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1 **Internet-based Cognitive Behavioral Therapy for Depression**

2 **An Individual Patient Data Network Meta-Analysis**

3

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7

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23

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25

26 **Key Points**

27 **Question:** What are the patient-specific relative effects of guided versus unguided iCBT for
28 depression over the short- and the long-term?

29

30 **Findings:** Patients differ in response to guided versus unguided iCBT. Individuals with
31 mild/subthreshold depression may have little or no benefit from therapeutic guidance, while
32 guided iCBT is superior in moderate and severe depression. Both iCBT modalities
33 outperformed the TAU regardless of depression severity.

34

35 **Meaning:** Although guided has greater effects compared to unguided iCBT on average,
36 many people with depression may still benefit from the iCBT without therapeutic guidance.
37 Optimising treatment assignment would considerably expand treatment coverage worldwide.

38

39 **IMPORTANCE** Personalized treatment choices would increase the effectiveness of internet-
40 based Cognitive Behavioral Therapy (iCBT) for depression to the extent that patients differ in
41 interventions that better suit them.

42

43 **OBJECTIVES** We aimed to provide personalized estimates of short- and long-term relative
44 efficacy of guided and unguided iCBT for depression, utilizing patient-level information.

45

46 **DATA SOURCES** We searched PubMed, Embase, PsycINFO and Cochrane Library to
47 identify randomized controlled trials (RCTs) published up to January 1st, 2019.

48

49 **STUDY SELECTION** Eligible RCTs were those comparing guided or unguided iCBT
50 against each other or against any control intervention in individuals with depression. We
51 sought individual patient data (IPD) from all eligible studies. Depression symptom severity
52 was assessed post-treatment, six- and 12-months post-randomization.

53

54 **DATA EXTRACTION AND SYNTHESIS** We conducted an IPD network meta-analysis
55 (IPD-NMA) and estimated relative treatment effects across different patient characteristics
56 through IPD network meta-regression.

57

58 **MAIN OUTCOME AND MEASURES** Patient Health Questionnaire-9 scores (PHQ-9)

59

60 **RESULTS** Of 42 eligible RCTs, 39 comprising 9,751 participants with depression
61 contributed IPD to our IPD-NMA, of which we were able to synthesize 8107 IPD. Overall,
62 both guided and unguided iCBT were more effective than controls over the short- and the
63 long-term. Guided iCBT was more effective than unguided iCBT [mean difference (MD) in
64 post-treatment PHQ-9 scores = -0.8, 95% Confidence Interval (CI) -1.4 to -0.2], but we found
65 no evidence of a difference at six- or 12-months post-randomization. Baseline depression was
66 found to be the most important modifier of the relative efficacy of guided versus unguided
67 iCBT. Differences between unguided and guided iCBT in people with baseline symptoms of
68 subthreshold depression (PHQ-9 scores 5-9) were small while guided iCBT resulted in
69 overall better outcomes in patients with baseline PHQ-9 > 9. We developed an interactive
70 web application generating estimated relative effects according to patients' characteristics:

71 <https://cinema.ispm.unibe.ch/shinies/iCBT/>

72

73 **CONCLUSION AND RELEVANCE** Although guided iCBT is on average more
74 efficacious than unguided iCBT for depression, benefits are more substantial in moderate to
75 severe depression. Unguided iCBT is as effective as guided iCBT among individuals with
76 symptoms of mild/subthreshold depression. Personalized treatment selection is entirely
77 possible and necessary to ensure the best allocation of treatment resources for depression.
78

79 Depression is a major public health issue, taking an enormous toll on individuals, public
80 healthcare systems, and society as a whole.¹⁻³ Broadly accessible treatment is required to
81 reduce this burden.⁴ Both psychotherapy and pharmacotherapy can treat depression
82 effectively.⁵ Nevertheless, psychotherapy is unavailable to the majority of the world's
83 population due to costs, availability of trained clinicians, and stigma.⁶ Further, the current
84 (COVID-19) pandemic has displaced and dislocated mental health services, while social and
85 community containment measures, associated distress, loss and potential financial difficulties
86 are likely to be long lasting and impactful.^{7,8}

87

88 Over the past 20 years, the mental health care available for depression has undergone a major
89 technological revolution. Psychological interventions, such as Cognitive Behavioral Therapy
90 (iCBT), are increasingly delivered over the internet.⁹ These interventions can be delivered
91 either with or without therapeutic support, usually termed guided and unguided iCBT.
92 Unguided iCBT is more scalable and affordable,^{10,11} but previous studies have shown that
93 guidance generally results in better outcomes.¹² These studies have mainly reported group
94 average effects of iCBT, providing little insight into patient attributes that may differentiate
95 outcomes. It may be that some patients are helped as much by unguided as guided iCBT. If
96 so, knowledge of attributes that predict such individual differences could be valuable in
97 guiding optimized resource allocation. Doing this is challenging as extensive examination of
98 prognostic moderator variable requires thousands of patients to be compared in order to
99 achieve sufficient statistical power.

