended
408 format was based on an adjunctive algorithm-driven online intervention which originally was
409 not designed to operate together with face-to-face therapy (Berger et al., 2011; Meyer et al.,
410 2009). It is therefore not specifically adjusted to face-to-face treatment, but rather works in
411 parallel on a relatively low level of integration. Thus, the effects of alternative designs, for
412 example with digital CBT-elements on-demand (Månsson et al., 2013; Månsson et al., 2017)
413 or with more manualized blends (Koositra et al., 2016; Schuster et al., 2019), might present
414 differently. Thirdly, the standard treatment condition only received routine psychotherapy, but
415 lacked an active online condition (e.g. online psychoeducation), which potentially could have
416 reduced the observed effects (Munder et al., 2018) or the risk for introducing bias. Contrary to
417 this limitation, however, the first study with active online control condition found superior
418 effects of comparable magnitude (Zwerenz et al., 2018), and we found a consistent pattern of
419 differential effects for psychological and physical variables in the present study. Still, future
420 studies should implement active controls in order to reduce potential sources of bias (e.g.

421 expectancy bias). Fourthly, regardless of the comparably large overall sample size certain
422 study findings should be interpreted with caution due to limited statistical power. According
423 to the provided power estimation, the study can be regarded sufficiently sensitive to detect
424 proposed effects of blended treatment. Furthermore, power for multiple linear regression
425 (deviation from zero in a fixed model, with medium effect size of $f^2 = 0.15$) for 10 predictors
426 was 99 %; and 96 % for a small effect of $f^2 = 0.08$. However, power to detect a medium
427 correlation of $r = 0.3$ for one unevenly distributed variable (low program utilization) was only
428 50 %. As a last aspect, the classification of face-to-face treatment was based on self-report.
429 While the proportions of CBT and PDT appear reliable, the CP group might have confounded
430 the subcategory client-centred therapy with talk therapy (as a non-specific expression for
431 psychotherapy in general). Therefore, this groups' reduced intervention usage cannot be
432 attributed with safety, and, thus, needs to be clarified in further studies.

433 Conclusion

434 Taken together, the present findings add to the ongoing literature on augmented effects of
435 combined Internet-based and face-to-face treatment for MDD. The effects of combined
436 treatment correspond to ongoing evidence from previous studies, with clinically meaningful
437 increases which persisted over time. Potential predictors of intervention usage were identified,
438 but treatment effectiveness was largely independent from such variables. Thus, bCBT should
439 be further investigated in the striving to optimize current gold-standard treatments. Future
440 studies should test diverse interventions in active control designs, together with more sensitive
441 assessment strategies of psychopathology.

442

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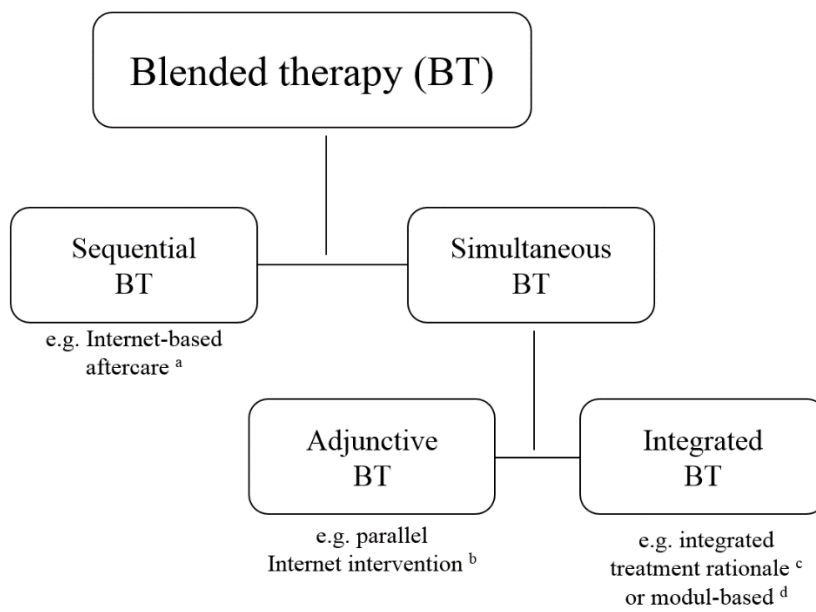


Figure 1. Types of blended treatment.

^a cf. Ebert et al., 2013. ^b cf. Berger et al., 2018. ^c cf. Kooistra et al., 2016. ^d cf. Månsson et al., 2017

Table 1. Demographic and clinical variables presented by treatment condition. Frequencies, means and standard deviations (in brackets).

