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Internet-based Cognitive Behavioral Therapy for Depression

An Individual Patient Data Network Meta-Analysis

Eirini Karyotaki, PhD;[1,2,3] Orestis Efthimiou, PhD[4,5], Clara Miguel Sanz, MSc [2,3]; Frederic Maas genannt Bermpohl, MSc[6]; Toshi A. Furukawa[7]*, MD, PhD[6]; Pim Cuijpers, PhD[2,3]*; for the Individual Patient Data Meta-Analyses for Depression (IPDMA-DE) Collaboration

*Toshi A. Furukawa and Pim Cuijpers share last authorship

[1]Department of Global Health and Social Medicine, Harvard Medical School, Boston, USA
[2]Department of Clinical Neuro- and Developmental Psychology, Vrije Universiteit Amsterdam, the Netherlands
[3]Amsterdam Public Health Research Institute, Amsterdam, the Netherlands
[4]Institute of Social and Preventive Medicine, University of Bern, Switzerland
[5]Department of Psychiatry, University of Oxford, Oxford, United Kingdom
[6]Department of Clinical Psychology and Psychotherapy, University of Wuppertal, Wuppertal, Germany
[7]Departments of Health Promotion and Human Behavior and of Clinical Epidemiology, Kyoto

Corresponding Author:

Dr Eirini Karyotaki,

Eirini_karyotaki@hms.harvard.edu or e.karyotaki@vu.nl

Department of Global Health and Social Medicine, Harvard Medical School

641 Huntington Avenue, Boston, MA 02115, USA

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Key Points

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Methods

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

Eligibility Criteria

Eligible studies were: (a) randomized controlled trials (RCTs); (b) comparing either guided and unguided iCBT against each other, or against any type of control condition (treatment as usual, waitlist); (c) in adults with depressive symptoms, as established by specified cut-offs on self-report scales or diagnostic interviews. Studies were excluded if the intervention: (a) did not include cognitive restructuring as one of the main components; (b) was delivered only through smartphones; (c) was blended with face-to-face treatment[17]; and (d) targeted primarily a physical illness. No language restrictions were applied.

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

Study Identification and Selection Process

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

Data Collection and Data Items

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

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

Risk of bias assessment

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

Data Analysis

This NMA focused on the differential effects of the examined interventions on depression symptom severity on the Patient Health Questionnaire-9 (PHQ-9)[23] at post-treatment. PHQ-9 was the most commonly used scale across the eligible studies (available for 4703 participants across 15 studies). Other depression scales were converted into PHQ-9 scores using established conversion algorithms[24]. When no conversion algorithms existed, the study was excluded. Outcomes were assessed at post-treatment, six- and 12-months post-randomization. To assess transitivity in the network[14], we checked the distribution of possible effect modifiers in the studies grouped by comparison. We assessed heterogeneity by estimating prediction intervals for all pairwise meta-analyses (PMAs), and via the estimated values of τ for aggregate data NMAs (AD-NMA). We checked inconsistency in the networks using a local approach ('back-calculation')[25] as well as a global test ('design-by-treatment').[26]To retain patients with missing outcomes in analyses, we created 20 multiply imputed datasets using the jomo package in R, taking into account the stratification of patients in studies.[27] In each multiply imputed dataset we performed PMAs after grouping studies comparing the same two interventions, as well as AD-NMA using the netmeta package in R.[28] We assumed random treatment effects, allowing for a common heterogeneity parameter (τ) for all comparisons in the network. This parameter corresponds to the standard deviation of the random effects of across trials (assumed normal). We synthesized results from all datasets using Rubin's rules.[29]

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

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

To assess small study effects (publication bias) that might compromise the validity of our results, we created contour-enhanced funnel plots and performed Egger's test[31] to check for asymmetry, after grouping active treatments. To explore whether there were systematic differences between available and unavailable studies that did not provide IPD, we synthesized the latter in AD-NMA, and compared results with the former. More details about the statistical methods are provided in the Supplement. Finally, we used the shiny package in R to develop a web application to showcase all results from our IPD network meta-regression model.