100

101 'Individual patient data' network meta-analysis (IPD-NMA) is an evidence synthesis method
102 that can be used to estimate the relative efficacy of multiple competing interventions by
103 pooling individual patient data across multiple studies.^{13,14} As this approach uses patient-level
104 data, interactions between baseline individual characteristics and treatment type can be
105 examined with more power than in individual trials.¹⁵

106

107 We performed an IPD-NMA to investigate the relative efficacy of guided versus unguided
108 iCBT for depression and the influence of patient characteristics on their relative efficacy.

109

110 **Methods**

111 The methods are described in detail in our study protocol (for discrepancies, see
112 Supplement).¹⁶

113

114 **Eligibility Criteria**

115 Eligible studies were: (a) randomized controlled trials (RCTs); (b) comparing either guided
116 and unguided iCBT against each other, or against any type of control condition (treatment as
117 usual, waitlist); (c) in adults with depressive symptoms, as established by specified cut-offs
118 on self-report scales or diagnostic interviews. Studies were excluded if the intervention: (a)
119 did not include cognitive restructuring as one of the main components; (b) was delivered only
120 through smartphones; (c) was blended with face-to-face treatment¹⁷; and (d) targeted
121 primarily a physical illness. No language restrictions were applied.

122

123 ‘Unguided iCBT’ was defined as CBT delivered via the internet, where automated and
124 technical support was permitted, but not support related to the therapeutic content.¹⁸ ‘Guided
125 iCBT’ was defined as CBT delivered via the internet that involved therapeutic support, either
126 synchronous or asynchronous, delivered by a professional or a paraprofessional (non-
127 specialists in mental health care but trained to deliver iCBT).

128

129 **Study Identification and Selection Process**

130 We used our established database of RCTs examining psychological treatments for adult
131 depression. This database is based on ongoing systematic searches of PubMed, Embase,
132 PsycINFO, and the Cochrane Library, and has been described in detail elsewhere.¹⁹ The
133 search algorithm for PubMed is available in the Supplement. We also searched reference lists
134 from previous meta-analyses and asked primary authors whether they were aware of other
135 eligible studies.

136

137 **Data Collection and Data Items**

138 The authors provided de-identified data for each patient, where available: baseline, six and
139 12-month post-randomization scores of depressive symptoms, age, sex, educational level
140 (primary, secondary, tertiary education), relationship status (in relationship yes/no),
141 employment status (employed, unemployed, student, other), and treatment adherence
142 (number of completed sessions / total number of sessions). Variables were chosen based on
143 previous literature^{20,21} and availability across included trials. We also extracted study-level
144 information (i.e., recruitment method). After obtaining all eligible datasets, two independent

145 authors merged all eligible datasets (EK and CM) and checked the data for accuracy against
146 the published reports of the papers.

147

148 **Risk of bias assessment**

149 Two independent authors (EK and FMgB) assessed the risk of bias in the included studies
150 using four items of the Cochrane Risk of bias tool: (a) random sequence generation, (b)
151 allocation concealment, (c) selective outcome reporting, and (d) other possible sources of
152 bias (i.e., baseline differences between the groups).²² We did not evaluate blinding of
153 participants, personnel, and assessors, because our primary outcome is based on self-report
154 measures, and blinding is rarely possible in psychotherapy research. We considered a trial at
155 high risk of attrition bias if it had overall >50% study dropout and/or >30% imbalance in
156 missing outcomes between groups.¹⁶

157

158 **Data Analysis**

159 This NMA focused on the differential effects of the examined interventions on depression
160 symptom severity on the Patient Health Questionnaire-9 (PHQ-9)²³ at post-treatment. PHQ-9
161 was the most commonly used scale across the eligible studies (available for 4703 participants
162 across 15 studies). Other depression scales were converted into PHQ-9 scores using
163 established conversion algorithms²⁴. When no conversion algorithms existed, the study was
164 excluded. Outcomes were assessed at post-treatment, six- and 12-months post-randomization.
165 To assess transitivity in the network¹⁴, we checked the distribution of possible effect
166 modifiers in the studies grouped by comparison. We assessed heterogeneity by estimating
167 prediction intervals for all pairwise meta-analyses (PMAs), and via the estimated values of τ
168 for aggregate data NMAs (AD-NMA). We checked inconsistency in the networks using a
169 local approach ('back-calculation')²⁵ as well as a global test ('design-by-treatment').²⁶ To
170 retain patients with missing outcomes in analyses, we created 20 multiply imputed datasets
171 using the jomo package in R, taking into account the stratification of patients in studies.²⁷ In
172 each multiply imputed dataset we performed PMAs after grouping studies comparing the
173 same two interventions, as well as AD-NMA using the netmeta package in R.²⁸ We assumed
174 random treatment effects, allowing for a common heterogeneity parameter (τ) for all
175 comparisons in the network. This parameter corresponds to the standard deviation of the
176 random effects of across trials (assumed normal). We synthesized results from all datasets
177 using Rubin's rules.²⁹