Variable	Blended treatment (<i>n</i> = 166)		Standard treatment (<i>n</i> = 174)	
	<i>n</i>	%	<i>n</i>	%
Gender				
Female	119	71.7	125	71.8
Male	47	28.3	49	28.2
Mean age (<i>SD</i>)	43.3 (11.3)		43.3 (10.4)	
Marital status				
Single	37	22.3	51	29.3
Partnership	41	24.7	31	17.8
Married	65	39.2	75	43.1
Divorced	20	12.0	16	9.2
Widowed	3	1.8	1	0.6
Education				
Compulsory or technical school	80	48.2	77	44.3
High school graduate or higher	86	51.8	97	55.7
Diagnosis (self-reported diagnoses)				
Depression (MDD)	139	83.7	148	85.1
Anxiety disorder	61	36.7	57	32.8
PTSD	24	14.5	29	16.7
Eating disorder	18	10.8	15	8.6
History of depression (self-report)				
< 2 depressive episodes	23	13.9	33	19.0
2-5 depressive episodes	65	39.2	77	44.3
6-10 depressive episodes	39	23.5	37	21.3
> 10 depressive episodes	39	23.5	27	15.5
Medication	139	83.7	147	84.5
Combined treatment				
CBT	49	29.5	69	39.7
PDT	40	24.1	31	17.8
CP	48	28.9	58	33.3
Other	29	17.5	16	9.1

Note. MDD = major depressive disorder; PTSD = post-traumatic stress disorder; SD = standard deviation; CBT = cognitive behavioural therapy; PDT = psychodynamic therapy; CP = client-centred or talk therapy.

Table 2. Descriptive statistics and effect sizes of main and secondary outcomes.

	Estimated means						Between effect sizes (estimated means)	
	Pre (<i>SE</i>)		Post (<i>SE</i>)		Follow-up (<i>SE</i>)		Post (Cohen's <i>d</i> ; [CI])	Follow-up (Cohen's <i>d</i> ; [CI])
	Blended therapy (<i>n</i> =166)	Standard therapy (<i>n</i> =174)	Blended therapy (<i>n</i> =166)	Standard therapy (<i>n</i> =174)	Blended therapy (<i>n</i> =166)	Standard therapy (<i>n</i> =174)		
PHQ-9	10.51 (0.298)	10.24 (0.292)	7.85 (0.289)	9.00 (0.262)	7.22 (0.312)	8.39 (0.269)	- 0.32** [- 0.11; - 0.53]	- 0.31 ** [- 0.09; - 0.52]
FEP-2	2.92 (0.047)	2.95 (0.046)	2.56 (0.047)	2.78 (0.046)	2.48 (0.049)	2.70 (0.048)	- 0.36 ** [- 0.15; - 0.58]	- 0.35 ** [- 0.13; - 0.56]
SF-12 MH	30.90 (0.798)	31.18 (0.777)	37.96 (0.808)	34.41 (0.786)	39.83 (0.847)	37.45 (0.823)	0.34 ** [0.13; 0.56]	0.22 * [0.01; 0.43]
SF-12 PH	47.08 (0.749)	47.04 (0.729)	46.73 (0.756)	47.79 (0.735)	46.64 (0.783)	47.12 (0.762)	- 0.11 [-0.32; 0.10]	- 0.05 [-0.26; 0.17]

Note. SE = standard error; PHQ-9 = Patient Health Questionnaire; FEP-2 = Questionnaire for the Evaluation of Psychotherapeutic Progress, SF-12 = Short-Form Health Survey; CI = 95 % confidence interval.

Table 3. Predictors of therapy success and online usage time

Predictor	PHQ-9 post score		Usage time	
	<i>Beta</i>	<i>p</i>	<i>Beta</i>	<i>p</i>
Age	-.036	.668	.208	.008 **
Gender	.078	.353	.124	.107
Education	.124	.131	.165	.028
Relation status (in relation)	-.063	.434	.018	.810
PHQ-9 baseline score	.268	.002 **	.221	.004 **
MASKED [Attitudes towards Internet-based treatment]	-.049	.555	.045	.566
Medication	.103	.211	-.025	.615
Combined treatment (CBT)	-.101	.279	.053	.545
Combined treatment (DP)	-.028	.732	-.083	.281
Combined treatment (CP)	-.105	.280	-.280	.002 **
No moderate usage (120 mins. or more)	-.159	.101	--	--
Usage (in minutes)	-.043	.901	--	--
Number of chats	.018	.750	--	--

Note. PHQ-9 = Patient Health Questionnaire; MASKED = Attitudes towards Internet-based treatment (MASKED); CBT = cognitive behavioural therapy; PDT = psychodynamic therapy; CP = client-centred or talk therapy; ** = significant after Bonferroni correction ($p < .01$).