HHS Public Access

Author manuscript

Lancet Psychiatry. Author manuscript; available in PMC 2022 June 01.

Published in final edited form as:

Lancet Psychiatry. 2021 June ; 8(6): 500–511. doi:10.1016/S2215-0366(21)00077-8.

Dismantling, optimising, and personalising internet cognitive behavioural therapy for depression: a systematic review and component network meta-analysis using individual participant data

A full list of authors and affiliations appears at the end of the article.

Summary

Background—Internet cognitive behavioural therapy (iCBT) is a viable delivery format of CBT for depression. However, iCBT programmes include training in a wide array of cognitive and behavioural skills via different delivery methods, and it remains unclear which of these components are more efficacious and for whom.

Methods—We did a systematic review and individual participant data component network meta-analysis (cNMA) of iCBT trials for depression. We searched PubMed, PsycINFO, Embase, and the Cochrane Library for randomised controlled trials (RCTs) published from database inception to Jan 1, 2019, that compared any form of iCBT against another or a control condition in the acute treatment of adults (aged ≥18 years) with depression. Studies with inpatients or patients with bipolar depression were excluded. We sought individual participant data from the original authors. When these data were unavailable, we used aggregate data. Two independent researchers identified the included components. The primary outcome was depression severity, expressed as incremental mean difference (iMD) in the Patient Health Questionnaire-9 (PHQ-9) scores when a component is added to a treatment. We developed a web app that estimates relative efficacies between any two combinations of components, given baseline patient characteristics. This study is registered in PROSPERO, CRD42018104683.

Findings—We identified 76 RCTs, including 48 trials contributing individual participant data (11 704 participants) and 28 trials with aggregate data (6474 participants). The participants' weighted mean age was 42·0 years and 12 406 (71%) of 17 521 reported were women. There was suggestive

Correspondence to: Prof Toshi A Furukawa MD, Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine/School of Public Health, Kyoto 606-8501, Japan, furukawa@kuhp.kyoto-u.ac.jp.

*Co-first authors

†Co-last authors

Contributors

TAF and OE conceived the study. TAF, AS, AC, OE, PCu, and EK designed the study. PCu, EK, CM, AS, EGO, and TAF selected the studies and extracted data. GA, CGB, JSh, TB, FWB, CBu, PCa, IC, HC, AM, JD, MJHH, DDE, LF, NRF, DRS, IDE, EF, VKr, AG, SG, EL, SB, HDH, LHS, RJ, RK, MK, CBj, AK, HR, JPK, JSchr, BM, SM, LB, OL, PJ, JL, JM, AWG, DCM, JM-M, JG-C, SN, A-CZ, KO, ADW, JMN, SP, RP, JSchn, WP, NEP, DR, IMR, SLR, LBS, JSm, VS, VJP, BU, KMPvB, SvL, NG, VKa, KV, LW, AvS, PZ, CK, and MH contributed the individual participant data. OE, EK, and PCu verified the data. OE analysed the data. TAF, AS, EGO, OE, EK, and PCu interpreted the results. TAF and OE wrote the first draft of the manuscript. All authors had access to all the data and provided critical input and revisions to the draft manuscripts and approved the final manuscript. TAF, AS, EGO, OE, EK, and PCu had final responsibility for the decision to submit for publication.

Data sharing

The full aggregate-level data and the analysis R codes are available online at GitHub. Individual-level data cannot be made available due to confidentiality agreements in the original studies.

evidence that behavioural activation might be beneficial (iMD −1·83 [95% credible interval (CrI) −2·90 to −0·80]) and that relaxation might be harmful (1·20 [95% CrI 0·17 to 2·27]). Baseline severity emerged as the strongest prognostic factor for endpoint depression. Combining human and automated encouragement reduced dropouts from treatment (incremental odds ratio, 0·32 [95% CrI 0·13 to 0·93]). The risk of bias was low for the randomisation process, missing outcome data, or selection of reported results in most of the included studies, uncertain for deviation from intended interventions, and high for measurement of outcomes. There was moderate to high heterogeneity among the studies and their components.

Interpretation—The individual patient data cNMA revealed potentially helpful, less helpful, or harmful components and delivery formats for iCBT packages. iCBT packages aiming to be effective and efficient might choose to include beneficial components and exclude ones that are potentially detrimental. Our web app can facilitate shared decision making by therapist and patient in choosing their preferred iCBT package.

Funding—Japan Society for the Promotion of Science.

Introduction

Cognitive behavioural therapy (CBT) is the most widely studied type of psychotherapy for depression.[1,2] CBT encompasses a wide array of cognitive and behavioural skills, which are sometimes administered alone but more commonly in various combinations. Moreover, training in these skills is generally administered in a flexible way, because it is believed that their efficacy is moderated by individual patients' characteristics. It is then of the utmost importance to know which of these components are more contributory to its effectiveness, and which combinations of them are optimal and for whom.[3]

Traditional approaches to examine components involved so-called dismantling studies, in which the whole treatment package is compared against a package that omits one component.[4,5] However, such studies have been typically underpowered and of poor methodological quality. Moreover, these studies have proved difficult to combine because each study examined very diverse components and covered heterogeneous conditions.[6] With new advances in the science of evidence synthesis, complex interventions can now be dismantled through component network meta-analysis (cNMA) by estimating the individual efficacies of the various components contained in a network of randomised controlled trials (RCTs).[7,8] cNMA increases statistical power by combining direct and indirect comparisons while fully respecting the randomised structure of the evidence—ie, treatment effects are estimated separately in each study, and then study-specific estimates are pooled across the network.[9]

One fundamental limitation of all previous dismantling studies and cNMAs is that they dealt mainly with face-to-face CBT, in which it is difficult to be sure that the claimed components have actually been administered as intended and that no other elements were introduced, unless treatment fidelity was monitored. In the past two decades, computerised or internet CBT (iCBT) has been introduced and widely tested in trials. It is now well established that guided iCBT can be as effective as face-to-face individual, group, or other delivery formats of CBT of similar length.[10–12] iCBT provides a unique platform whereby each cognitive

and behavioural skill is offered uniformly and as intended by the programme developers. Moreover, iCBT brings additional clinical questions regarding delivery methods to improve its adherence.

The aim of this individual participant data cNMA was to elucidate which of the skills and delivery methods commonly included in the broadly conceived iCBT packages are efficacious and for whom.

Methods

Search strategy, selection criteria, and data extraction

In this systematic review and individual participant data cNMA we used an existing database of psychological treatments for depression, which is updated annually through comprehensive literature searches in PubMed, PsycINFO, Embase, and the Cochrane Library.[13] Searches combined terms for depression and psychotherapies with filters for randomised controlled trials without any language restrictions. The full search strings are in the appendix (pp 4–8). EK and PCu independently checked this database for eligible studies; disagreements were resolved by discussion. The last update search was done on Jan 1, 2019.

We included all RCTs that compared any form of iCBT against another form of iCBT or a control condition in the acute phase treatment of adults (aged ≥18 years) with depression, either diagnosed as unipolar major or minor depression according to operationalised diagnostic criteria, such as DSM-5 or ICD-10, or judged so by elevated scores on self-report measures with satisfactory reliability and validity. We excluded studies with inpatients or patients with bipolar depression.

We conceptualised CBT broadly as psychotherapy involving training in any of the cognitive or behavioural skills, including cognitive restructuring, behavioural activation, interpersonal skills, structured problem solving, or third wave components. The iCBT had to be a web-based or app-based programme using the internet to deliver the CBT contents. We excluded studies of telephone CBT, computerised CBT available only on a clinic-based computer, and when therapists delivered CBT through teleconferencing or emails.

The control conditions of interest were being on a waiting list for treatment, no treatment, attention or psychological placebo, and treatment as usual. Studies have defined different conditions as treatment as usual.[14,15] In our study, treatment as usual was defined as including conventional drug treatment either as part of the general practitioners' care or as part of the study protocol. Watchful waiting or follow-up by community nurses were classified as attention or psychological placebo, even when it was regarded as treatment as usual in some settings.

The definitions of our components of interest for the intervention and control arms, as conceptualised and defined by TAF and PC who are expert clinicians and researchers in CBT and iCBT, are shown in the panel. The various forms of iCBT and control conditions as conceptualised from the component perspective are shown in the table. The intervention could be of any duration.

Pairs of two independent reviewers (TAF, AS, EGO) classified all identified treatment arms and their constituent components according to the definitions in the panel and table, using all available information from the publications, the iCBT programmes if accessible, and inquiries with the original investigators. The component could be of any length. A CBT skill component was judged present when it was mentioned as such in the publication or was allocated a session or lesson in the programme. When skills not covered in this classification (eg, expressive writing, dreamwork) were included, we assumed such interventions to have some non-specific treatment effects only. The impact of this assumption was tested in a sensitivity analysis excluding such trials.

Pairs of two independent reviewers (TAF, AS, EGO) independently assessed the validity of the included studies using the revised risk of bias tool by Cochrane.[17] The assessment was strictly on the primary outcome used in this review, which was depression severity derived either from the individual participant data or the aggregate data, depending on data availability. Any disagreement was resolved through discussion or through consultation with a third reviewer.

Authors of the identified studies were contacted via email and requested to contribute individual-level data. When data provision was explicitly declined or the authors did not respond after three attempts, the individual participant data were deemed unavailable. After collecting individual participant data, two independent reviewers (EK, TAF) cross-examined the provided data against the original publications. When the numbers did not match, we contacted the authors for clarification. Duplicate data were excluded.