178

179 As a sensitivity analysis, we performed a complete case analysis, i.e. only including patients
180 with information on their final outcome at post-intervention and follow-up assessments. In
181 addition, we ran a series of subgroup network meta-analyses to test possible differences in the
182 examined studies: (i) commercial vs. nonprofit iCBT programs; (ii) guidance provided by
183 paraprofessionals/ lay therapists vs. BA/ MSc/ PhD student in Clinical psychology vs.
184 licensed psychologists and/or psychotherapists; (iii) Studies conducted in the USA vs. other;
185 and (iv) studies that originally used PHQ-9 vs other. To facilitate clinical interpretation of our
186 findings, we calculated response rates ($\geq 50\%$ reduction of the baseline symptoms) for the
187 comparison guided vs. unguided iCBT. To further explore the effect of baseline severity on
188 response rates, we ran a subgroup analysis using baseline PHQ-9 scores: < 10 (mild
189 depressive symptoms); 10-15 (moderate depression); 15-19 (moderately severe depression);
190 > 19 (severe depression).

191

192 Next, we performed a separate Bayesian IPD network meta-regression in each multiply
193 imputed dataset. To avoid possible issues with overfitting, and aiming at better
194 generalizability of results, we used Bayesian LASSO to model treatment-covariate
195 interactions. Bayesian analyses were performed using rjags in R.³⁰

196

197 To assess small study effects (publication bias) that might compromise the validity of our
198 results, we created contour-enhanced funnel plots and performed Egger's test³¹ to check for
199 asymmetry, after grouping active treatments. To explore whether there were systematic
200 differences between available and unavailable studies that did not provide IPD, we
201 synthesized the latter in AD-NMA, and compared results with the former. More details about
202 the statistical methods are provided in the Supplement. Finally, we used the shiny package in
203 R to develop a web application to showcase all results from our IPD network meta-regression
204 model.

205

206 To evaluate the certainty of evidence, we used the GRADE methodology (Supplement).³²

207

208 **Results**

209 **Study Selection and IPD obtained**

210 The PRISMA flow diagram shows the study selection process (Supplement). Up to January
211 2019, we screened 2552 full texts and identified 42 eligible RCTs, 39 of which provided

212 patient-level data on 9751 individuals.³³⁻⁷¹ Three studies (7%) did not contribute their data
213 due to university regulations^{72,73} or administrative burden.⁷⁴

214

215 **Study Characteristics**

216 Table 1. presents the study characteristics. Twenty-four out of 39 included studies recruited
217 participants in the community, 11 through clinical or mixed sources, and four used other
218 recruitment sources (i.e., workplace). Twenty-one studies compared the effects of guided
219 iCBT to control, and 13 studies unguided iCBT to control. Control groups included treatment
220 as usual (n = 15) and waitlist (n = 22). Five studies compared guided and unguided iCBT
221 directly with each other. Twelve studies used a commercial iCBT program, while in 27 RCTs
222 the iCBT program was developed in-house/ nonprofit. The interventions comprised 5 to 18
223 online sessions (mean = 8.0, SD = 2.8) delivered over five to 14 weeks (mean = 9 weeks, SD
224 = 2.5). In guided iCBT groups, guidance was provided by paraprofessionals/ lay therapists (n
225 = 6), BA/ MSc/ PhD student in Clinical psychology (n = 14), and licensed psychologists
226 and/or psychotherapists (n = 5). Figure 1 shows the network graph. The studies were
227 conducted across 12 countries (across Europe, North America, and China).

228

229 **Risk of Bias Assessment**

230 Overall, risk of bias was low across the included studies. All but one study had an acceptable
231 sequence generation and allocation concealment. One trial was at high risk of selection bias
232 because the study recruiter drew colored balls from a bag to randomize.⁶² We had access to
233 the full databases of the included studies, thus we could use all available depression measures
234 regardless of whether they have been included in the published reports of the trials.
235 Therefore, all trials were at low risk of selective reporting. Moreover, the included trials were
236 free from other sources of bias except for one study that reported baseline imbalances.³⁶
237 Following our protocol¹⁶, we did not evaluate performance and assessment bias. However,
238 we acknowledge that performance bias can occur and accordingly, we have considered this in
239 our GRADE assessment (Supplement). Finally, we retained all randomized individuals in our
240 analysis and thus our findings are at relatively low risk of attrition bias.

241

242 **IPD Synthesis**

243 Of the 9751 participants in the 39 studies, 1071 (10.9%) did not have usable information on
244 our primary outcome measure (i.e., there was no established algorithm to convert the
245 depression measure into PHQ-9 scores^{34,45}) and were excluded from further analyses. We

246 also excluded 312 participants because their baseline depression scores were below the
247 threshold of mild depressive symptoms (PHQ-9 < 5). Finally, one study had 50% dropout in
248 the intervention and 0% in the control.⁶¹ Following the protocol, we excluded this study from
249 all subsequent analyses (Supplement). Thus, we report the outcomes of 8107 patients across
250 36 studies. The PHQ-9 mean (SD) scores at baseline were 13.7 (4.3) for guided iCBT, 14.2
251 (4.9) for unguided iCBT, 15.2 (5.3) for TAU, and 13.2 (4.6) for waitlist and at post-treatment
252 7.6 (5.0), 9.2 (5.9), 9.8 (SD 5.5), and 12.0 (6.4) for guided iCBT, unguided iCBT, TAU, and
253 waitlist, respectively. Overall, assessment of transitivity did not indicate systematic
254 differences across comparisons.

