Do Guided Internet-Based Interventions Result in Clinically Relevant Changes for Patients with Depression? An Individual Participant Data Meta-Analysis

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ABSTRACT

Little is known about clinically relevant changes in guided Internet-based interventions for depression. Moreover, methodological and power limitations preclude the identification of patients' groups that may benefit more from these interventions. This study aimed to investigate response rates, remission rates, and their moderators in randomized controlled trials (RCTs) comparing the effect of guided Internet-based interventions for adult depression to control groups using an individual patient data meta-analysis approach. Literature searches in PubMed, Embase, PsycINFO and Cochrane Library resulted in 13,384 abstracts from database inception to January 1, 2016. Twenty-four RCTs (4889 participants) comparing a guided Internet-based intervention with a control group contributed data to the analysis. Missing data were multiply imputed. To examine treatment outcome on response and remission, mixed-effects models with participants nested within studies were used. Response and remission rates were calculated using the Reliable Change Index. The intervention group obtained significantly higher response rates (OR = 2.49, 95% CI 2.17 – 2.85) and remission rates compared to controls (OR = 2.41, 95% CI 2.07 – 2.79). The moderator analysis indicated that older participants (OR = 1.01) and native-born participants (1.66) were more likely to respond to treatment compared to younger participants and ethnic minorities respectively. Age (OR = 1.01) and ethnicity (1.73) also moderated the effects of treatment on remission. Moreover, adults with more severe depressive symptoms at baseline were more likely to remit after receiving internet-based treatment (OR = 1.19). Guided Internet-based interventions lead to substantial positive treatment effects on treatment response and remission at post-treatment. Thus, such interventions may complement existing services for depression and potentially reduce the gap between the need and provision of evidence-based treatments.

Keywords: Internet-based guided self-help, psychotherapy, depression, meta-analysis.

Introduction

Major Depressive Disorder (MDD) is highly prevalent (Alonso, et al., 2004; Kessler, Chiu, Demler, & Walters, 2005; Waraich, Goldner, Somers, & Hsu, 2004) and associated with substantial impairment (Saarni, et al., 2007; Üstün, Ayuso-Mateos, Chatterji, Mathers, & Murray, 2004) and economic costs (Berto, D'Ilario, Ruffo, Virgilio, & Rizzo, 2000; Greenberg & Birnbaum, 2005; Smit, et al., 2006). Psychological treatments have been shown to be effective in the treatment of depression (Cuijpers, et al., 2014; Cuijpers, van Straten, Andersson, & van Oppen, 2008). However, the majority of depressed people remain untreated (Kohn, Saxena, Levav, & Saraceno, 2004; Wittchen, et al., 2011). Epidemiological data from Europe have shown that only 14% and 38% of those who experience mood disorders receive psychotherapy and pharmacotherapy respectively (Alonso, et al., 2004). These percentages are lower (7-21%) in low- and middle-income countries where mental health care facilities are scarce (Chisholm, et al., 2016).

Using the Internet to provide guided interventions may help overcome some of the limitations of traditional treatment services (Andersson & Titov, 2014; Ebert, Lehr, Baumeister, et al., 2014). A guided internet-based intervention is a psychotherapeutic intervention primarily based on self-help material delivered via the Internet with some form of minimal guidance related to the therapeutic content. This guidance is considered minimal if provided at low intervals through electronic means, such as emails, phones and e-chats (e.g., briefly weekly emails after each online session). Such guided Internet-based interventions (a) provide high accessibility, (b) may attract people who do not use traditional mental health services, and (c) are easily scalable. A relatively recent meta-analysis (MA) showed that guided Internet-based interventions for depression can have positive effects on depressive symptoms (Richards & Richardson, 2012). However, statistical comparisons based on group means provide limited information about clinical significance (Jacobson & Truax, 1991). Therefore, response and remission have been suggested as the outcome criteria of choice for depression treatment (Keller, 2003; Rush, et al., 2006). Remission is generally considered a state in which symptoms of the illness are (nearly) absent (Rush, et al., 2006). It is associated with better functioning (Hirschfeld, et al., 2002; Riso, et al., 1997), lower relapse rates, and improved long-term prognosis (Bech, Lönn, & Overø, 2010; Fava, Fabbri, & Sonino, 2002; Karp, et al., 2004; Kennard, et al., 2009; Ogrodniczuk, Piper, & Joyce, 2004; Taylor, Walters, Vittengl, Krebaum, & Jarrett, 2010). It is the accepted goal of treatment of acute depression (Anderson, et al., 2008; Gelenberg, et al., 2010; Lam, et al., 2009; NICE, 2010; Thase & Ninan, 2001). However, while not all patients achieve remission (Cuijpers, et al., 2014), some may still be classified as responders, i.e. achieve a clinically significant reduction in depressive symptoms (Frank, et al., 1991).