This protocol for this study has already been published.[18] This report follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statements for network meta-analysis[19] and for individual participant data meta-analysis.[20] The PRISMA-individual participant data checklist is provided in the appendix (pp 84–87).

Statistical analyses

Our primary outcome was depression severity as measured on a continuous scale for depression at the end of the acute phase treatment. We accepted any depression measures with established reliability and validity. The scale scores were converted into the most frequently used scale, the Patient Health Questionnaire-9 (PHQ-9),[21] when the established conversion algorithms were available.[22,23]

Our secondary outcomes were dropout from treatment, defined as completing less than 80% of the contents of the programme in individual participant data studies or according to the original authors' definition in aggregate data studies, and dropout from the end-of-treatment assessment for any reason.

We first did a network meta-analysis at the treatment level to examine if the network of the identified trials was amenable to network meta-analysis. A fundamental pre-requisite for network meta-analyses is the so-called transitivity—ie, to have effect modifiers evenly distributed across comparisons. We therefore examined the distribution of potential effect modifiers in studies grouped by treatment comparison. We did a two-step random

effects network meta-analysis at the treatment level, using both aggregate data and individual participant data studies; for aggregate data studies we used the published data, and for individual participant data studies we used multiple imputations based on individual participant data to impute missing data. We did the network meta-analysis in a frequentist setting in R using netmeta,[24] assuming common heterogeneity for all treatment comparisons.[25] We checked network inconsistency, a statistical expression of intransitivity, using the back-calculation[26] and the design-by-treatment methods.[27]

Subsequently, we used cNMA models that jointly synthesised aggregate data and individual participant data studies. We did both a two-step and a one-step cNMA. In the two-step approach, we calculated trial-level estimates of treatment effects from studies for which individual participant data were available and therefore could be re-analysed, and used published trial-level estimates from studies for which individual participant data were not available. In the one-step approach, we used the full individual participant data including patient-level covariates when available and trial-level estimates of treatment effects when individual participant data were not available. The models disentangled the effects of components assuming additivity,[9] and examined component–covariate interactions using shrinkage methods.[28] We estimated component-specific incremental mean differences (iMD; the added benefit of adding a component to a treatment). The component-covariate interactions were modelled assuming linearity. We examined the robustness of the assumption of additive component effects by doing a sensitivity analysis including two-way interactions. We used the parameter estimates to develop a web app for which the inputs are patient characteristics and two combinations of components, and the output is the estimated relative treatment effects between the two combinations. By using individual-level data, we were able to examine prognostic factors (baseline characteristics which predict the outcome regardless of the intervention) and effect modifiers (those which predict differential response to treatments) and to estimate individual relative treatment effects based on these factors.

We repeated the procedure for the two secondary outcomes, using a binomial likelihood, to estimate incremental odds ratios (iORs) for each component.[7] For the dropout from treatment outcome, we only used studies comparing active treatments, because this outcome cannot be measured for controls (waiting list, treatment as usual, no treatment, attention or psychological placebo).

We did four prespecified sensitivity analyses by excluding studies without formal diagnosis of major depression, excluding studies with patients from special populations, excluding arms that used skills not covered in our classifications, and limiting the analysis to studies with high adherence, for the primary outcome. We also did two post-hoc analyses by excluding arms which taught more than four CBT components, and by using a model that assumed two-way interactions between the components.

Details of statistical models used and of fitting procedures are given in the appendix (pp 9–15). The appendix (p 16) lists changes from the protocol.

We examined whether studies providing individual participant data were systematically different from studies not providing individual participant data by comparing the baseline

characteristics and symptom changes of included participants. We examined possible small study effects and publication bias by visually inspecting contour-enhanced funnel plots of pairwise meta-analyses for efficacy between all active arms versus waiting list. This study is registered in PROSPERO (CRD42018104683)

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Up to Jan 1, 2019, we screened 21 162 citations, of which we examined 131 potentially eligible studies in full text. We finally included 76 trials and sought individual participant data from the original authors. Authors of 48 (63%) studies agreed to provide individual participant data representing 11 704 randomly assigned participants; the remaining 28 studies were included as aggregate data, representing 6474 randomly assigned participants (appendix p 17). The lists of the included studies (with responses to author queries), excluded studies (with reasons), and studies awaiting assessment are included in the appendix (pp 18–41).

The participants' weighted mean age was 42·0 years, and 12 406 (71%) of 17 521 reported participants were women. Operationalised diagnostic criteria were used in 27 studies.

The 76 included studies had 179 arms. These arms included all of our pre-specified components of interest, ranging from behaviour therapy for insomnia in four arms to conventional drug treatment in 143 arms. The inter-rater reliability of judgements for components was excellent, with a mean percentage agreement of 93·3% (range 84·0–98·6%) and a mean κ of 0·76 (range 0·38–0·96) for the 17 components (panel; appendix pp 42–51). We were able to access five iCBT programmes ourselves (Sadness Program, Wellbeing Course, Kokoroapp, BeatingTheBlues, and MoodGym), which were used in 20 of the included studies (appendix pp 42–51). The identified components were confirmed by the co-authors who contributed the individual participant data (appendix pp 18–28). Using the conceptualisations in the table, the type of therapy or control condition was represented in the following number of arms: CBT (n=72), cognitive therapy (n=2), behavioural activation (n=11), problem-solving therapy (n=11), third-wave cognitive behavioural therapy (n=6), psychoeducation (n=6), waiting list (n=51), treatment as usual (n=10), attention or psychological placebo (n=9), or no treatment (n=1). The treatment duration ranged from 3 to 24 weeks (median 8 weeks). The median completion rate of programme lessons was 72% (range 25–95%) in 46 studies that reported the values. Antidepressant use was reported by 4031 (40%) of 10 041 participants (appendix pp 52–57).

The risk of bias according to the Cochrane's revised risk of bias tool[17] was low in 66 studies (86%) for randomisation process, in six studies (8%) for the deviation from intended interventions, in 64 studies (83%) for missing outcome data, in two studies (3%) for measurement of the outcome, and 53 studies (69%) for selection of the reported results. The inter-rater reliability of risk of bias assessment was satisfactory, with a mean percentage

agreement of 93·9% (range 87·5–97·8%) and a mean weighted κ of 0·52 (range 0·17–0·84) for the five domains (appendix pp 58–59).

In the individual participant data studies a small minority of patients (387 [3·5%] of 11 122) had scores of less than 5 points on PHQ-9 at baseline and would be classified as euthymic according to the commonly accepted cutoff.[21] We excluded such patients in the analyses because they would not normally be targets for treatment for acute depression. Patients missing both baseline and endpoint scores (390 [3·5%] of 11 122) were also excluded. Two studies[29,30] used scales that could not be converted into PHQ-9 and were therefore excluded from the analyses.

The mean age of the participants was 42·9 years (SD 12·3) in the 48 trials with individual participant data and 39·3 years in the 28 studies with aggregate data. In the individual participant data trials, 6732 (65%) of 10 309 reported participants were women and in the aggregate data trials 3117 (71%) of 4389 reported participants were women. The mean baseline score was 13·2 (SD 4·7) and the mean endpoint PHQ-9 score was 9·0 (SD 5·5) in individual participant data trials; and the mean baseline score was 13·0 (SD 5·5) and the mean endpoint PHQ-9 score was 8·8 (SD 4·8) in aggregate data trials. Overall, there was no indication of systematic differences between individual participant data and aggregate data studies.

Figure 1 shows the network geometry for the primary outcome. Figure 2 shows the results from the pairwise meta-analyses and network meta-analysis at the treatment level, using the two-step approach in which we generated trial-level results based on the individual participant data as described earlier when individual participant data were available and could be re-analysed, and used trial-level results as reported in the original publications when individual participant data were not available. Cognitive therapy, behavioural activation, third-wave cognitive behavioural therapy, CBT, psychoeducation, and problem-solving therapy were all shown to be more efficacious than waiting list. Forest plots of pairwise meta-analyses with more than five studies are shown in the appendix (pp 61–63). Transitivity was assessed by investigating the distribution of potential effect modifiers, including age, gender, and baseline severity of depression (appendix pp 64–65). One comparison (cognitive therapy *vs* attention or psychological placebo) had much higher baseline severity than all other comparisons but otherwise these effect modifiers appeared to be evenly distributed across comparisons (appendix pp 64–65). The design-by-treatment test for global inconsistency showed strong evidence of global inconsistency (Q=37·8, 17 df, p=0·0026); however, the back-calculation method identified only one comparison of 18 that showed evidence of inconsistency, a proportion that would be empirically expected[31] (appendix p 65). Common heterogeneity τ was considered moderate to high. The contour-enhanced funnel plot comparing all active treatments versus waiting list showed no evidence of publication bias (appendix p 66).

Figure 3 shows the main effects from the individual participant data cNMA, using the one-step approach in which we analysed individual participant data if available but also used trial-level results when individual participant data were not available. There was stronger evidence that the behavioural activation and non-specific treatment effects components had

beneficial effects, but the relaxation component was detrimental. There was weaker evidence that behaviour therapy for insomnia was also helpful, showing large point estimates but with wider confidence intervals.