255

256 **Aggregated Data Network Meta-Analyses**

257 All pairwise meta-analyses are reported in the Supplement. There was evidence of
258 considerable heterogeneity in most comparisons. The outcomes of AD-NMAs at post-
259 treatment assessment (Table 2) indicated that guided iCBT was more effective than unguided
260 iCBT [mean difference (MD) in PHQ-9 = -0.8, 95% Confidence Interval (CI) -1.4 to -0.2],
261 TAU (MD = -1.7, 95% CI -2.3 to -1.1) and waitlist (MD = -3.3, 95% CI -3.9 to -2.6).
262 Unguided iCBT reduced symptoms compared to TAU (MD = -0.9, 95% CI -1.5 to -0.3) and
263 waitlist (MD = -2.5, 95% CI -3.2 to -1.8). The heterogeneity parameter was $\tau = 0.6$. Main
264 results are also presented as Standardized Mean Difference (SMD) in Supplement. Similar
265 outcomes were observed using a complete cases analysis and when including only recent
266 trials (published after 2012 and 2013 - Supplement). Moreover, the CI of the estimates
267 largely overlapped in the rest of the examined subgroups, suggesting that there was no strong
268 evidence of subgroup differences (Supplement). The average study dropout rate was 25% for
269 guided iCBT, 29% for unguided iCBT, 19% for waitlist, and 22% for TAU. Among the 25
270 studies reporting on treatment adherence, the average adherence was 76% for guided iCBT
271 and 54% for unguided iCBT.

272

273 Eight studies reported six-month post-randomization data. Results of AD-NMA showed no
274 significant difference between guided and unguided iCBT at six months (Table 3). Both
275 guided and unguided iCBT reduced depressive symptoms compared to TAU at 6-months
276 post-randomization (MD for guided iCBT vs. TAU = -1.1, 95% CI, -1.7 to -0.5). Similar
277 outcomes were observed across eight studies reporting on 12-month post-randomization
278 outcomes (MD for guided iCBT vs. TAU = -0.5, 95% CI, -1.1 to 0.1).

279

280 In all analyses, we found no evidence of network inconsistency, but we found weak evidence
281 of publication bias.

282

283 **Response rates**

284 Overall, 48% of participants receiving guided iCBT responded, while 37% responded in
285 unguided iCBT. When splitting participants into severity groups, we found that 46% of those
286 with moderate depressive symptoms at the baseline (n = 3164) responded in the guided iCBT
287 group compared to 39% in the unguided iCBT group (difference in response rate: 7%).
288 However, 55% of those with moderately severe symptoms (n = 1762) at the baseline
289 responded in the guided iCBT group compared to 40% in unguided iCBT (difference in
290 response rate: 13%). Results of response rates are provided in the Supplement.

291

292 **IPD Network Meta-analyses**

293 We performed an IPD network meta-regression using baseline depression severity, gender,
294 age, relationship and employment status as covariates that were reported in the majority of
295 the studies. Results indicated that baseline severity was the most important prognostic factor.
296 Higher depression at baseline was associated with higher symptoms at all post-treatment
297 assessments. Not being employed was also associated with poorer outcomes, while gender
298 had a minimal effect (Supplement). We found strong evidence that baseline severity modified
299 the relative effects of guided and unguided iCBT, such that the higher the baseline severity,
300 the larger the benefit of therapeutic guidance. For a PHQ-9 of 5-9 (mild/subthreshold
301 depression) there was either no or a small difference in post-intervention outcome between
302 guided and unguided iCBT. However, guided iCBT resulted in better outcomes than
303 unguided iCBT for moderate depression (PHQ-9 = 10-14), with increasing advantage
304 estimated for moderately severe (PHQ-9 = 15-19) and severe depression (PHQ-9 > 19). Both
305 iCBT modalities were superior to TAU and waitlist regardless of baseline severity. Common
306 τ was 0.9. Because of the large number of possible combinations of patient characteristics,
307 we provide the estimates of guided compared to unguided iCBT at post-treatment for four
308 random case examples in Table 4. The full range of estimated relative treatment effects for
309 any combination of patient covariates, at post-treatment, six- and 12-month post-
310 randomization can be explored using an interactive online application:
311 <https://cinema.ispm.unibe.ch/shinies/iCBT/>.