Neither remission nor response has been addressed in any meta-analyses of guided Internet-based interventions for depression (Andersson & Cuijpers, 2009; Andersson, Cuijpers, Carlbring, Riper, &

Hedman, 2014; Andrews, Cuijpers, Craske, McEvoy, & Titov, 2010; Johansson & Andersson, 2012; Richards & Richardson, 2012). Inconsistencies in methodology for defining response and remission as well as missing reports of these outcomes in studies hinder their evaluation using conventional meta-analytic approaches. Another issue not yet addressed is the possibility that not all subgroups of patients benefit from this specific treatment delivery. For example, it may be argued that patients with severe symptoms are too impaired to gain substantial effects in terms of remission/response with guided Internet-based interventions (Kiluk, et al., 2011). Consequently, the only treatment guideline that currently include guided Internet-based interventions [UK NICE guidelines (NICE, 2010)] recommends its use only for mild-to-moderate symptoms (NICE, 2010). Other subgroups of participants, such as those with low education, may not be able to apply therapeutic self-help strategies and thus, respond poorly (Warmerdam, van Straten, Twisk, & Cuijpers, 2013), and older adults may have difficulties in utilizing Internet-based technologies (Donker, et al., 2013).

Given that the number of people from specific subgroups is often small in single trials, and randomized trials are usually powered to detect overall treatment effects, randomized controlled trials (RCTs) are mostly underpowered to adequately examine subgroup and moderator analysis (Brookes, et al., 2004). As studies also seldom report effectiveness for different patient characteristics, it is impossible to examine patient-level moderators using traditional meta-analytic approaches. Individual participant data meta-analyses (IPDMA) can overcome some of the limitations of the conventional study level MAs (Clarke, 2005; Jones, Riley, Williamson, & Whitehead, 2009; Riley, Lambert, & Abo-Zaid, 2010). By pooling the raw data of individual trials, it is possible to conduct analyses not reported in original studies and obtain large sample sizes with sufficient power to both examine effects in relevant subgroups and identify outcome moderators (Cooper & Patall, 2009).

The present study aimed to examine response and remission rates in randomized controlled trials for the effect of guided Internet-based interventions on adult depression at the post-treatment by using an IPDMA approach. Additionally, the effects on response and remission were evaluated in specific subgroups of interest and tested for potential moderating effects.

Methods

Identification and selection of studies

We included randomized trials in which the effects of a guided Internet-based interventions treatment was compared with either an active or inactive comparison group (waiting list, care-as-usual, attention placebo, other) in adults with acute depression (diagnosed based on either a clinical interview or cut-off scores on self-report questionnaires). Guidance could be provided by either a professional or a paraprofessional. Studies were excluded if they a) provided interventions with face-

to-face guidance (blended treatment and videoconferencing), b) were delivered to the individual via a group format, c) required the individual to travel to use the program (e.g., a clinic), d) used a primarily app-based intervention, e) compared the intervention to an active face-to-face treatment. No restrictions were applied synchronous / asynchronous guidance and language. For the identification of potential studies for inclusion, we used an existing database, which includes all records of randomised controlled trials examining the effects of psychotherapeutic treatments for adult depression and it is described in detail elsewhere (Cuijpers, van Straten, Warmerdam, & Andersson, 2008). For this database, a literature search was conducted for studies published from database inception to January 2016 (see supplement for PubMed full search strings). The study selection was performed independently by two authors (E.K. and P.C.). Disagreements were solved through discussion.