Baseline severity was the strongest prognostic factor but the estimated effect modifications (ie, interactions with treatment components) were relatively small. Full results for the interaction terms, the network diagrams at the component level, and results from cNMA at the aggregate data level are given in the appendix (pp 67–72).

On the basis of these results we can estimate patient-specific relative effects between any combinations. For example, for a 45-year-old female patient, in a relationship, and with a baseline PHQ-9 score of 12, the relative effect of an efficient iCBT package consisting of psychoeducation, behavioural intervention, and problem solving using automated and human encouragement (ie, non-specific treatment effects plus psychoeducation plus behavioural activation plus problem solving plus automated encouragement plus human encouragement) versus waiting list control can be estimated as −4·9 (95% credible interval [95% CrI] −6·8 to −3·1). Our web app provides estimates of relative efficacies between any two combinations of components, for any given patient characteristics.

For dropouts from treatment, we did a cNMA of studies comparing active treatments from five trials providing aggregate data and ten providing individual participant data. Because of the small sample size, we only did a two-step cNMA. The obtained estimates for the components were imprecise but there was some suggestion that automated encouragement and human encouragement reduced dropout from treatment (combined iOR 0·32 [95% CrI 0·13–0·93]; appendix p 73). For dropouts from assessment, both the two-step and one-step cNMA were done (appendix pp 74–76).

The results of the pre-specified and post-hoc sensitivity analyses for the primary outcome are shown in the appendix (pp 77–83); these results were concordant with the primary analyses.

Discussion

We did a network meta-analysis of the broadly conceived iCBT treatments for depression and their control conditions, and a cNMA of 17 components variably included in these packages based on 48 trials with individual participant data and 28 trials with aggregate data. All iCBT treatment packages were found to be superior to the waiting list control. There was evidence that the non-specific treatment effects and behavioural activation components might have beneficial effects whereas the relaxation component might have negative effects, and weaker evidence that the behaviour therapy for insomnia component might be helpful. Having automated encouragement via emails or text messaging and human encouragement by telephone or email without reference to the therapeutic contents might enhance adherence to the treatment. Baseline severity of depression emerged as the strongest prognostic factor; given the baseline severity, age, gender, and relationship status, our web app can estimate the relative effects of any combination treatment over another.

López-López and colleagues'[8] cNMA of CBT for depression found no evidence of specific effects for any skills or delivery formats. These negative findings might be due to the fact that the authors included mostly face-to-face CBT interventions, which generally allowed broad discretion to therapists who might have reduced, modified, or even left out some contents and introduced new contents outside the therapy manual, unless the trials were rigorously monitored for fidelity. López-López and colleagues' decomposition of the CBT contents also raised some concerns because some arms had only homework as their content while many arms did not have psychoeducation (few CBT programmes would take place without psychoeducation about depression and its cognitive behavioural model).

In our study behavioural activation emerged as a beneficial component. This finding is in line with the systematic review of dismantling studies, which estimated a pooled standardised mean difference (SMD) of −0·46 (95% CI −0·91 to −0·01) for the additive effect of behavioural activation.[6] Given that the typical standard deviation of PHQ-9 is approximately 6, the iMD of −1·83 (95% CrI −2·90 to −0·80) for behavioural activation in our cNMA corresponds to a standardised effect size of −0·31 (95% CrI −0·48 to −0·13) and is largely consistent with the estimate of the systematic review.

The same systematic review found no additive effect of cognitive restructuring; the SMD based on three dismantling studies was −0·06 (95% CI −0·68 to 0·55).[6] This result is again concordant with our current findings, which estimated the iMD for cognitive restructuring to be 0·30 (95% CrI −0·87 to 1·41), corresponding to a standardised effect size of 0·05 (95% CrI −0·15 to 0·24).

The non-specific treatment effects component had a robust additive effect of an iMD of −1·41 (95% CrI −2·52 to −0·30), corresponding to a standardised effect size of −0·24 (95% CrI −0·42 to −0·05). In our decomposition model, the non-specific treatment effects component includes both the placebo effect and the common or non-specific psychotherapy factor,[33,34] and can contribute to the efficacy of many bona fide treatments in comparison with non-active controls.

There was suggestive evidence that behaviour therapy for insomnia could be beneficial. However, this therapy was included as a component in only four studies and the estimates for its efficacy were imprecise. It must be pointed out that these four studies did not limit their participants to those having depression and insomnia. The effects of behaviour therapy for insomnia warrants further research.

By contrast, relaxation emerged as potentially harmful in our cNMA, with iMD of 1·20 (95% CrI 0·17 to 2·27). We are aware of no dismantling study for relaxation in depression treatments. However, the cNMA of CBT for panic disorder has identified muscle relaxation as detrimental.[7] There are various potential explanations for this. Relaxation tended to be included in CBT arms that included a greater number of skills, which might have allowed less time to learn and practise those particular skills and have reduced their efficacy. However, when we ran a sensitivity analysis limiting the included number of CBT skills per arm to four or fewer, the estimates were similar to those of the primary analysis. Relaxation might be conceived as working in the opposite direction of exposure, which

might be a principal therapeutic mechanism in anxiety, and behavioural activation, which might be a principal therapeutic mechanism in depression. Relaxation might also plausibly exert its effects by reducing hyperarousal symptoms but this reduction might have been unpleasant for patients with depression who already feel flat and under-aroused. In our network, relaxation exercises were included in 36 arms but the reports generally did not specify what patients actually did in each programme.

With regard to delivery formats of iCBT, we studied the effects of initial face-to-face contact, automated encouragement, human encouragement, and therapeutic guidance. We found that human encouragement in conjunction with automated encouragement decreases dropout from treatment (combined iOR 0·32 [95% CrI 0·13 to 0·93]; appendix p 73) and might be able to promote therapy efficacy (combined iMD −0·55 [95% CrI −1·75 to 0·65]; figure 3). Because human encouragement without reference to the therapeutic contents can be provided by trained lay people, these findings if replicated could increase scalability of iCBT.

The findings about therapeutic guidance might appear surprising given that guided iCBT has been shown to be superior to unguided iCBT,[10] especially among patients with higher baseline severity of depression.[35] In our decomposition, guided iCBT could involve human encouragement only or both human encouragement and therapeutic guidance; the additive effect of guidance could then be due to human encouragement or due to the combination of human encouragement plus therapeutic guidance when the baseline severity was high at 25 points; the incremental effect decreased when the baseline severity was lower. The component perspective also brought some insight into the nature of the current unguided iCBT programmes. These programmes often included relaxation as a component: 14 (48%) of 29 programmes used relaxation when neither human encouragement nor therapeutic guidance was used, 13 (45%) of 29 programmes used relaxation when only human encouragement was used, but only nine (20%) of 44 programmes used relaxation when human encouragement plus therapeutic guidance were used (Fisher's exact p=0·021; appendix pp 43–51). There might therefore be room for unguided iCBT itself to improve its efficacy by appropriately choosing the included components.

There are several important limitations to this study. First, the included studies were limited to iCBT. Any conclusions about specific efficacy of CBT skills therefore pertain to iCBT and will inform which components to include in the efficacious and efficient iCBT package, but such findings might not readily generalise to face-to-face CBT. For example, behavioural activation emerged as beneficial but cognitive restructuring did not in the current analyses, not because of these skills' intrinsic efficacy but simply because of their ease of learning within iCBT. However, the concordance between our findings and those of face-to-face dismantling studies[6] is encouraging. Similarly, our conclusions are applicable to the components and delivery modes as implemented in the included studies. There are potentially different ways for a particular component to be delivered and it is always possible that a specific form of the same component might prove to be efficacious. Second, although the median completion rate of the programme lessons was 72% and, thus, we can assume that most participants had actually completed a majority of the included components, no data were available as to exactly which components were

completed and by whom. Our analysis considered components as being simply present or absent on the basis of the descriptions of each programme. In reality, components might have varied between programmes in terms of their length, depth, and content. Even when present, some components might have been less comprehensively executed than others—eg, when they were offered later in the iCBT package than earlier or when they were presented along with many other components. Additionally, there is no guarantee that the completion of a component means that the participants had acquired the corresponding skill. The present analyses, therefore, can only speak to the effects of the decision to include particular components as their principal ones in the iCBT programme at the start of the treatment, as per the intention-to-treat principle of interpreting RCTs. To appreciate the effects of actual execution of the treatment, we would need more detailed data of individual participants' adherence, their learned contents, and different analytical approaches.[36] Third, several programmes had components not covered in the current scheme, including expressive writing, dreamwork, positive psychology, graded exposure, worry time, or physical exercises. Such trials might have had a slightly different focus, such as the transdiagnostic programme including graded exposure in which the same cognitive restructuring technique might have been presented slightly differently than when it is used mainly as a therapy for depression. A sensitivity analysis excluding trials that used such miscellaneous components, however, corroborated the primary analysis results. Fourth, there was indication of intransitivity for a comparison between cognitive therapy and attention or psychological placebo and of global inconsistency in the network. However, this intransitivity is unlikely to have affected the estimates for the components to a great extent, because the components included in the cognitive therapy and attention or psychological placebo comparison were also included in other comparisons. We only assessed the transitivity assumption for a small number of possible effect modifiers, thus, our network might have been confounded by unobserved imbalances across comparisons, such as antidepressant use and treatment duration. Fifth, when the individual participant data were pooled, there were only four commonly reported patient characteristics that we could analyse as prognostic factors or effect modifiers. Important potential effect modifiers, such as childhood adversities[37] or baseline cognitive or behavioural skills,[38] were therefore not included in our model. Researchers are encouraged to agree on essential measurements to be taken in future iCBT trials. Lastly, we assumed additivity of the component effects—ie, that for any given component (c), the relative effect of c plus X versus X only is the same for any X, where X represents any combination of components not including c. Thus, our results assumed no interactions between components. Although a post-hoc sensitivity analysis examining potential interactions among components provided similar results to the additive model, the study was possibly underpowered to detect interactions among components. Combinations of components can be justified only so far as they are clinically sensible. We must be careful when extrapolating the combinations beyond those examined in the current dataset: as more and more components are combined to build packages not explored in the trials included in this study, the uncertainty around the estimates increases, and possible deviations from our assumptions (eg, additivity of component effects) might have a bigger impact on the validity of our results than when we limit the combinations to those included in this study. More and larger studies varying in included components (eg, in the form of fully factorial trials[39,40]) are necessary to extend and consolidate the estimates.