312

313 There was no evidence of a systematic difference between available and unavailable studie⁷²⁻
314 ⁷⁴ (Supplement).

315

316 **Discussion**

317 We assessed data from 36 RCTs including 8107 participants with symptoms of depression
318 from 12 countries. Both guided and unguided iCBT were associated with greater reduction in
319 depressive symptoms than TAU and waitlist at post-treatment, at six- and 12-months post-
320 randomization. Overall, guided iCBT was more effective than unguided iCBT at post-
321 treatment, but differences diminished over the long-term. Because both unguided and guided
322 iCBT were associated with better outcomes than control conditions over the long-term,
323 unguided iCBT has considerable potential for improving long-term results of interventions
324 with constrained economic and workforce resources. However, baseline severity was a
325 substantial modifier of the differential benefit of guided over unguided iCBT, suggesting that
326 even the short-term incremental benefit of guided versus unguided iCBT is limited to patients
327 with baseline PHQ-9 scores of > 9.

328

329 The finding that guided iCBT is more effective than unguided is consistent with previous
330 literature examining their average effects.¹² The methodology of IPD-NMA allowed us to
331 identify subgroups of patients for whom such average effects might not apply. For instance,
332 post-treatment effects of guided and unguided iCBT do not differ among male patients with
333 mild depressive symptoms who were employed and in a relationship. The effect-modifying
334 role of baseline severity is in line with previous research showing that individuals with more
335 severe initial depression are more likely to respond to guided internet-based interventions.⁷⁵

336

337 The finding that unguided iCBT was more effective than TAU in both the short and longer-
338 term contrasts with the findings of our previous conventional NMA, which showed no
339 evidence of difference between unguided iCBT and TAU at post-treatment.¹² However, in the
340 present IPD-NMA we could include two of the largest RCTs examining the effects of
341 unguided iCBT^{49,70} (> 2000 participants), which were not included in our previous work.¹²
342 Also, our current analyses were performed using all randomized participants, which is not
343 always possible in conventional NMAs. Therefore, the present IPD-NMA provides stronger
344 evidence and improves the precision of previous findings.

345

346 We were also able to identify long-term differential effects in subgroups of patients (see the
347 online application: <https://cinema.ispm.unibe.ch/shinies/iCBT/>). Conclusions regarding
348 longer-term outcomes should be interpreted cautiously due to the small number of studies
349 (n=8), although these studies had large sample sizes and our analyses had adequate power (n
350 > 3700 at both follow-ups).

351

352 **Strengths and Limitations**

353 Among the strengths of the present study was its high power to detect effect modification, by
354 synthesizing IPD from direct and indirect comparisons. Moreover, we examined differential
355 effects of guided and unguided iCBT in both the short- and the long-term. We were also able
356 to include the vast majority of eligible RCTs (93%) with 8107 participants, making this the
357 largest study on individual patient differences in response to iCBT for depression to date.
358 Finally, the risk of bias in the included trials was overall low and we did not find strong
359 evidence for small-study effects, publication bias or network inconsistency, suggesting that
360 our analyses were relatively free from critical biases.

361

362 Some limitations should be considered when interpreting our findings. First, we were not able
363 to examine all factors previous research has indicated as influencing depression prognosis
364 (i.e., duration of symptoms, number of previous episodes, comorbidities). In an effort to
365 retain as many observations as possible, we focused on commonly reported variables across
366 the included trials. Second, the included trials were mostly conducted in Western countries,
367 potentially limiting the generalizability to other settings. Third, although the estimated
368 difference between guided and unguided iCBT is small in some individuals with mild
369 symptoms (i.e., if baseline PHQ-9 = 7), the confidence intervals of the pooled estimates are
370 wide, suggesting that we cannot yet exclude the possibility of a clinically significant benefit of
371 guided over unguided iCBT. Finally, only 9 studies recruited participants mainly from
372 clinical settings. However, these were some of the largest studies included in the present IPD-
373 NMA (n = 4269 participants). Therefore, in this sample there was a good representation of
374 patients referred from clinical services. Furthermore, people seeking treatment in the
375 community represent the population that is likely to access iCBT services in the real-world.

376

377 **Conclusions**

378 The present findings open new avenues for treatment decision making. Sub-threshold
379 depression (PHQ-9 = 5-9) is prevalent in approximately 15%-20% of the general

380 population.^{23,76,77} Given that individuals with mild depressive symptoms may benefit
381 comparably from guided and unguided iCBT, the latter could be disseminated to a large
382 number people experiencing mild depressive symptoms at a favorable cost, with therapeutic
383 guidance being prioritized for patients with moderate and severe symptoms. Further,
384 currently, a plethora of online self-help programs are available in the community. Individuals
385 who seek self-treatment on the internet are making an implicit “no guidance” choice. Our
386 work indicates that this may not be the best choice for everyone and that individuals signing
387 up for fully automated programs should be advised that they might benefit from therapeutic
388 support working through the program.