Data collection and extraction

Corresponding authors were contacted for each of the identified papers and were asked to provide raw data from their study and whether they were aware of other RCTs that met our inclusion criteria but were not yet published. Of the 27 studies identified from the search, data were obtained from 24 (Andersson, et al., 2005; Berger, Hammerli, Gubser, Andersson, & Caspar, 2011; Buntrock, et al., 2015; Carlbring, et al., 2013; Choi, et al., 2012; Ebert, Lehr, Boß, et al., 2014; Geraedts, Kleiboer, Wiezer, van Mechelen, & Cuijpers, 2014; Hallgren, et al., 2015; Imamura, et al., 2014; Johansson, Ekbladh, et al., 2012; Johansson, et al., 2012; Kenter, Cuijpers, Beekman, & van Straten, 2016; Kivi, et al., 2014; Klein, et al., 2016; Newby, et al., 2013; Nobis, et al., 2015; Perini, Titov, & Andrews, 2009; Ruwaard, et al., 2009; Sheeber, et al., 2012; Unlu Ince, et al., 2013; van Bastelaar, Pouwer, Cuijpers, Riper, & Snoek, 2011; Vernmark, et al., 2010; Warmerdam, van Straten, Twisk, Riper, & Cuijpers, 2008; Williams, Blackwell, Mackenzie, Holmes, & Andrews, 2013). Data from three studies (Titov, et al., 2015; Titov, et al., 2011; Williams, et al., 2013) could not be obtained. Two reviewers extracted data independently (E.K and S.B) based on a generic standardised protocol of integrating IPD datasets. For further details, the reader is referred to the supplement of Karyotaki and colleagues (2017). Disagreements and unclear items of data coding were resolved through discussion

Risk of bias assessment

The validity of the included studies was assessed using four criteria from the Cochrane 'Risk of Bias assessment tool (Higgins & Altman, 2008). This tool identifies possible sources of bias, including: the adequate generation of allocation sequence, the allocation concealment, the prevention of knowledge of the allocated intervention, and dealing with incomplete outcome data (this was assessed as positive when intention-to-treat analyses were conducted, meaning that all randomized patients

were included in the analyses). We did not examine blinding of participants and personnel because this is not possible in psychotherapy research due to the nature of the treatment. Moreover, we had access to primary datasets and thus, selective reporting is not applicable for our analyses. Finally, there was no indication for other sources of bias (e.g., extreme baseline differences). Two researchers conducted the quality assessment independently (E.K. and D.E.).

Calculating response and remission rates

The majority of the studies used either the Center for Epidemiological Studies Depression Scale [CES-D (Radloff, 1977)] or the Beck Depression Inventory I or II [BDI-I (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961); BDI-II (Beck, Steer, & Brown, 1996)] as an outcome measure. Two studies used the Patient Health Questionnaire–9 [PHQ-9 (K. Kroenke, R. L. Spitzer, & Williams, 2001)] and the Montgomery–Asberg Depression Rating Scale [MADRS (Davidson, Turnbull, Strickland, Miller, & Graves, 1986)], respectively. For all measures, we calculated response rates according to the widely used Reliable Change Index (Jacobson & Truax, 1991). Reliable change was calculated separately for each included study using the standard deviation at baseline and the test-retest reliability coefficient of the measures [CES-D: 0.87 (Miller, Anton, & Townson, 2008); BDI-I: 0.72 (Yin & Fan, 2000); BDI-IA: 0.82 (Beck, Steer, & Carbin, 1988); BDI-II: 0.93 (Beck & Steer, 1984); PHQ-9: 0.76 (Kroenke, Spitzer, & Williams, 2001); MADRS: 0.78 (Fantino & Moore, 2009)]. In the absence of reliable cut-off scores for remission and in order to maintain consistency in defining remission across different measures, we applied Jacobson's method to define a near symptom-free state (Jacobson & Truax, 1991). Accordingly, patients were classified as remitters if they moved two standard deviations below the mean of the clinical group in each study. The resulting cut-off scores represent a rather high-end state of functioning.