The major strengths of the study are as follows. We used state-of-the-art evidence synthesis methods to elucidate specific efficacies of various skills and delivery methods of iCBT. The cNMA increased precision by including more studies than narrowly defined dismantling studies and by combining direct and indirect estimates. The included studies were generally of adequate quality except for the domains for which psychotherapy trials cannot escape possible biases due to unfeasibility of blinding. The decomposition of treatments sometimes called for subtle judgements and publications might have failed to provide enough information; with detailed definitions as described in the table and inquiries of the authors when necessary (see appendix pp 18–41 for results of our communications), we were able to achieve satisfactory to excellent inter-rater agreement. In the current network, there was no evidence of data availability bias for individual participant data or of publication bias of active treatments over the waiting list, the most frequent control condition. Lastly, by using individual participant data we were able to estimate relative efficacies of any combination of components based on patients' baseline characteristics.

In conclusion, this individual participant data cNMA of iCBT has identified potentially helpful and less helpful components and delivery formats for reducing depression and enhancing adherence to the programme with suggestive evidence. Future iCBT packages aiming to be effective and efficient might include behavioural activation but not relaxation. Behavioural therapy for insomnia and problem solving might also be included in packages but cognitive restructuring would probably not be chosen. To boost adherence, automated encouragement and human encouragement might be used. Such packages have the potential to be more efficacious, less burdensome for users, and less demanding on provider resources, with the net effect of rendering iCBT even more scalable. However, readers should note that our analyses are limited by several important factors as previously outlined; moreover, the evidence supporting some of these recommendations, especially for cognitive restructuring, problem solving, or therapeutic guidance is still relatively imprecise, warranting further experimentations to refine iCBT packages.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Authors

Toshi A Furukawa*,
Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine/School of Public Health, Kyoto, Japan

Aya Suganuma*,
Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine/School of Public Health, Kyoto, Japan

Edoardo G Ostinelli*,
Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford, UK

Gerhard Andersson,

Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet and Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden

Department of Behavioral Sciences and Learning, Linköping University, Linköping, Sweden

Christopher G Beevers,
Department of Psychology and Institute for Mental Health Research, University of Texas at Austin, Austin, TX, USA

Jason Shumake,
Department of Psychology and Institute for Mental Health Research, University of Texas at Austin, Austin, TX, USA

Thomas Berger,
Department of Clinical Psychology and Psychotherapy, University of Bern, Bern, Switzerland

Florien Willemijn Boele,
Patient Centred Outcomes Research Group, Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, UK

Claudia Buntrock,
Department of Clinical Psychology and Psychotherapy, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany

Per Carlbring,
Department of Psychology, Stockholm University, Stockholm, Sweden

Isabella Choi,
Central Clinical School, Brain and Mind Centre, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia

Helen Christensen,
Black Dog Institute and University of New South Wales, Prince of Wales Hospital, Sydney, NSW, Australia

Andrew Mackinnon,
Black Dog Institute and University of New South Wales, Prince of Wales Hospital, Sydney, NSW, Australia

Jennifer Dahne,
Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA

Marcus J H Huibers,
Department of Clinical, Neuro and Developmental Psychology, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

David D Ebert,

Department for Sport and Health Sciences, Chair for Psychology & Digital Mental Health Care, Technical University Munich, Germany

Louise Farrer,
Centre for Mental Health Research, The Australian National University, Canberra, Australia

Nicholas R Forand,
Department of Psychiatry, The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA

Daniel R Strunk,
Department of Psychology, The Ohio State University, Columbus, OH, USA

Iony D Ezawa,
Department of Psychology, The Ohio State University, Columbus, OH, USA

Erik Forsell,
Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet and Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden

Viktor Kaldo,
Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet and Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden

Department of Psychology, Faculty of Health and Life Sciences, Linnaeus University, Växjö, Sweden

Anna Geraedts,
Soulve Innovations, Utrecht, Netherlands

Simon Gilbody,
Department of Health Sciences, University of York, York, UK

Elizabeth Littlewood,
Department of Health Sciences, University of York, York, UK

Sally Brabyn,
Department of Health Sciences, University of York, York, UK

Heather D Hadjistavropoulos,
Department of Psychology, University of Regina, Regina, SK, Canada

Luke H Schneider,
Anxiety Treatment and Research Clinic, St Joseph's Healthcare Hamilton, Hamilton, ON, Canada

Robert Johansson,
Department of Psychology, Stockholm University, Stockholm, Sweden

Robin Kenter,

Department of Clinical Psychology, Faculty of Psychology, University of Bergen, Bergen, Norway

Marie Kivi,
Department of Psychology, University of Gothenburg, Gothenburg, Sweden

Cecilia Björkelund,
Primary Health Care, School of Public Health and Community Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden

Annet Kleiboer,
Department of Clinical, Neuro and Developmental Psychology, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Heleen Riper,
Department of Clinical, Neuro and Developmental Psychology, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Jan Philipp Klein,
Department of Psychiatry and Psychotherapy, Luebeck University, Luebeck, Germany

Johanna Schröder,
Institute for Sex Research, Sexual Medicine and Forensic Psychiatry, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Björn Meyer,
Research Department, GAIA AG, Hamburg, Germany

Steffen Moritz,
Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Lara Bücker,
Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Ove Lintvedt,
Norwegian Center for E-health research, Tromsø, Norway

Peter Johansson,
Department of Health, Medicine and Caring Sciences, Linköping University, Norrköping, Sweden

Johan Lundgren,
Department of Health, Medicine and Caring Sciences, Linköping University, Norrköping, Sweden

Jeannette Milgrom,
Parent-Infant Research Institute and Austin Health, Melbourne School of Psychological Sciences, University of Melbourne, VIC, Australia

Alan W Gemmill,

Parent-Infant Research Institute and Austin Health, Melbourne School of Psychological Sciences, University of Melbourne, VIC, Australia

David C Mohr,
Center for Behavioral Intervention Technologies, Department of Preventive Medicine, Northwestern University, Chicago, IL, USA

Jesus Montero-Marin,
Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford, UK

Javier Garcia-Campayo,
Aragon Institute for Health Research, Miguel Servet University Hospital, Zaragoza, Spain

Primary Care Prevention and Health Promotion Research Network, RedIAPP, Madrid, Spain

Stephanie Nobis,
Klinikum Osnabrück, Osnabrück, Germany

Anna-Carlotta Zarski,
Department of Clinical Psychology and Psychotherapy, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany

Kathleen O'Moore,
Black Dog Institute and University of New South Wales, Prince of Wales Hospital, Sydney, NSW, Australia

Alishia D Williams,
Department of Psychology, Faculty of Science, The University of New South Wales, Sydney, NSW, Australia

Jill M Newby,
School of Psychology, University of New South Wales at the Black Dog Institute, Sydney, NSW, Australia

Sarah Perini,
Clinical Research Unit for Anxiety and Depression, St Vincent's Hospital, Sydney, NSW, Australia

Rachel Phillips,
Faculty of Medicine, School of Public Health, Imperial College London, London, UK

Justine Schneider,
School of Sociology & Social Policy and Institute of Mental Health, University of Nottingham, Nottingham, UK

Wendy Pots,
Department of Psychology, Health & Technology, University of Twente, Enschede, Netherlands

Nicole E Pugh,
Private practice, Vancouver, BC, Canada

Derek Richards,
University of Dublin, Trinity College, School of Psychology, E-mental Health Research Group, Dublin, Ireland

SilverCloud Health, Clinical Research & Innovation, Dublin, Ireland

Isabelle M Rosso,
McLean Hospital, Belmont, MA, USA

Scott L Rauch,
McLean Hospital, Belmont, MA, USA

Lisa B Sheeber,
Oregon Research Institute, Eugene, OR, USA

Jessica Smith,
Imperial Clinical Trials Unit, Imperial College London, London, UK

Viola Spek,
School of Applied Psychology, Fontys University of Applied Science, Eindhoven, Netherlands

Victor J Pop, MD,
Department of Medical & Clinical Psychology, Tilburg University, Tilburg, Netherlands

Burçin Ünlü,
PsyQ Online, Haarlem, Netherlands

Kim M P van Bastelaar,
Amsterdam University Medical Centre, Amsterdam, Netherlands

Sanne van Luenen,
Department of Clinical Psychology, Leiden University, Leiden, Netherlands

Nadia Garnefski,
Department of Clinical Psychology, Leiden University, Leiden, Netherlands