389

390 To further inform personalized treatment selection, future studies should systematically
391 examine a range of possible effect modifiers, such as number of previous depressive
392 episodes, symptom duration, concurrent use of medications, and comorbidities. Such trials
393 should examine the actual clinical utility of these predictors, for instance, by using adaptive
394 treatment strategies.⁷⁸ Future efforts should also focus on challenges of scaling up iCBT,
395 including improving adherence, especially for unguided programs. Furthermore, only few
396 studies include disadvantaged individuals who may experience difficulties in using the
397 internet due to poverty, locality or education. Moreover, future trials should investigate
398 whether outcomes differ by ethnic or racial minority status and how to enrich our knowledge
399 on how to approach different groups in the population. Finally, before disseminating and
400 implementing iCBT widely, it is important to further examine its effectiveness and
401 acceptability in treating major depression in primary and secondary mental healthcare
402 settings. Further research is warranted on actual dissemination and implementation of iCBT.

403

404 In summary, personalized treatment selection is possible and very much needed, as “one size
405 doesn’t fit all”. To assist clinicians and patients in choosing the right iCBT modality, we have
406 developed an interactive application available at <https://cinema.ispm.unibe.ch/shinies/iCBT/>
407 Shared clinical decision making should involve the patients’ values and preferences, history
408 and any previous or concurrent treatments so as to provide the best and most suitable
409 intervention while maximizing human resources available.

410

411 **Authors Contributions:** EK, OE, HR, TAF, and PC designed the study and protocol. AM,
412 AWG, ASY, AL, ADW, AM, AG, AvS, BM, CB, CK, CGB, CB, DRS, DCM, DK, DR, EL,
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415 SLR, SG, SM, TB, VP, VK, VS, and YF contributed data to the IPD-NMA. OE did the
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417 and revisions to the draft manuscripts and approved the final manuscript.

418

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439

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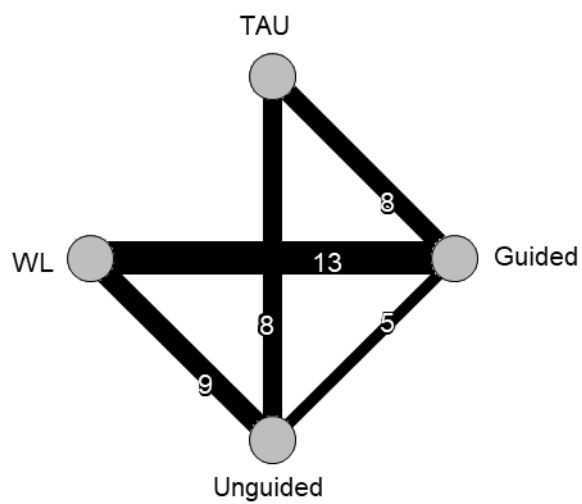


Figure 1. Network plot for depression severity at post-treatment under guided iCBT, unguided iCBT, treatment as usual (TAU) or waiting list (WL). Edges are weighted according to the number of studies for each comparison, also denoted upon each edge.

Table 1. Studies Characteristics

Study	Sample	PHQ-9 BL (SD)	Comparison	N	Sessions/ weeks	Commercial program	ECoaches Category ^a	FU (m)	RoB ^b	Country
Andersson et al. 2005 ³³	Com.	14.2 (4.9)	Guided iCBT vs. WL	124	5s/ 8w	No	B	-	0	SE
Beevers et al. 2017 ³⁴	Com.	N/A ^b	Unguided iCBT vs. WL	376	11s/ 8w	Deprexis	N/A	-	0	US
Berger et al. 2011 ³⁵	Com.	15.5 (4.2)	Unguided vs. Guided iCBT vs. WL	76	11s/ 10w	Deprexis	B	-	0	CH
Choi et al. 2012 ³⁶	Com.	11.1 (4.5)	Guided iCBT vs. WL	55	6s/ 8w	No	A	-	1	AU
Christensen et al. 2004 ³⁷	Com.	8.8 (5.1)	Unguided iCBT vs. AP	525	5s/ 6w	No	N/A	6; 12	0	AU
de Graaf et al. 2011 ³⁸	Com.	14.7 (3.8)	Unguided iCBT vs. TAU	303	9s/ 9w	No	N/A	6; 12	0	NL
Farrer et al. 2011 ³⁹	Other	16.1 (5.1)	Unguided iCBT vs. TAU	155	5s/ 6w	No	N/A	-	0	AU
Forand et al. 2017 ⁴⁰	Com.	16.9 (4.2)	Guided iCBT vs. WL	89	8s/ 8w	BtB US b	B	-	0	US
Forsell et al. 2017 ⁴¹	Com.	11.6 (3.6)	Guided iCBT vs. TAU	42	10s/ 10w	No	B	-	0	SE
Geraedts et al. 2014 ⁴²	Other	10.9 (3.6)	Guided iCBT vs. TAU	231	6s/ 6w	No	B	6;12	0	NL
Gilbody et al. 2015 ⁴³	Clin.	16.6 (4.2)	Unguided iCBT vs. TAU	691	6s/ 6w	BtB	N/A	12	0	UK
Gilbody et al. 2017 ⁴⁴	Clin.	16.4 (3.9)	Unguided vs. Guided iCBT	454	6s/ 6w	No	A	12	0	UK
Hallgren et al. 2016 ⁴⁵	Mixed	N/A ^c	Guided iCBT vs. TAU	629	14s/ 12w	No	B	-	0	SE
Johansson et al. 2012 ⁴⁶	Com.	13.7 (3.9)	Guided iCBT vs. AP	121	10s/ 10w	No	B	6	0	SE
Kessler et al. 2009 ⁴⁷	Clin.	20.7 (3.6)	Guided iCBT vs. WL	297	10s/ 14w	No	C	-	0	UK
Kivi et al. 2014 ⁴⁸	Clin.	13.9 (4.6)	Guided iCBT vs. TAU	90	7s/ 12w	Depressionshjälpen®	C	-	0	SE
Klein, et al. 2016 ^{49; d}	Mixed	10.2 (2.4)	Unguided vs. Guided iCBT vs. TAU	1013	11s/ 12w	Deprexis	B	6	0	DE
Lintvedt et al. 2013 ⁵⁰	Com.	8.5 (4.8)	Unguided iCBT vs. WL	163	5s/ 5w	No	N/A	-	0	NO
Meyer et al. 2009 ⁵¹	Com.	17.4 (5.4)	Unguided iCBT vs. WL	396	11s/ 9w	Deprexis	N/A	-	0	DE
Meyer et al. 2015 ⁵²	Mixed	16.9 (3.6)	Unguided iCBT vs. TAU	163	11s/ 12w	Deprexis	N/A	6	0	DE
Milgrom et al. 2016 ⁵³	Com.	11.9 (3.9)	Guided iCBT vs. TAU	43	6s/ 6w	No	B	-	0	AU
Mira et al. 2017 ⁵⁴	Com.	4.9 (3.9)	Unguided iCBT vs. WL	124	8s/ 12w	No	N/A	-	0	ES
Mohr et al. 2013 ⁵⁵	Clin.	15.5 (4.9)	Unguided vs. Guided iCBT vs. WL	101	18s/ 12w	No	A	-	0	US
Montero-Marín et al.	Clin.	11.8 (2.8)	Unguided vs. Guided iCBT vs. TAU	296	10s/ 10w	No	C	6; 12	0	ES

