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**Article:**

Karyotaki, Eirini, Efthimiou, Orestis, Sanz, Clara Miguel et al. (70 more authors) (2021) Internet-based Cognitive Behavioral Therapy for Depression : An Individual Patient Data Network Meta-Analysis. *JAMA Psychiatry*. pp. 361-371. ISSN 2168-6238

<https://doi.org/10.1001/jamapsychiatry.2020.4364>

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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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6 the Individual Patient Data Meta-Analyses for Depression (IPDMA-DE) Collaboration  
7

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23

24 Word Count for text only: 3515 words

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 1<sup>st</sup>, 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.<sup>1-3</sup> Broadly accessible treatment is required to  
81 reduce this burden.<sup>4</sup> Both psychotherapy and pharmacotherapy can treat depression  
82 effectively.<sup>5</sup> Nevertheless, psychotherapy is unavailable to the majority of the world's  
83 population due to costs, availability of trained clinicians, and stigma.<sup>6</sup> 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.<sup>7,8</sup>

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.<sup>9</sup> 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,<sup>10,11</sup> but previous studies have shown that  
93 guidance generally results in better outcomes.<sup>12</sup> 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.<sup>13,14</sup> 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.<sup>15</sup>

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).<sup>16</sup>

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 treatment<sup>17</sup>; 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.<sup>18</sup> ‘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.<sup>19</sup> 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<sup>20,21</sup> 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).<sup>22</sup> 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.<sup>16</sup>

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)<sup>23</sup> 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 algorithms<sup>24</sup>. 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 network<sup>14</sup>, 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  $\tau$   
168 for aggregate data NMAs (AD-NMA). We checked inconsistency in the networks using a  
169 local approach ('back-calculation')<sup>25</sup> as well as a global test ('design-by-treatment').<sup>26</sup> 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.<sup>27</sup> 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.<sup>28</sup> We assumed  
174 random treatment effects, allowing for a common heterogeneity parameter ( $\tau$ ) 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.<sup>29</sup>

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.<sup>30</sup>

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 test<sup>31</sup> 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).<sup>32</sup>

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.<sup>33-71</sup> Three studies (7%) did not contribute their data  
213 due to university regulations<sup>72,73</sup> or administrative burden.<sup>74</sup>

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.<sup>62</sup> 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.<sup>36</sup>  
237 Following our protocol<sup>16</sup>, 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<sup>34,45</sup>) 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.<sup>61</sup> 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  $\tau$  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 studie<sup>72-</sup>  
314 <sup>74</sup> (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.<sup>12</sup> 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.<sup>75</sup>

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.<sup>12</sup> However, in the  
340 present IPD-NMA we could include two of the largest RCTs examining the effects of  
341 unguided iCBT<sup>49,70</sup> (> 2000 participants), which were not included in our previous work.<sup>12</sup>  
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.<sup>23,76,77</sup> 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.<sup>78</sup> 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,  
413 EF, FF, FW, GA, HH, HC, IDE, IC, IMR, JPK, JS, JG-C, JM, JS, JM-M, JM. N, JBL, JS,  
414 KV, LB, LBS, LW, LF, MH, MJHH, M, MK, NRF, NP, NL, OL, PZ, PC, RP, RJ, SB, SP,  
415 SLR, SG, SM, TB, VP, VK, VS, and YF contributed data to the IPD-NMA. OE did the  
416 analysis. EK wrote the initial draft of the manuscript, and all authors provided critical input  
417 and revisions to the draft manuscripts and approved the final manuscript.

418

419 **Conflict of Interest Disclosures:** CGB reports receiving grant support from the National  
420 Institute of Health and compensation from the Association for Psychological Science for his  
421 work as a journal editor. In the past 3 years, RCK received support for his epidemiological  
422 studies from Sanofi Aventis; was a consultant for Datastat, Inc, Sage Pharmaceuticals, and  
423 Takeda; TAF reports personal fees from Mitsubishi-Tanabe, MSD and Shionogi, and a grant  
424 from Mitsubishi-Tanabe, outside the submitted work. TAF has a patent 2018-177688  
425 pending.

426

427 **Funding/ Support:** Dr Eirini Karyotaki was supported by the Netherlands Organization for  
428 Health Research and Development (NWO; project number 019.182SG.001). Dr Orestis  
429 Efthimiou was supported by project grant No. 180083 from the Swiss National Science  
430 Foundation (SNSF).

431

432 **Role of the Funder/Sponsor:** the Netherlands Organization for Health Research and  
433 Development and the Swiss National Science Foundation had no role in the design and  
434 conduct

435 of the study; collection, management, analysis, and interpretation of the data; preparation,  
436 review, or approval of the manuscript; and decision to submit the manuscript for publication.  
437 The decision to submit the article for publication was a condition of the funding and was  
438 made before any results were available.

439

440 **Additional Contributions:** Dr Eirini Karyotaki and Dr Orestis Efthimiou had full access to  
441 all the data in the study and takes responsibility for the integrity of the data and the accuracy  
442 of the data analysis. We would like to dedicate this research to the memory of Dr Jeroen  
443 Ruwaard, formerly of the GGZ in Geest Specialized Mental Health Care in Amsterdam, who  
444 contributed individual patient data from an original trial to this IPD-NMA but sadly passed



445 away during this project. Therefore, we would like to express our sincere appreciation to  
446 Jeroen's contribution to the field of internet-based interventions.

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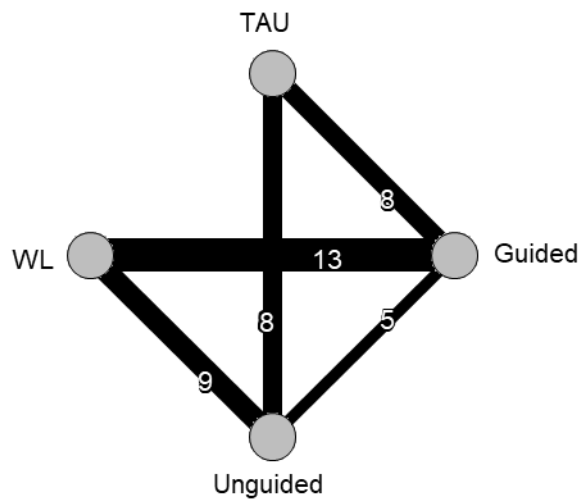
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**Figure 1.** Network plot for depression severity at post-treatment under guided iCBT, unguided iCBT, treatment as usual (TAU) or waiting list (WL). Edges are weighted according to the number of studies for each comparison, also denoted upon each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

**Table 1. Studies Characteristics**

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



2016<sup>56</sup>

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

<sup>a</sup>ECoaches 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

<sup>b</sup>Sum 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.

<sup>c</sup>Depression scales could not be converted into PHQ-9 scores

<sup>d</sup>Klein 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.

<sup>e</sup>Participants 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 <sup>a</sup>	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

<sup>a</sup>These are case examples of fictitious patients.