Vivian Kraaij,
Department of Clinical Psychology, Leiden University, Leiden, Netherlands

Kristofer Vernmark,
Department of Behavioral Sciences and Learning, Linköping University, Linköping, Sweden

Lisanne Warmerdam,
National Health Care Institute, Diemen, Netherlands

Annemieke van Straten,
Department of Clinical, Neuro and Developmental Psychology, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Pavle Zagorscak,
Department of Education and Psychology, Freie Universität Berlin, Berlin, Germany

Christine Knaevelsrud,
Department of Education and Psychology, Freie Universität Berlin, Berlin, Germany

Manuel Heinrich,
Department of Education and Psychology, Freie Universität Berlin, Berlin, Germany

Clara Miguel,
Department of Clinical, Neuro and Developmental Psychology, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Andrea Cipriani,
Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford, UK

Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK

Orestis Efthimiou[†],
Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford, UK

Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

Eirini Karyotaki[†],
Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA

Pim Cuijpers[†]
Department of Clinical, Neuro and Developmental Psychology, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Affiliations

Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine/School of Public Health, Kyoto, Japan

Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine/School of Public Health, Kyoto, Japan

Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford, UK

Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet and Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden

Department of Behavioral Sciences and Learning, Linköping University, Linköping, Sweden

Department of Psychology and Institute for Mental Health Research, University of Texas at Austin, Austin, TX, USA

Department of Psychology and Institute for Mental Health Research, University of Texas at Austin, Austin, TX, USA

Department of Clinical Psychology and Psychotherapy, University of Bern, Bern, Switzerland

Patient Centred Outcomes Research Group, Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, UK

Department of Clinical Psychology and Psychotherapy, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany

Department of Psychology, Stockholm University, Stockholm, Sweden

Central Clinical School, Brain and Mind Centre, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia

Black Dog Institute and University of New South Wales, Prince of Wales Hospital, Sydney, NSW, Australia

Black Dog Institute and University of New South Wales, Prince of Wales Hospital, Sydney, NSW, Australia

Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA

Department of Clinical, Neuro and Developmental Psychology, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Department for Sport and Health Sciences, Chair for Psychology & Digital Mental Health Care, Technical University Munich, Germany

Centre for Mental Health Research, The Australian National University, Canberra, Australia

Department of Psychiatry, The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA

Department of Psychology, The Ohio State University, Columbus, OH, USA

Department of Psychology, The Ohio State University, Columbus, OH, USA

Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet and Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden

Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet and Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden

Department of Psychology, Faculty of Health and Life Sciences, Linnaeus University, Växjö, Sweden

Soulve Innovations, Utrecht, Netherlands

Department of Health Sciences, University of York, York, UK

Department of Health Sciences, University of York, York, UK

Department of Health Sciences, University of York, York, UK

Department of Psychology, University of Regina, Regina, SK, Canada

Anxiety Treatment and Research Clinic, St Joseph's Healthcare Hamilton, Hamilton, ON, Canada

Department of Psychology, Stockholm University, Stockholm, Sweden

Department of Clinical Psychology, Faculty of Psychology, University of Bergen, Bergen, Norway

Department of Psychology, University of Gothenburg, Gothenburg, Sweden

Primary Health Care, School of Public Health and Community Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden

Department of Clinical, Neuro and Developmental Psychology, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Department of Clinical, Neuro and Developmental Psychology, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Department of Psychiatry and Psychotherapy, Luebeck University, Luebeck, Germany

Institute for Sex Research, Sexual Medicine and Forensic Psychiatry, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Research Department, GAIA AG, Hamburg, Germany

Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Norwegian Center for E-health research, Tromsø, Norway

Department of Health, Medicine and Caring Sciences, Linköping University, Norrköping, Sweden

Department of Health, Medicine and Caring Sciences, Linköping University, Norrköping, Sweden

Parent-Infant Research Institute and Austin Health, Melbourne School of Psychological Sciences, University of Melbourne, VIC, Australia

Parent-Infant Research Institute and Austin Health, Melbourne School of Psychological Sciences, University of Melbourne, VIC, Australia

Center for Behavioral Intervention Technologies, Department of Preventive Medicine, Northwestern University, Chicago, IL, USA

Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford, UK

Aragon Institute for Health Research, Miguel Servet University Hospital, Zaragoza, Spain

Primary Care Prevention and Health Promotion Research Network, RedIAPP, Madrid, Spain

Klinikum Osnabrück, Osnabrück, Germany

Department of Clinical Psychology and Psychotherapy, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany

Black Dog Institute and University of New South Wales, Prince of Wales Hospital, Sydney, NSW, Australia

Department of Psychology, Faculty of Science, The University of New South Wales, Sydney, NSW, Australia

School of Psychology, University of New South Wales at the Black Dog Institute, Sydney, NSW, Australia

Clinical Research Unit for Anxiety and Depression, St Vincent's Hospital, Sydney, NSW, Australia

Faculty of Medicine, School of Public Health, Imperial College London, London, UK

School of Sociology & Social Policy and Institute of Mental Health, University of Nottingham, Nottingham, UK

Department of Psychology, Health & Technology, University of Twente, Enschede, Netherlands

Private practice, Vancouver, BC, Canada

University of Dublin, Trinity College, School of Psychology, E-mental Health Research Group, Dublin, Ireland

SilverCloud Health, Clinical Research & Innovation, Dublin, Ireland

McLean Hospital, Belmont, MA, USA

McLean Hospital, Belmont, MA, USA

Oregon Research Institute, Eugene, OR, USA

Imperial Clinical Trials Unit, Imperial College London, London, UK

School of Applied Psychology, Fontys University of Applied Science, Eindhoven, Netherlands

Department of Medical & Clinical Psychology, Tilburg University, Tilburg, Netherlands

PsyQ Online, Haarlem, Netherlands

Amsterdam University Medical Centre, Amsterdam, Netherlands

Department of Clinical Psychology, Leiden University, Leiden, Netherlands

Department of Clinical Psychology, Leiden University, Leiden, Netherlands

Department of Clinical Psychology, Leiden University, Leiden, Netherlands

Department of Behavioral Sciences and Learning, Linköping University, Linköping, Sweden

National Health Care Institute, Diemen, Netherlands

Department of Clinical, Neuro and Developmental Psychology, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Department of Education and Psychology, Freie Universität Berlin, Berlin, Germany

Department of Education and Psychology, Freie Universität Berlin, Berlin, Germany

Department of Education and Psychology, Freie Universität Berlin, Berlin, Germany

Department of Clinical, Neuro and Developmental Psychology, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford, UK

Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK

Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford, UK

Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA

Department of Clinical, Neuro and Developmental Psychology, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Acknowledgments

This study was supported, in part, by the Japan Society for the Promotion of Science grant-in-aid for scientific research (grant number 17K19808) to TAF. EGO is supported by the National Institute for Health Research (NIHR) Oxford Cognitive Health Clinical Research Facility and by the NIHR Oxford Health Biomedical Research Centre (grant BRC-1215–20005). JD is supported by the National Institute on Drug Abuse (NIDA K23 DA045766). HDH is supported by the Canadian Institutes of Health Research (152917). DCM is supported by grants from the National Institute of Mental Health (P50 MH119029, R01 MH111610). AC is supported by the NIHR Oxford Cognitive Health Clinical Research Facility, by an NIHR Research Professorship (grant RP-2017–08ST2–006), the NIHR Oxford and Thames Valley Applied Research Collaboration, and the NIHR Oxford Health Biomedical Research Centre (grant BRC-1215–20005). OE was supported by project grant number 180083 from the Swiss National Science Foundation. EK was supported by the Netherlands Organisation for Health Research and Development (project number 019.182SG.001). The views expressed are those of the authors and not necessarily those of any of the funding agencies listed here.

Declaration of interests

TAF reports grants from Japan Society for Promotion of Science, during the conduct of the study; grants and personal fees from Mitsubishi-Tanabe, personal fees from MSD, grants and personal fees from Shionogi, outside the submitted work; a patent 2018–177688 concerning smartphone CBT apps pending; and an intellectual properties for Kokoro-app licensed to Tanabe-Mitsubishi. AC reports personal fees from Italian Network for Paediatric Trials and CARIPLO Foundation; and grants and personal fees from Angelini Pharma, outside the submitted work. EGO reports personal fees from Angelini Pharma, outside the submitted work. PCa reports personal fees from Osmond Foundation and Sandoz, outside the submitted work. JD is co-owner of Behavioral Activation Tech LLC, a small business that develops and evaluates mobile app-based treatments for depression and co-occurring disorders. DDE has served as a consultant to or on the scientific advisory boards of Sanofi, Novartis, Minddistrict, Lantern, Schoen Kliniken, Ideamed, German health insurance companies (BARMER, Techniker Krankenkasse), and a number of federal chambers for psychotherapy; is a stakeholder of the Institute for health training online (GET.ON), which aims to implement scientific findings related to digital health interventions into routine care. NRF is an employee of AbleTo. JPK reports grants and personal fees from Servier; personal fees

from Beltz, Elsevier, Hogrefe, and Springer, outside the submitted work; funding for clinical trials (German Federal Ministry of Health and Servier); payments for presentations on internet interventions (Servier); and payments for workshops and books (Beltz, Elsevier, Hogrefe, and Springer) on psychotherapy for chronic depression and on psychiatric emergencies. BM is an employee of GAIA AG. DCM reports personal fees from Apple, Pear Therapeutics, and Otsuka Pharmaceuticals and has an equity interest in Adaptive Health, outside the submitted work. JMM is supported by a Wellcome Trust Grant (104908/Z/14/Z). SN is an employee of GET.ON Institut. DR is an employee of SilverCloud Health. LBS is an employee of Influents Innovations. PZ reports grants and non-financial support from Techniker Krankenkasse (German public health insurance company), outside the submitted work. CK reports personal fees from Oberbergklinik and Servier; and grants and non-financial support from Techniker Krankenkasse, outside the submitted work. MH reports grants and non-financial support from Techniker Krankenkasse, outside the submitted work. All other authors declare no competing interests.