2016⁵⁶

Moritz et al. 2012 ⁵⁷	Com.	15.3 (5.2)	Unguided iCBT vs. WL	210	11s/ 8w	Deprexis	N/A	-	0	DE
Perini et al. 2009 ⁵⁸	Com.	14.1 (4.2)	Guided iCBT vs. WL	45	6s/ 8w	No	C	-	0	AU
Phillips et al. 2014 ⁵⁹	Other	14.6 (5.5)	Unguided iCBT vs. AP	637	5s/ 5w	No	N/A	-	0	UK
Pugh et al. 2016 ⁶⁰	Com.	9.9 (2.8)	Guided iCBT vs. WL	50	7s/ 10w	No	B	-	0	CA
Richards et al. 2015 ⁶¹	Com.	11.1 (2.3)	Guided iCBT vs. WL	188	7s/ 8w	Mind Balance v.1	A	-	0	IE
Rosso et al. 2016 ⁶²	Com.	14.7 (3.9)	Guided iCBT vs. AP	78	6s/ 10w	No	A	-	1	US
Ruwaard et al. 2009 ⁶³	Com.	13.9 (3.8)	Guided iCBT vs. WL	54	8s/ 11w	Interapy	B	-	0	NL
Sheeber et al. 2012 ⁶⁴	Other	12.6 (5.3)	Guided iCBT vs. WL	70	8s/ 14w	No	A	-	0	US
Smith et al. 2017 ⁶⁵	Com.	16.6 (4.1)	Unguided iCBT vs. WL	112	6s/ 12w	No	N/A	-	0	AU
Spek et al. 2007 ⁶⁶	Com.	9.8 (3.9)	Unguided iCBT vs. WL	202	8s/ 8w	No	N/A	12 ^e	0	NL
Vernmark et al. 2010 ⁶⁷	Com.	15.1 (4.1)	Guided iCBT vs. WL	58	7s/ 8w	No	B	-	0	SE
Warmerdam et al. 2008 ⁶⁸	Com.	13.8 (3.8)	Guided iCBT vs. WL	263	8s/ 8w	No	B	-	0	NL
Williams et al 2013 ⁷¹	Com.	12.8 (4.6)	Guided iCBT vs. WL	63	6s/ 10w	No	C	-	0	AU
Yeung et al. 2017 ⁶⁹	Clin.	12.3 (4.9)	Unguided iCBT vs. WL	75	5s/ 5w	No	N/A	-	0	CN
Zagorscak et al. 2018 ⁷⁰	Clin.	11.7 (3.4)	Unguided vs. Guided iCBT	1089	7s/ 6w	No	B	6; 12	0	DE