To test the robustness of our main findings, we conducted sensitivity analyses applying alternative criteria for response and remission. For response, we chose 50% symptom improvement (a relative instead of an absolute improvement; Rush et al., 2006). For remission, we used established cut-offs for the outcome measures [BDI-I <13 (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961); BDI-II <10; CESD <16 (Radloff, 1977)]; PHQ-9 < 5 (Kroenke, et al., 2001) and MADRS < 7(Davidson, et al., 1986)].

Missing data

Analyses were conducted according to the intention-to-treat principle using the statistical software Stata (version 14.2). Missing data were handled using multiple imputation under the missing-at-random assumption (100 imputations). To multiply impute the missing data we used complete baseline variables, such as age, gender, baseline depression severity, group, and study ID. Multiple

imputation produces often unbiased estimates in the case of non-missing at random (NMAR) data (Schafer & Graham, 2002). In addition, we performed a complete case analysis using data from participants who completed post-treatment assessment under the missing completely at random assumption (MCAR).

Multiple treatments within one study

In two studies two treatments were compared to a single control group (Johansson, Sjoberg, et al., 2012; Warmerdam, Straten, Twisk, Riper, & Cuijpers, 2008). In these cases, we treated each comparison as a separate study and avoided double counting of controls by randomly assigning half of the controls to each comparison.

IPD meta-analysis

Effects were calculated using the one-stage IPDMA approach where we merged all individual participant data from the available studies with participants clustered on studies (Riley, et al., 2010). One-stage IPDMA approach is preferred because it allows for a more sophisticated modelling of covariates compared to two-stage IPDMA approach. All analyses were conducted with Stata (version 14.2) (StataCorp, 2015). We performed a logistic multilevel analysis to examine the effect of guided Internet based interventions on response and remission rates. Response and remission were used as dependent variables and treatment group was used as the independent variable. A random intercept for study was added to each model.

We examined baseline individual-level variables (age, gender, educational level, ethnicity, relationship status, employment status, comorbid anxiety, baseline depression severity, previous depressive episodes, medication use and alcohol use) to explore their moderating effects on treatment outcomes. Response and remission were used as outcome variables and each of the aforementioned baseline variables and treatment group were used as independent variables. We added the interaction between each examined variable and treatment group into the multilevel mixed effect logistic regression model.

In addition to the one-step IPDMA, we also performed a two-stage IPDMA to test the robustness of our findings and to examine several additional study-level variables of interest (diagnosis, target group, type of control, recruitment, outcome measure, number of online sessions, intervention type and risk of bias). We first calculated event rates for each study separately based on the imputed data. Then, pooled event rates across studies were calculated using a random-effect model as implemented in the Comprehensive MA software package, which accounts for between-study heterogeneity (Abo-Zaid, et al., 2013). We proceeded to calculate the odds ratio (OR) for each study and pooled the results across the studies using a random-effects DerSimonian-Laird model

(DerSimonian & Laird, 1986). For our main outcomes we also calculated the numbers needed to treat (NNT) and their 95%-confidence intervals as compared to the control groups (Laupacis, Sackett, & Roberts, 1988).

To test study-level moderators we conducted a series of subgroup-analyses, using the mixed-effect model. The following subgroups were investigated: *Study characteristics:* MDD confirmed using an established diagnostic interview (yes/no), type of control group (non-active/active); recruitment (community/clinical setting); recruitment location; outcome measure (BDI/other); risk of bias (low [4]/some risk [<4]), *Intervention characteristics:* intervention type [internet-based Cognitive Behaviour Therapy (iCBT)/other], number of modules (4-5/6-7/≥8).

We calculated the I^2-statistic as an indicator of heterogeneity (Ioannidis & Trikalinos, 2007). A value of 0% indicates no observed heterogeneity, 25% low, 50% moderate, and 75% high heterogeneity. We calculated 95% confidence intervals using the non-central chi-squared-based approach (Stata) (Orsini, Bottai, Higgins, & Buchan, 2005). We also calculated the Q-statistic, but only report whether this was significant.