References

1. Barth J, Munder T, Gerger H, et al. Comparative efficacy of seven psychotherapeutic interventions for patients with depression: a network meta-analysis. PLoS Med 2013; 10: e1001454. [PubMed: 23723742]
2. Cuijpers P, Karyotaki E, de Wit L, Ebert DD. The effects of fifteen evidence-supported therapies for adult depression: a meta-analytic review. Psychother Res 2019; 30: 1–15.
3. Institute of Medicine. Psychosocial interventions for mental and substance use disorders: a framework for establishing evidence-based standards. Washington, DC: The National Academies Press, 2015.
4. Ahn H, Wampold BE. Where oh where are the specific ingredients? A meta-analysis of component studies in counseling and psychotherapy. J Couns Psychol 2001; 48: 251–57.
5. Bell EC, Marcus DK, Goodlad JK. Are the parts as good as the whole? A meta-analysis of component treatment studies. J Consult Clin Psychol 2013; 81: 722–36. [PubMed: 23688145]
6. Cuijpers P, Cristea IA, Karyotaki E, Reijnders M, Hollon SD. Component studies of psychological treatments of adult depression: a systematic review and meta-analysis. Psychother Res 2017; 29: 1–15. [PubMed: 29254460]
7. Pompoli A, Furukawa TA, Efthimiou O, Imai H, Tajika A, Salanti G. Dismantling cognitive-behaviour therapy for panic disorder: a systematic review and component network meta-analysis. Psychol Med 2018; 48: 1945–53. [PubMed: 29368665]
8. López-López JA, Davies SR, Caldwell DM, et al. The process and delivery of CBT for depression in adults: a systematic review and network meta-analysis. Psychol Med 2019; 49: 1937–47. [PubMed: 31179960]
9. Welton NJ, Caldwell DM, Adamopoulos E, Vedhara K. Mixed treatment comparison meta-analysis of complex interventions: psychological interventions in coronary heart disease. Am J Epidemiol 2009; 169: 1158–65. [PubMed: 19258485]
10. Cuijpers P, Noma H, Karyotaki E, Cipriani A, Furukawa TA. Effectiveness and acceptability of cognitive behavior therapy delivery formats in adults with depression: a network meta-analysis. JAMA Psychiatry 2019; 76: 700–07. [PubMed: 30994877]
11. Wagner B, Horn AB, Maercker A. Internet-based versus face-to-face cognitive-behavioral intervention for depression: a randomized controlled non-inferiority trial. J Affect Disord 2014; 152–154: 113–21.
12. Karyotaki E, Ebert DD, Donkin L, et al. Do guided internet-based interventions result in clinically relevant changes for patients with depression? An individual participant data meta-analysis. Clin Psychol Rev 2018; 63: 80–92. [PubMed: 29940401]
13. Cuijpers P, Karyotaki E, Ciharova M. A meta-analytic database of randomised trials on psychotherapies for depression. 2020. https://osf.io/825c6/ (accessed March 16, 2021).
14. Watts SE, Turnell A, Kladnitski N, Newby JM, Andrews G. Treatment-as-usual (TAU) is anything but usual: a meta-analysis of CBT versus TAU for anxiety and depression. J Affect Disord 2015; 175: 152–67. [PubMed: 25618002]
15. Cuijpers P, Quero S, Papola D, Cristea IA, Karyotaki E. Care-as-usual control groups across different settings in randomized trials on psychotherapy for adult depression: a meta-analysis. Psychol Med 2019; published online Dec 17. 10.1017/S0033291719003581.

16. Roemer L, Erisman SM, Orsillo SM. Mindfulness and acceptance-based treatments for anxiety disorders. In: Antony MM, Stein MB, eds. Oxford Handbook of Anxiety and Related Disorders. Oxford: Oxford University Press, 2008: 476–87.
17. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898. [PubMed: 31462531]
18. Furukawa TA, Karyotaki E, Suganuma A, et al. Dismantling, personalising and optimising internet cognitive-behavioural therapy for depression: a study protocol for individual participant data component network meta-analysis. BMJ Open 2019; 8: e026137.
19. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015; 162: 777–84. [PubMed: 26030634]
20. Stewart LA, Clarke M, Rovers M, et al. Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. JAMA 2015; 313: 1657–65. [PubMed: 25919529]
21. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001; 16: 606–13. [PubMed: 11556941]
22. Wahl I, Löwe B, Bjorner JB, et al. Standardization of depression measurement: a common metric was developed for 11 self-report depression measures. J Clin Epidemiol 2014; 67: 73–86. [PubMed: 24262771]
23. Furukawa TA, Reijnders M, Kishimoto S, et al. Translating the BDI and BDI-II into the HAMD and vice versa with equipercentile linking. Epidemiol Psychiatr Sci 2019; 29: e24. [PubMed: 30867082]
24. Rücker G, Krahn U, König J, Efthimiou O, Schwarzer G. netmeta: network meta-analysis using frequentist methods. 2019. https://github.com/guido-s/netmeta (accessed April 23, 2021).
25. Efthimiou O, Debray TP, van Valkenhoef G, et al. GetReal in network meta-analysis: a review of the methodology. Res Synth Methods 2016; 7: 236–63. [PubMed: 26754852]
26. König J, Krahn U, Binder H. Visualizing the flow of evidence in network meta-analysis and characterizing mixed treatment comparisons. Stat Med 2013; 32: 5414–29. [PubMed: 24123165]
27. White IR, Barrett JK, Jackson D, Higgins JP. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Res Synth Methods 2012; 3: 111–25. [PubMed: 26062085]
28. Seo M, White IR, Furukawa TA, et al. Comparing methods for estimating patient-specific treatment effects in individual patient data meta-analysis. Stat Med 2020; 40: 1553–73. [PubMed: 33368415]
29. Beevers CG, Pearson R, Hoffman JS, Foulser AA, Shumake J, Meyer B. Effectiveness of an internet intervention (Deprexis) for depression in a united states adult sample: a parallel-group pragmatic randomized controlled trial. J Consult Clin Psychol 2017; 85: 367–80. [PubMed: 28230390]
30. Day V, McGrath PJ, Wojtowicz M. Internet-based guided self-help for university students with anxiety, depression and stress: a randomized controlled clinical trial. Behav Res Ther 2013; 51: 344–51. [PubMed: 23639300]
31. Veroniki AA, Vasiliadis HS, Higgins JP, Salanti G. Evaluation of inconsistency in networks of interventions. Int J Epidemiol 2013; 42: 332–45. [PubMed: 23508418]
32. Seo M, Furukawa TA, Veroniki AA, et al. The Kilim plot: a tool for visualizing network meta-analysis results for multiple outcomes. Res Synth Methods 2021; 12: 86–95. [PubMed: 32524754]
33. Wampold BE. How important are the common factors in psychotherapy? An update. World Psychiatry 2015; 14: 270–77. [PubMed: 26407772]
34. Cuijpers P, Reijnders M, Huibers MJH. The role of common factors in psychotherapy outcomes. Annu Rev Clin Psychol 2019; 15: 207–31. [PubMed: 30550721]
35. Karyotaki E, Efthimiou O, Miguel C, et al. Internet-based cognitive behavioral therapy for depression: a systematic review and individual patient data network meta-analysis. JAMA Psychiatry 2021; published online Jan 20. 10.1001/jamapsychiatry.2020.4364.
36. Hernán MA, Hernández-Díaz S. Beyond the intention-to-treat in comparative effectiveness research. Clin Trials 2012; 9: 48–55. [PubMed: 21948059]

37. Nemeroff CB, Heim CM, Thase ME, et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. Proc Natl Acad Sci USA 2003; 100: 14293–96. [PubMed: 14615578]

38. Cheavens JS, Strunk DR, Lazarus SA, Goldstein LA. The compensation and capitalization models: a test of two approaches to individualizing the treatment of depression. Behav Res Ther 2012; 50: 699–706. [PubMed: 22982085]

39. Uwatoko T, Luo Y, Sakata M, et al. Healthy campus trial: a multiphase optimization strategy (MOST) fully factorial trial to optimize the smartphone cognitive behavioral therapy (CBT) app for mental health promotion among university students: study protocol for a randomized controlled trial. Trials 2018; 19: 353. [PubMed: 29973252]

40. Watkins E, Newbold A, Tester-Jones M, et al. Implementing multifactorial psychotherapy research in online virtual environments (IMPROVE-2): study protocol for a phase III trial of the MOST randomized component selection method for internet cognitive-behavioural therapy for depression. BMC Psychiatry 2016; 16: 345. [PubMed: 27716200]

Research in context

Evidence before this study

Psychotherapy is a complex intervention, comprising multiple components in various combinations. There are two types of research to disentangle specific contributions of psychotherapy components: so-called dismantling studies and, more recently, component network meta-analyses. We searched PubMed from inception to Oct 9, 2020, for relevant reviews with the following terms in titles and abstracts: (“Mental Disorders”[Mesh] “Psychotherapy”[Mesh] dismantl*) and (“Mental Disorders”[Mesh] “Psychotherapy” [Mesh] component network meta-analysis). We identified three systematic reviews of dismantling studies and two component network meta-analyses. Earlier reviews of dismantling studies found no additive effects of specific components among dismantling studies; however, the most recent review focusing on depression found behavioural activation, but not cognitive restructuring or mindfulness, to have significant additive effects. A component network meta-analysis of face-to-face cognitive behavioural therapy (CBT) for panic disorder singled out muscle relaxation to be harmful; a component network meta-analysis of CBT for depression found no evidence of specific effects of any components or their combinations.