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

Results

Study Selection and IPD obtained

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

patient-level data on 9751 individuals.[33-71] Three studies (7%) did not contribute their data due to university regulations[72,73] or administrative burden.[74]

Study Characteristics

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

Risk of Bias Assessment

Overall, risk of bias was low across the included studies. All but one study had an acceptable sequence generation and allocation concealment. One trial was at high risk of selection bias because the study recruiter drew colored balls from a bag to randomize.[62] We had access to the full databases of the included studies, thus we could use all available depression measures regardless of whether they have been included in the published reports of the trials. Therefore, all trials were at low risk of selective reporting. Moreover, the included trials were free from other sources of bias except for one study that reported baseline imbalances.[36] Following our protocol[16], we did not evaluate performance and assessment bias. However, we acknowledge that performance bias can occur and accordingly, we have considered this in our GRADE assessment (Supplement). Finally, we retained all randomized individuals in our analysis and thus our findings are at relatively low risk of attrition bias.

IPD Synthesis

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

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

Aggregated Data Network Meta-Analyses

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

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

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

Response rates

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

IPD Network Meta-analyses

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

There was no evidence of a systematic difference between available and unavailable studie[72-74] (Supplement).

Discussion

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

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

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

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

Strengths and Limitations

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

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

Conclusions

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

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

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

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

Authors Contributions: EK, OE, HR, TAF, and PC designed the study and protocol. AM, AWG, ASY, AL, ADW, AM, AG, AvS, BM, CB, CK, CGB, CB, DRS, DCM, DK, DR, EL, EF, FF, FW, GA, HH, HC, IDE, IC, IMR, JPK, JS, JG-C, JM, JS, JM-M, JM. N, JBL, JS, KV, LB, LBS, LW, LF, MH, MJHH, M, MK, NRF, NP, NL, OL, PZ, PC, RP, RJ, SB, SP, SLR, SG, SM, TB, VP, VK, VS, and YF contributed data to the IPD-NMA. OE did the analysis. EK wrote the initial draft of the manuscript, and all authors provided critical input and revisions to the draft manuscripts and approved the final manuscript.

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

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

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

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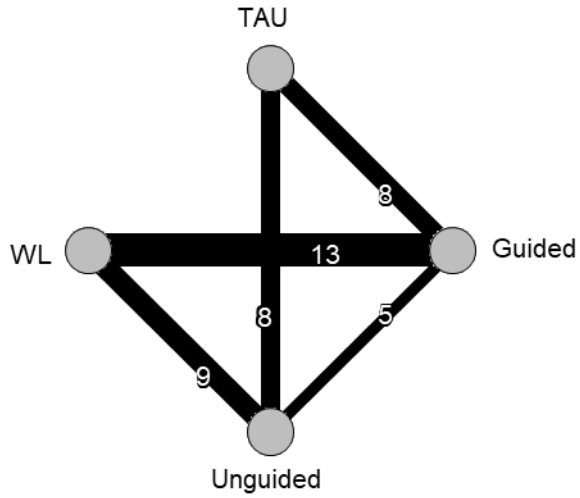

Figure 1. Network plot for depression severity at post-treatment under guided iCBT, unguided iCBT, treatment as usual (TAU) or waiting list (WL). Edges are weighted according to the number of studies for each comparison, also denoted upon each edge.

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 a.l 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-Marin et al.	Clin.	11.8 (2.8)	Unguided vs. Guided iCBT vs. TAU	296	10s/ 10w	No	C	6; 12	0	ES

2016[56]										
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

[a]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

[b]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.

[c]Depression scales could not be converted into PHQ-9 scores

[d]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.

[e]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[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

[a] These are case examples of fictitious patients.