Abbreviations: AP = attention placebo; AU = Australia; BL = Baseline; CA = Canada; CH = Switzerland; Clin. = Clinical; CN = China; Com = Community; DE = Germany; ES = Spain; FU = Follow-up; iCBT = internet- based Cognitive Behavioral Therapy; IE = Ireland; m = months; Mixed = community and clinical sample; N = total number of participants; N/A = not available; NL = the Netherlands; NO = Norway; PhQ-9 = Patient Health Questionnaire – 9 Items; RoB = Risk of Bias Assessment; SD = Standard deviation; SE = Sweden; TAU = treatment as usual; UK = United Kingdom; US = United States; vs. = versus; W = weeks; WL = waiting list

^aECoaches categories: A = Paraprofessionals/ Lay therapists; B = BA/ MSc/ PhD student in Clinical psychology; C = Licensed psychologists and/or psychotherapists; N/A: not applicable – unguided iCBT trial

^bSum of high-risk quality criteria: i. sequence generation, ii. allocation concealment, iii. selective reporting, iv. Other sources of bias. A value of 1 was assigned in case of high risk of bias while 0 was assigned when the risk of bias was low.

^cDepression scales could not be converted into PHQ-9 scores

^dKlein et al. 2016 trial provided therapeutic support to participants with moderate symptoms of depression at the baseline (PHQ-9 > 9) while participants with mild depressive symptoms received no support throughout the trial. Participants of this trial were stratified by severity of depression during randomization and thus, we decided to split this trial into two (unguided iCBT vs. TAU & guided iCBT vs. TAU) in all the analyses of the present IPDNMA.

^eParticipants in the waiting list group received the intervention after the end of the trial.

Table 2. Aggregated meta-analytic effects for efficacy at post-treatment

Guided iCBT	-0.6 (-1.6 to 0.3)	-1.7 (-2.5 to -0.9)	-3.3 (-4.1 to -2.6)
-0.8 (-1.4 to -0.2)	Unguided iCBT	-0.9 (-1.5 to -0.2)	-2.5 (-3.3 to -1.6)
-1.7 (-2.3 to -1.1)	-0.9 (-1.5 to -0.3)	TAU	-
-3.3 (-3.9 to -2.6)	-2.5 (-3.2 to -1.8)	-1.6 (-2.4 to -0.8)	WL

The number in each cell shows the relative treatment effects between the column-defining treatment and the row-defining treatment. The outcome is depression symptom severity in PHQ-9, and results are presented as Mean Difference - MD (95% Confidence Intervals). Estimates below the diagonal are derived from aggregated data network meta-analysis, where MD<0 favors the column-defining treatment of each cell. Estimates above the diagonal are derived from the pairwise meta-analyses, where MD<0 favors the row-defining treatment of each cell.

Abbreviations: iCBT: internet-based Cognitive Behavioral Therapy; TAU: treatment as usual; WL: waiting list

Table 3. Aggregated meta-analytic effects for efficacy over the long-term

6 months post-randomization			
Guided iCBT	-0.2 (-0.8 to 0.3)	-1.1 (-1.5 to -0.4)	-
-0.1 (-0.6 to 0.3)	Unguided iCBT	-1.2 (-1.7 to -0.6)	-
-1.1 (-1.7 to -0.5)	-1.0 (-1.5 to -0.5)	TAU	-
12 months post-randomization			
Guided iCBT	0.1 (-0.4 to 0.6)	-0.8 (-1.8 to 0.2)	-
0.0 (-0.4 to 0.5)	Unguided iCBT	-0.6 (-1.2 to 0.0)	-1.1 (-2.3 to 0.2)
-0.5 (-1.1 to 0.1)	-0.6 (-1.1 to 0.0)	TAU	-
-1.1 (-2.4 to 0.3)	-1.1 (-2.3 to 0.2)	-0.5 (-1.9 to 0.8)	WL

Interpretation of this Table as per Table 2.

Table 4. Case examples of individual patient response to guided vs. unguided iCBT vs. TAU. A mean difference (MD) < 0 for the comparison of A vs. B favors treatment A.

Case ^a	PHQ-9 BL	Age	Relationship status	Sex	Employment Status	Guided vs. Unguided MD (95% CrI)	Guided vs. TAU MD (95% CrI)	Unguided vs. TAU MD (95% CrI)
1	25	35	Not in relationship	F	Unemployed	-2.2 (-3.6, -0.8)	-3.3 (-4.8, -1.8)	-1.1 (-2.2, -0.1)
2	14	41	Not in relationship	F	Employed	-0.9 (-1.7, -0.1)	-1.9 (-2.7, -1.0)	-0.9 (-1.7, -0.2)
3	10	55	In relationship	M	Employed	-0.2 (-1.2, 0.7)	-1.3 (-2.3, -0.4)	-1.1 (-1.9, -0.3)
4	8	65	In relationship	M	Other	0.2 (-1.1, 1.5)	-1.0 (-2.3, 0.3)	-1.2 (-2.4, -0.1)

Abbreviations: BL: baseline; CrI: credible intervals; F: female; M: male; MD: Mean Difference; PHQ-9: Patient Health Questionnaire - 9 items; TAU: treatment as usual

^aThese are case examples of fictitious patients.