Added value of this study

Three new features strengthened the precision, sensitivity, and clinical relevance of our study. First, component network meta-analysis increased precision of estimates by including more studies than narrowly defined dismantling studies and by combining direct and indirect estimates while maintaining randomised comparisons. Second, by focusing on iCBT, we could be certain that the components had been offered and made accessible as intended by the researchers, in contrast to face-to-face CBT, for which the contents might have been modified or skipped when its conduct was not well monitored. Third, the use of individual participant data allowed us to identify prognostic factors and effect modifiers and thus estimate personalised relative effects among different interventions, depending on individual patients’ characteristics. We found suggestive evidence that non-specific treatment effects (including placebo effect and common factors) and behavioural activation might have beneficial effects, whereas relaxation might be detrimental. Combining human encouragement to proceed with the iCBT programme with automated encouragement decreased the number of patients who dropped out from treatment. We developed a web app that estimates relative efficacies between any two combinations of components based on baseline patient characteristics.

Implications of all the available evidence

Future iCBT packages aiming to be effective and efficient might include behavioural activation but not relaxation. These packages might further include behaviour therapy for insomnia and problem solving, but probably not cognitive restructuring. Automated encouragement could be used in iCBT packages along with human encouragement to increase adherence. Our web app can facilitate shared decision making by therapist and patient in choosing their preferred iCBT package.

Panel: Components, their definitions, and the number of trial arms including each component

Waiting component; 52 arms

Participants know that they can receive an active treatment, after a waiting phase. Usually patients on a waiting list do not receive any treatment during the waiting phase. However, in some trials the patients allocated to a waiting list received some non-specific therapeutic components, such as psychological placebo, psychoeducation, or treatment as usual. In such cases, we assumed that the waiting component was present, recorded the interventions provided while waiting, and classified such an arm as waiting list.

Conventional drug treatment; 143 arms

Treatment as usual or care as usual can denote many different conditions in the literature.[14,15] In this study we focused on the use of conventional drug treatment and extracted the data on whether conventional drug treatment was present (drug treatment was part of the protocol treatment), allowed, or absent. When the drug was used to the same extent in both arms, the conventional drug treatment component was assumed to be present.

Non-specific treatment effects; 142 arms

Effects of an intervention due to the patients' belief that they are receiving some form of treatment (placebo effect) and to the common or non-specific factors of psychotherapies. These two elements were indistinguishable in the current network of psychotherapies.

Psychoeducation about depression; 111 arms

Provision of information about the cause and nature of depression. Patients are taught their symptoms can be interpreted under a particular psychopathological model. For example, if cognitive distortion is cited as the cause of depression, such an explanation was counted towards the psychoeducation about depression component as defined here. We considered psychoeducation to be present only if there was a dedicated module (psychoeducation or introductory). Advice about lifestyle modification (eg, exercise, food, sleep hygiene as opposed to cognitive behavioural therapy [CBT] for insomnia) or provision of information about depression in informational websites were regarded as a form of psychoeducation.

Cognitive restructuring; 74 arms

This component teaches the patient to evaluate and modify their own irrational, maladaptive, or dysfunctional thoughts using strategies such as Socratic questioning and guided imagery.

Behavioural activation; 84 arms

This component aims to help people increase potentially reinforcing experiences through activity scheduling and increased engagement in pleasant activities.

Interpersonal skills training; 31 arms

Training in appropriate social behaviours. Includes assertiveness training, which teaches the patient to stand up for their own rights by expressing their feelings and wishes in an honest and respectful manner that does not insult or hurt others.

Problem solving; 55 arms

This skill includes the following step-by-step approach to personal problems: defining personal problems, generating multiple solutions, selecting the best solution, working out a systematic plan for this solution, and evaluating whether the solution has resolved the problem.

Relaxation; 36 arms

This skill is aimed at reducing general tension through induction of a relaxed body state. The most common techniques are Jacobson's progressive muscle relaxation and applied relaxation.

Third-wave components; 14 arms

Various techniques are aimed at helping patients to develop more adaptive emotional responses to situations, such as the ability to observe symptomatic processes without overly identifying with them or without reacting to them in ways that cause further distress.[16] Some typical examples are training in mindfulness, self-compassion, or acceptance.

Behaviour therapy for insomnia; 4 arms

This skill aims at treating chronic insomnia based on the principles of sleep restriction and stimulus control. This skill might also involve cognitive restructuring around maladaptive beliefs for sleep or teaching sleep hygiene; however, sleep hygiene only would count towards lifestyle modification and would be included in the psychoeducation about depression component.

Relapse prevention; 62 arms

Review of learned skills and listing action plans for foreseeable future problems based on the skills learned. An explanation of relapse in depression only would be counted as the psychoeducation about depression component; to qualify for the relapse prevention component, more participation is needed from the patient.

Homework required; 68 arms

When completion of some homework assignment is required (or explicitly encouraged repeatedly) before proceeding with the programme, either checked by humans or mandated by a computer program. The homework must pertain to an exercise in applying the learned CBT or other skills related to the participant's own situation and must require some active participation from the participant. Simple reviewing of the materials or further reading were not regarded as homework.

Initial face-to-face contact; 57 arms

Initial face-to-face human contact, such as the initial evaluation session or the initial orientation session, is present. We also considered this component to be present when

the patients were receiving conventional drug treatment and the doctors were aware that the patients were in the trial, or when the patients were referred from their general practitioner for the trial.

Automated encouragement to proceed with internet cognitive behavioural therapy (iCBT); 48 arms

Provision of automated, fixed prompts or encouragements to proceed with the treatment programme. Such prompts should not contain any support related to the therapeutic contents.

Human encouragement to proceed with iCBT; 73 arms

Prompts or encouragements are prepared and provided by human beings to proceed with the treatment programme via telephone or email. Such prompts should not contain any support related to the therapeutic contents. Peer support such as discussion groups counted towards this component.

Therapeutic guidance for iCBT; 44 arms

Guidance regarding the contents of iCBT. Therapeutic guidance related to the treatment content could be provided on a scheduled basis or as needed. Provision of technical support only did not count toward this component.

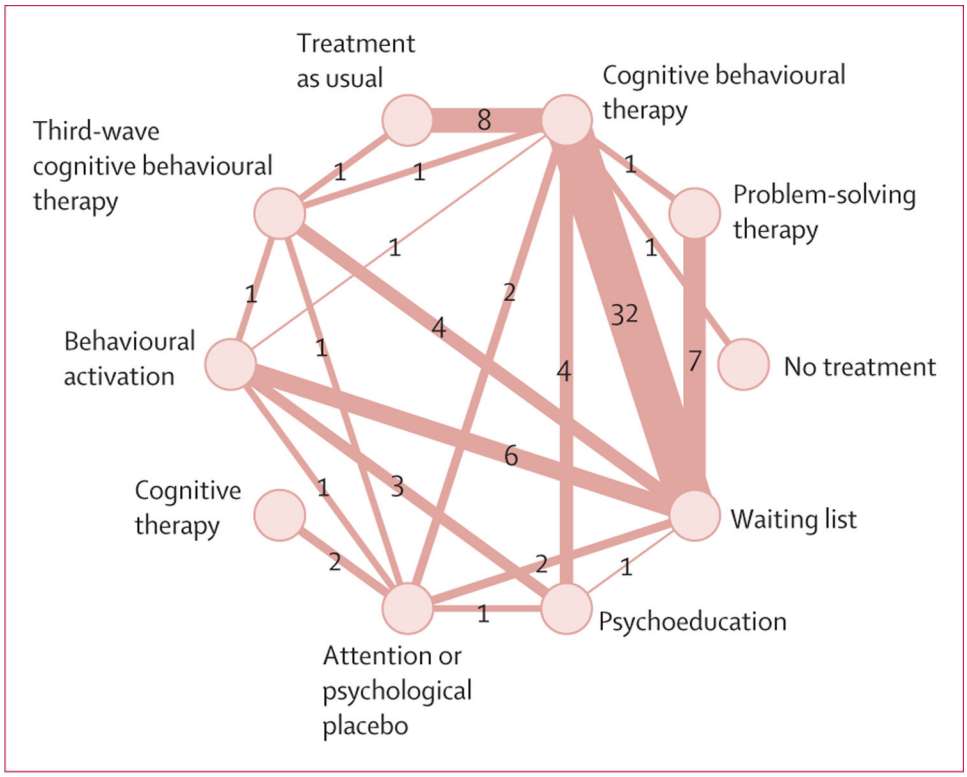


Figure 1: Network diagram

The width of the lines is proportional to the number of comparisons, which is given on each line.