Publication bias was examined by inspecting the funnel plot, by Egger's test (Egger, Smith, Schneider, & Minder, 1997) and Duval and Tweedie's trim-and-fill procedure (Duval & Tweedie, 2000), which yields an estimate of the effect size after publication bias has been taken into account (Borenstein, Hedges, Higgins, & Rothstein, 2009).

Results

Study selection

Figure 1 shows the selection process for the included studies. The systematic literature search resulted in 16,407 references (4562 abstracts in PubMed, 2530 in PsycINFO, 4243 in Embase, and 5072 in the Cochrane Library). After removal of duplicates, 13,384 articles were screened in titles and abstracts. This led to 1885 articles screened in full text. Twenty-seven studies met our inclusion criteria. Of those studies, 24 provided IPD for this analysis. In a systematic literature search we ran on January 2018, we found 8 more eligible studies for inclusion (Boeschoten, et al., 2017; Ebert, et al., 2017; Forand, et al., 2017; Forsell, et al., 2017; Milgrom, et al., 2016; Newby, et al., 2017; Rosso, et al., 2016; Smith, et al., 2017). However, an IPD meta-analysis is time- and resource-intensive. Therefore, we could not obtain data from these recent trials timely to update our IPD dataset.

Characteristics of included studies & participants

A total of 4889 cases were included from 24 studies (26 comparisons) conducted in 7 different countries. In the supplement Table 1 displays selected study characteristics, and Table 2 shows patient

characteristics. MDD was confirmed using a diagnostic interview in 15 studies. Most interventions were based on iCBT (n=17) or internet-based Problem-Solving Therapy (iPST) (n=6). The most common control was non-active delayed access to the program (n=13), but in eleven studies, an active comparison (brief scheduled therapist support, web-based discussion groups or treatment as usual) was used as control.

Risk of bias

Overall, risk of bias was low. All studies reported an adequate sequence generation and allocation to conditions by an independent party. Twenty studies reported blinding of outcome assessors or used only self-report outcomes. All studies were coded as having handled missing data adequately, as intention-to-treat analyses were applied. Twenty met all four-quality criteria, while the remaining five met three out of four criteria. Agreement between independent raters on the risk of bias was 95% across studies.

One stage IPD – response

Overall effects on response are presented in Table 3. At post-treatment the pooled response rate was 56.19% (95% CI 53.99 – 58.38%) in the intervention and 35.13% (95%CI: 33.07 – 37.20%) in the control conditions. Response rates were significantly higher in the intervention groups compared to controls, with an OR of 2.49 (95% CI: 2.17-2.85; $p < .001$ and NNT = 4.74, 95% CI = 4.21 – 5.46). Comparable results were found in the complete case analysis. Applying the alternative response criteria (50% symptom reduction) resulted in lower response rates in both the intervention (39.63%, 95% CI 37.49 – 41.77) and control conditions (19.12%, 95% CI 17.39 – 20.85), but the effect was slightly higher (OR = 2.83, 95% CI 2.45 – 3.28; p = .000).

Moderator analysis showed that the effect of guided Internet-based interventions on response was higher in native-born participants compared to ethnic minorities (OR = 1.66, 95% 1.07 – 2.59; p = 0.02), and in participants in a relationship compared to single adults (OR = 1.33, 95% CI; 1.01 – 1.74). We also found that older adults responded better compared to younger adults (OR of age = 1.01, 95% CI 1.00 – 1.02; p =0.03). Baseline severity moderated treatment outcome in the complete case analysis but not in the intention to treat analysis (OR = 1.16, 95% CI 1.00 – 1.35; p = 0.05). None of the other examined variables moderated the effects of treatment on response.

