Chapter 8

General Discussion

Aims of this thesis

The primary aim of this thesis was to evaluate the clinical and cost-effectiveness of a web-based guided self-help intervention on the onset of diagnosed major depression in adults with subthreshold depression. In this final chapter, I will summarise and integrate the main findings of both studies:

- How do the results compare to previous research on depression prevention?
- What are the limitations of the presented studies?
- What are clinical implications?
- And what future research is still needed?

Finally, I will end with a brief general conclusion of this thesis.

Main findings

Below, I will briefly summarise the main findings presented in this thesis. For an extended summary of these findings, I refer to the overall summary of this thesis or to the specific chapters, respectively.

- Results of our meta-analysis showed that prevention of depression using psychological interventions seems feasible and it might in conjunction to treatment be an effective way to prevent or at least delay the onset of major depressive disorder (**chapter 2**).
- Results from our first randomised controlled trial indicated a greater reduction in depressive symptom severity in the intervention as compared to the control group at post-treatment. These effects were sustained at 6- and 12-month follow-up (**chapter 4**).
- Findings from the first study also suggested that the web-based guided self-help intervention could effectively reduce the risk of depression onset, or at least delay its onset. The number-needed-to-treat (NNT) to prevent one new case of major depressive disorder was 6, which is comparable to NNTs in the treatment of major depression (**chapter 5**).
- In addition, the intervention has an appealing likelihood of being more cost-effective than enhanced usual care (**chapter 6**).
- Findings from the second trial showed that, compared with a waitlist control group, the same web-based intervention using an adherence-focussed guidance concept was effective in reducing observer-rated and self-reported depressive symptom severity compared with a waitlist control condition (**chapter 7**).

Comparing with previous research

Clinical effectiveness

Treating subthreshold depression

The between-group effect sizes at post-treatment in the first trial (d = 0.69, 95% CI 0.49 - 0.89, based on the CES-D) and in the second trial (d = 0.40, 95% CI 0.12 - 0.68, based on the QIDS; d = 0.84, 95% CI 0.55 - 1.13, based on the CES-D) compare favourably to the results from a recent meta-analysis on psychological interventions for the treatment of subthreshold depression. This meta-analysis showed a small to moderate effect size of psychological interventions at post-treatment (g = 0.35, 95% CI 0.23 - 0.47) (1). The difference might be explained by the high heterogeneity in the meta-analysis with respect to target groups, treatments, and type of control groups. For example, most of the studies included in the meta-analysis evaluated the effectiveness of a psychological intervention in older adults and pregnant women (i.e., (2, 3).

Up to date, three studies targeted an adult population (18 - 65 years) without additional risk factors (4-6). Between-group effect sizes ranged from d = 0.20 (6) to d = 0.80 (5). So far, only Spek and colleagues evaluated the effects of an internet-based self-help cognitive behaviour therapy intervention for the treatment of subthreshold depression. Compared to a waitlist control condition, the reported between-group effect size of d = 0.55 (6) is comparable to the findings from our trials. However, in our trials, the effect size measure was represented by the standardised mean differences. That is, between-group effect sizes were calculated by subtracting the mean score of the intervention group from the mean score of the control group, and dividing the result by the pooled standard deviations. Based on this measure, the effect size was reduced to d = 0.27 (95% CI -0.01 - 0.54) in the study by Spek and colleagues.

The pre- to post-treatment within-group effect sizes in the intervention group observed in our trials (first trial based on the CES-D: d = 1.06, 95% CI 0.86 - 1.27 and second trial based on the QIDS: d = 0.95, 95% CI 0.66 - 1.24) are also comparable to effect sizes found by Spek and colleagues (based on the BDI-II: d = 1.00; d = 0.94, 95% CI 0.65 - 1.23 using standardised mean differences as described above) (6).

Preventing the onset of depressive disorders

To the best of our knowledge, this is the first randomised controlled trial that examined the effectiveness of a web-based guided intervention on the onset of major depressive disorder. The hazard ratio of 0.59 (95% CI 0.42 - 0.82) seen in our first study compares favourably to results from other indicated prevention studies focusing on an adult population without additional risk factors. To our knowledge, only three of such studies on non-web-based interventions have been conducted so far, revealing mixed results with incidence rate ratios

(IRRs) ranging from of 0.66 (95% CI 0.40 - 1.09; (7)) to 1.62 (95% CI 0.82 - 3.18; (8)). Results of the presented study are also comparable to preventive effects of psychological interventions in at-risk populations (i.e., HR = 0.60 (95% CI 0.31 - 1.16) in physically ill patients; (9)).

Economic evaluation

To the best of our knowledge, this is the first trial-based study evaluating the cost-effectiveness of a web-based guided self-help intervention to prevent the onset of major depressive disorders in an adult subclinical depressive sample. However, some evidence exists that indicated face-to-face and brief bibliotherapy interventions for the prevention of depression represent good value-for-money (10). At this point, five studies have economically evaluated preventive interventions in adults (11-15). All of these studies suggest that prevention of depression is a good investment associated with acceptable levels of cost-effectiveness and may even be cost-saving. Yet, because of the use of different outcome measures (i.e., disability-adjusted life years) it is difficult to compare the present study with previous findings, but the conclusions are roughly similar. Thus in spite of methodological differences, we begin to see converging evidence pointing to favourable levels of cost-effectiveness and sometimes even costs-savings of depression prevention.