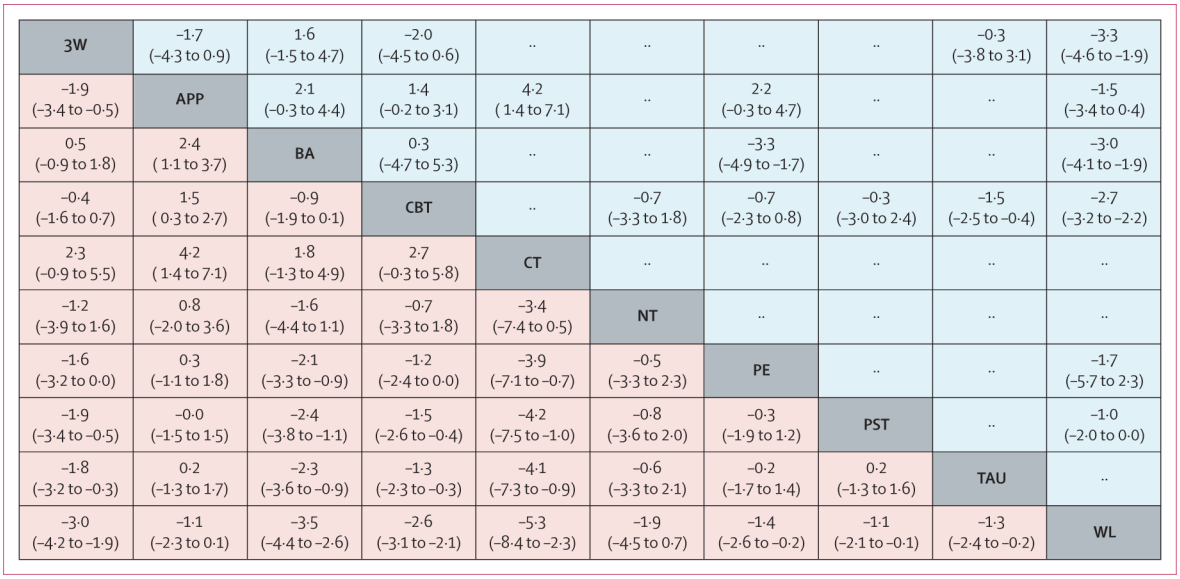
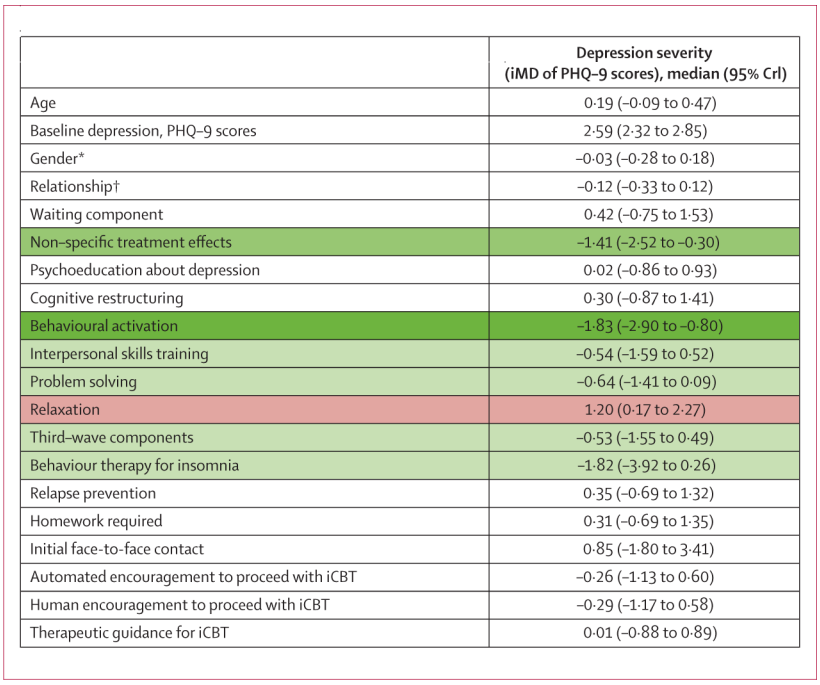


Figure 2: Relative effects (mean differences in PHQ-9 scores with 95% CIs) of internet cognitive behavioural therapy of depression

Treatments (listed in alphabetical order) are shown in grey, direct effects (pairwise meta-analyses) are shown in blue, and the network meta-analysis results are shown in red. Common heterogeneity τ was estimated to be 1·1 in terms of the PHQ-9 scores. An effect size of less than 0 in the network meta-analysis results shows that the treatment in the column is favoured (ie, lower PHQ-9 scores) versus the treatment in the row. An effect size of less than 0 in the pariwise meta-analyses results shows that the treatment in the row is favoured versus the treatment in the column. 3W=third-wave cognitive behavioural therapy. APP=attention or psychological placebo. BA=behavioural activation. CBT=cognitive behavioural therapy. CT=cognitive therapy. NT=no treatment. PE=psychoeducation. PHQ-9=Personal Health Questionnaire-9. PST=problem-solving therapy. TAU=treatment as usual. WL=waiting list.



	Depression severity (iMD of PHQ-9 scores), median (95% CrI)
Age	0·19 (−0·09 to 0·47)
Baseline depression, PHQ-9 scores	2·59 (2·32 to 2·85)
Gender*	−0·03 (−0·28 to 0·18)
Relationship†	−0·12 (−0·33 to 0·12)
Waiting component	0·42 (−0·75 to 1·53)
Non-specific treatment effects	−1·41 (−2·52 to −0·30)
Psychoeducation about depression	0·02 (−0·86 to 0·93)
Cognitive restructuring	0·30 (−0·87 to 1·41)
Behavioural activation	−1·83 (−2·90 to −0·80)
Interpersonal skills training	−0·54 (−1·59 to 0·52)
Problem solving	−0·64 (−1·41 to 0·09)
Relaxation	1·20 (0·17 to 2·27)
Third-wave components	−0·53 (−1·55 to 0·49)
Behaviour therapy for insomnia	−1·82 (−3·92 to 0·26)
Relapse prevention	0·35 (−0·69 to 1·32)
Homework required	0·31 (−0·69 to 1·35)
Initial face-to-face contact	0·85 (−1·80 to 3·41)
Automated encouragement to proceed with iCBT	−0·26 (−1·13 to 0·60)
Human encouragement to proceed with iCBT	−0·29 (−1·17 to 0·58)
Therapeutic guidance for iCBT	0·01 (−0·88 to 0·89)

Figure 3: Individual participant data component network meta-analysis for depression severity

Potentially beneficial components are shown in green (darker green for stronger statistical evidence) and potentially harmful components are shown in red according to an index similar to the Z-score (median of the posterior distribution divided by the corresponding standard deviation for Bayesian analyses), thus taking account of the magnitude of the effect estimates and their uncertainty.[32] More details about the colouring scheme are provided in the appendix (p 68). The specific efficacy for conventional drug treatment could not be estimated because this component was either present or absent in all comparisons in the network. Common heterogeneity τ was estimated to be 1·20 (95%CrI 0·89 to 1·57) in terms of the PHQ-9 scores. iCBT=internet cognitive behavioural therapy. iMD=incremental mean difference. CrI=credible interval. PHQ-9=Patient Health Questionnaire-9. *0=female and 1=male. †0=not in a relationship (single, separated, divorced, or widowed) and 1=in a relationship (married or having a stable partner).

Table:

Conceptualisation of internet cognitive behavioural therapy or control conditions from the component perspective

	Possible decompositions into components
Cognitive behavioural therapy	ns ± pe ± re + cr + (ba ± ps ± at ± bi) ± rp ± dt ± ae ± he ± tg ± ff ± hw
Cognitive therapy	ns ± pe ± re + cr ± rp ± dt ± ae ± he ± tg ± ff ± hw
Behavioural activation	ns ± pe ± re + ba ± rp ± dt ± ae ± he ± tg ± ff ± hw
Problem-solving therapy	ns ± pe ± re + ps ± rp ± dt ± ae ± he ± tg ± ff ± hw
Third-wave cognitive behavioural therapy	ns ± pe ± re ± cr ± ba ± ps ± at ± bi + 3w ± rp ± dt ± ae ± he ± tg ± ff ± hw
Psychoeducation	ns + pe ± rp ± dt ± ae ± he ± tg ± ff
Waiting list	w ± ns ± pe ± dt ± ff
Treatment as usual	ns + dt + ff
Attention or psychological placebo	ns ± ff
No treatment	± ff

The first component and a component marked with a + denotes that the component is required. A component marked with a ± denotes that the component is optional. At least one of the components within brackets is required. 3w=third-wave components. ae=automated encouragement to proceed with internet cognitive behavioural therapy. ba=behavioural activation. ba=behaviour therapy for insomnia. cr=cognitive restructuring. dt=conventional drug treatment. ff=initial face-to-face contact. he=human encouragement to proceed with internet cognitive behavioural therapy. hw=homework required. is=interpersonal skills training. ns=non-specific treatment effects. pe=psychoeducation about depression. ps=problem solving. re=relaxation. rp=relapse prevention. tg=therapeutic guidance for internet cognitive behavioural therapy. w=waiting component.