One stage IPD – remission

Mean remission rates at post-treatment across 26 comparisons were 38.51% (95% CI: 36.35 – 40.68) in the intervention and 21.52% (95% CI: 19.74 – 23.31) in the control conditions leading to an OR of 2.41 (95% CI 2.07 - 2.79; $p < .001$) and NNT = 5.98, 95% CI 4.35 – 6.80). Complete case analysis

revealed similar outcomes. The alternative remission criteria resulted in slightly higher rates (intervention: 41.98%; 95% CI 39.74 – 44.2; control: 26.40%; 95% CI 24.40 – 28.23) and a slightly higher OR of 2.17 (95% CI 1.89 – 2.49; p < .001).

Moderator analyses resulted in similar findings as the ones found for response. Age (OR = 1.01, 95% CI 1.00 – 1.03; p = 0.02), ethnicity (OR = 1.73, 95% CI 1.07 – 2.81; p = 0.03) and baseline depression severity (OR = 1.19, 95% CI 1.01 – 1.39; p = 0.04) significantly moderated effect on remission. However, relationship status was not a significant moderator of remission (p = 0.31). Problematic alcohol drinking moderated response in the complete case analysis but not in the intention to treat analysis. None of the other variables moderated the effect of treatment on remission rates.

Two stage IPD – response

Results of the two-stage IPD showed similar results as those of the one-stage IPD on response rates (Table 4 and eFigure 1). Effects on response rates at post-treatment were significant and in favor of Internet-based treatments (OR = 2.76, 95% CI 2.23 – 3.41; p < .001). The NNT was 4.16 (95% CI: 3.41 – 5.26). Heterogeneity was moderate I^2 = 58% (95% CI 35 – 73; p = .000). Inspection of the funnel plot and Egger's test indicated some possible publication bias. After adjustment for missing studies (8 imputed studies) using the Duval-Tweedie trim-and-fill procedure, OR for response at post-test was 2.15 (95% CI 1.72 – 2.70). Complete case analysis resulted in similar outcomes. Effects on response were significantly moderated by type of control groups in complete case analysis (higher effects of waiting list groups compared to active control groups; p = 0.02), but this was not replicated in the intention to treat analysis (p = 0.05). All other differences in effects estimates between subgroups on response were non-significant in both intention to treat and complete case analyses (Table 4).

Two-stage IPD – remission

Table 4 and eFigure 2 show the results of the two-stage IPD analyses on remission rates. Remission rates at the post-treatment were significantly higher in the intervention groups compared to control groups, with an OR of 2.80 (95% CI 2.21 – 3.56; p < .001) and a NNT of 5.26 (95% CI 4.34 – 6.66). Heterogeneity was moderate (I^2 = 54%, 95% CI 29 – 71; p = .001). There was some indication of publication bias. Duval-Tweedie trim-and-fill procedure resulted in 7 missing studies. The adjusted OR was 2.17 (95% CI 1.90 – 2.48). Eggers test was significant (p <0.05). Complete case analysis showed similar outcomes. Subgroup analysis did not result in significant associations.

Discussion

This IPD MA provides a precise estimation of the overall and specific subgroup effects of internet-based guided self-help on response and remission. Effects on response were within the range of effects found in a recent meta-analysis for face-to-face psychotherapy (Cuijpers, et al., 2014). Remission rates were slightly lower both in the intervention (38.51%) and in the control conditions (21.52%) compared to face-to-face psychotherapy (43% vs. 27%; HAM-D_{17} cut-off for "no depression" < 7). However, when using the alternative remission criteria based on cut-offs for no depression on the examined scales, which is more comparable to the criteria used in the MA for face-to-face psychotherapy, remission rates were similar (41.98% vs. 26.40%).

Older adults and were more likely to respond and remit after treatment. Moreover, people with depressive symptoms were found to have significantly higher remission rates. These findings are of particular importance as these patient groups are often underrepresented in Internet intervention trials; it was until now unclear whether results from randomized trials could be generalized to these populations (Gerhard Andersson & Titov, 2014). Different engagement levels between older and younger adults may explain the better outcomes for older adults. A recent IPD meta-analysis on unguided interventions showed that younger adults have higher risk of treatment dropout compared to older adults (Karyotaki, et al., 2015). Nevertheless, it should be borne in mind that age had a very small moderation effect (as age increases by 10 years, the odds of responding/remitting after guided Internet-based interventions increases by 0.10 units). Thus, it is possible that the statistical significance of this effect may have been a result of the high statistical power of our sample. Nevertheless, we can safely conclude that these interventions are at least as effective in older adults. Moreover, the substantial effects found for the severely depressed individuals are in line with the findings of the IPDMA of Bower et al. (2013) (Bower, et al., 2013) of low-intensity interventions. This result may reflect differences in motivation, as severely depressed adults may be more motivated to engage with the treatment. It should, however, be noted that baseline depression moderated the effects of the interventions on remission and not on treatment response ($p = .05$). Therefore, we cannot draw firm conclusions regarding the moderating effect of baseline depression severity.

Ethnicity was also found to moderate outcome. Ethnic minorities had significantly lower response and remission rates than natives. Cultural adaptations may be needed to serve the needs of ethnic minority groups. Perhaps the interventions are not enough adapted to suit the needs of the different minorities. Another plausible explanation for this finding may be potential cultural bias in assessment instruments. A common way of assessing ethnicity is by selecting checkbox on questionnaires. This may not be a comprehensive way to capture ethnic identity and acculturation. In other words, it is possible that not all ethnic minorities have lower response and remission rates. Moreover, patients with a partner had significantly better outcomes than those without, suggesting

possibly that partners may actively support patients during treatment or the feeling of loneliness may predispose single adults to benefit less. This result contrasts findings from a recent IPDMA of unguided iCBT for depression (Karyotaki, Riper, Twisk, & et al., 2017). This difference in findings between the two IPDMAs may be partly explained by differences in the nature of guided and unguided Internet-based interventions or in differences between baseline participant characteristics. To our knowledge, there is no other IPD meta-analysis on online or face-to-face psychotherapy, which has tested the association between relationship status and treatment effects. Moreover, individual trials do not have enough power to examine such association sufficiently.

We did not find significant moderating effects of several individual- and study-level variables. For instance, variables such as the number of online sessions, depression diagnosis, comorbid anxiety, or use of antidepressants did not influence remission and response rates. Therefore, guided Internet-based interventions can be helpful for many individuals with different characteristics. Furthermore, since the intervention's length does not affect outcomes, brief interventions can be considered equally effective with lengthy interventions.

When interpreting results from this study, several limitations must be considered. First, when we performed our searched in January 2016, we identified 27 eligible studies. However, we could not include three of these studies. In additional searches we performed in January 2018, we found eight more eligible trials. Thus, availability bias cannot be ruled out. Second, most of the internet-based interventions exclude patients with severe symptoms or active suicidal ideation. Therefore, the present analysis could not grasp the full magnitude of the effect of baseline depression severity. Third, we were only able to test for effects and effect modifiers when sufficient information was available across studies. Thus, there may be other relevant patient-characteristics associated with differential effects of guided Internet-based interventions treatment, where such treatment is less or possibly not effective at all [i.e. chronic depression (de Maat, Dekker, Schoevers, & de Jonghe, 2007) or comorbid personality disorders (Newton-Howes, Tyrer, & Johnson, 2006)]. Fourth, although two studies (Choi, et al., 2012; Unlu Ince, et al., 2013) were directed at ethnic minorities (Turkish and Chinese migrants), all studies were conducted in Western, high-income countries. Thus, results may not be generalizable to low and middle-income countries. Fifth, eleven included studies recruited participants exclusively through the community and only six studies recruited participants exclusively through the routine care, thereby limiting the generalizability of the current findings to clinical samples. Self-referred patients in guided Internet-based interventions may differ from patients accessing face-to-face treatment in several ways. For example, IGHS patients may have greater motivation and thus, higher chances of treatment response. However, we did not find any indication that the way of recruitment was associated with effects. Sixth, in our analyses we observed moderate heterogeneity that could not be fully explained by the examined sub-group analyses. Heterogeneity might be a result of differences

in the population, interventions, and the design of the trials. For instance, we compared Internet-based interventions to various control condition ranging from waiting list to care as usual services. Although we did not find significant differences between the examined controls, the obvious variability among them might have still influenced the overall heterogeneity. Thus, results should be interpreted with caution. Seventh, there was some indication of publication bias, showing that the current analysis may have over-estimated effects because studies with negative results remained unpublished. However, after adjusting for missing studies, results remained significant and in favor of guided Internet-based interventions. Eighth, the majority of the included studies examined guided iCBT (20/26 examined comparisons) or iPST (6/26 examined comparisons). Therefore, the generalizability of the current findings to other types of psychotherapeutic interventions is limited as our sample consists mostly of iCBT or iPST trials.

Conclusions

The present study has implications for research, clinical practice, and policy. The substantial effects on response and remission strongly support the use of Internet-based guided self-help treatments for depression as an evidence-based treatment option in routine care. Therefore, the use of guided Internet-based interventions, such as iCBT, may be a valuable strategy to bridge the gap between the demand for psychological interventions and the supply available (Kohn, et al., 2004). In the included studies, either professionals or paraprofessional provided the therapeutic guidance, suggesting that these interventions do not require the involvement of professionals. Thus, Internet-based interventions can be delivered by either nurses or general practitioners in primary care. Similarly, clinical psychologists or psychiatrists can deliver these interventions in secondary care.

Nevertheless, future effectiveness studies should further explore the benefit of these interventions in routine care. Also, the current results indicate that the application of such interventions does not need to be restricted to certain patient populations (i.e. patients with mild-to-moderate symptoms), which is currently recommended by the NICE clinical guideline (NICE, 2010). Guided Internet-based interventions could very well be used as a first step in a stepped-care approach (Bower, et al., 2013; van Straten, Hill, Richards, & Cuijpers, 2015). In these approaches, a less resource-intensive treatment, such as guided Internet-based interventions, can first be offered, with those patients not responding in these interventions subsequently referred to more intensive psychological treatments. Since psychotherapists trained in evidence-based methods are a limited resource, guided Internet-based interventions treatment can help allocate face-to-face therapy to those most in need of intensive care. However, given that (a) acceptance of an intervention by the target population is always a necessary prerequisite for utilizing interventions (Andrade, et al., 2014;

Baumeister, et al., 2014; Ebert, et al., 2015), (b) studies indicate that different patients may prefer different types of treatment modalities (i.e. face-to-face psychotherapy, medications, guided self-help) (Musiat, Goldstone, & Tarrier, 2014; van Schaik, et al., 2004) and (c) preferences may affect treatment uptake utilization and outcome (Kwan, Dimidjian, & Rizvi, 2010), we nevertheless caution that guided Internet-based interventions should only be offered as one treatment alternative alongside other evidence-based options. Moreover, future research should examine the relative effectiveness of guided Internet-based interventions compared to existing treatments.

It should further be acknowledged that depending on the criteria, between 44-61% of the participants did not show response, and 58-62% did not achieve remission. It may be the case that a subgroup of these patients would have benefited from other forms of treatment. Also, if initial patient treatment expectations are not met in one treatment modality, it may adversely affect general treatment expectations, which may impact the likelihood that these patients engage in or benefit from different future treatment deliveries (Ebert, Lehr, Baumeister, et al., 2014; Rozental, et al., 2014). However, this is a yet unanswered question that should be addressed in future studies. This study also indicates that more research is needed to determine the effectiveness of guided Internet-based interventions (a) for specific subgroups of patients in the long-term, (b) for patients in non-Western and low/middle-income countries, (c) for specific conditions such as comorbid general medical disorders (Nobis, et al., 2013) and (d) in relation to different theoretical treatment modalities and patient-characteristics (e.g. cognitive therapy vs. behavioral activation in severe depression or old age). Finally, future research should examine predictors of treatment and study dropout to shed light on factors influencing the attrition from guided Internet-based interventions. Such analysis might provide valuable knowledge about how to improve adherence in guided Internet-based interventions.

In conclusion, the present study provides evidence that guided Internet-based interventions is an effective treatment for depression in patients with a wide range of characteristics and may thus complement existing services.

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