Limitations

First, we excluded applicants from the study who had a major depressive episode within the previous six months based on Kupfer's model (20), which suggests that a patient is regarded as being recovered six months after remission is reached. However, we did not assess lifetime history of major depressive disorder at baseline. Previous depressive episodes are a risk indicator for depression onset (21) and history of depression should be investigated in future studies. Findings from our study likely refer to a mixed sample of first depression onsets and depression recurrences. Hence, we cannot draw conclusion about whether the intervention is equally effective in both subsamples. In addition, we did not assess (chronic) medical conditions. Experiencing (chronic) medical conditions might also be a risk indicator for the onset of a major depressive disorder. Future studies should thus assess such conditions or evaluate the effects of web-based guided self-help interventions directly in such patient groups, respectively.

Second, we evaluated the effects of the intervention compared to care-as-usual, the usual comparator in pragmatic trials. However, this approach has also some drawbacks. For example, we did not standardize care-as-usual across GPs, which added noise to the study. In the German health care system, psychological interventions (i.e., cognitive behavioural interventions) are not provided to people suffering from subthreshold depression. Care-as-usual

for subthreshold depression mainly includes visits to the GP and the GP might inform the patient about i.e. the nature of depressive symptoms and might make suggestions about improving one's lifestyle (i.e., engaging in physical activity, adhering to a regular sleep pattern, etc.) and available treatment options if depressive symptoms deteriorate. However, not all GPs thoroughly provide this information to their patients. Hence, care-as-usual was likely to be heterogeneous across GPs. If depressive symptoms deteriorate (i.e., major depressive episode), patients will be treated according to the German S3-Guideline/National Disease Management Guideline Unipolar Depression. Care-as-usual then consists of basic and subsequently more intensive interventions depending on the length and severity of depressive symptoms (i.e., visits to psychiatrists, psychotherapists, and the prescription of medication). As GPs were not known to us, we could not adjust for GP in the analyses.

Third, as we conducted pragmatic trials, we permitted the use of antidepressant medication as part of usual care and it was not an exclusion criterion. As we excluded those participants with a major depressive disorder in the previous six months, we assumed that we did not include participants in the study who were treated for depression. However, we cannot rule out that for some participants the web-based intervention was an adjunct to concurrent antidepressant treatment (i.e., secondary prevention).

Fourth, the first randomised controlled trial had only a 12-month follow-up period. Therefore, it is not without doubt whether the web-based guided self-help intervention actually prevented the onset of major depressive disorders or just delayed its onset. Prevention trials should comprise a follow-up of 18 to 24 months to cover the preventive effects of the interventions (16). In our meta-analysis, we showed a small positive association between effects of preventive interventions during the first months of follow-up, indicating that with passing months, the intervention effects get somewhat larger. However, meta-regression analyses suggested that the effects of interventions are lower at longer follow-up periods of one to two years. Assuming diminishing long-term effects, the cost-effectiveness of the web-based intervention will also decline. However, only a few studies had longer follow-up periods than two years. Thus, more research with longer follow-up periods are needed to assess the long-term effectiveness and cost-effectiveness of preventive (web-based) interventions.

Fifth, in the first trial, study conditions were not balanced with regard to human attention as no eCoach was involved in the web-based psychoeducational intervention. Therefore, it cannot be ruled out that parts of the observed preventive effects were caused by human attention. With regard to the second trial, we cannot rule out a potential nocebo effect in the control condition even though patients in the control group had full access to usual care (17).

Sixth, in the first study, we assessed depressive symptom severity exclusively with self-report measures, such as the Centre for Epidemiologic Studies Depression Scale (CES-D). There is evidence that the CES-D does not specifically measure depressive symptoms, as the utility of the CES-D for detecting major depressive disorder is approximately equal to its utility for detecting generalised anxiety disorder (18). Observer-based ratings, such has the Hamilton Rating Scale for Depression (HRSD) are clearly recommended for future studies. Notwithstanding, depending on the symptom severity of an individual, self-report or clinician ratings might be more suitable. Therefore, it seems best to include both kinds of assessment in clinical research.

Seventh, we did not assess the duration of depressive symptoms at baseline meaning that we do not know whether depressive symptoms were first onset or persistent. Consequently, we do not know whether the reduction in depressive symptom severity was influenced by the duration of depressive symptoms. Knowing for how long participants have been suffering from depressive symptoms before they were enrolled in the study would have allowed assessing the point at which subthreshold depression becomes sufficiently persistent to warrant treatment.

Finally, participants in our trials were better educated as compared to the general population and were predominately female. Evidence suggests that better adherence is predicted by higher education (19). It might be that by virtue of increased levels of education, study participants are more motivated to engage in a web-based intervention, and are, therefore, more responsive. In our trial, only 2% of participants were low educated. Hence, we cannot predict the uptake of such an intervention in less educated people or among people with a lower socioeconomic status. Conclusions drawn from the present study may therefore not generally be applicable to other populations.

Clinical implications

Currently, major depressive disorder is one of the single most important cause of years lived with disability (YLDs) (20). Effective preventive interventions could contribute to a further reduction of the disease burden attributable to mental disorders. Given low participation rates in face-to-face preventive services, it would be worthwhile to scale up web-based interventions to efficiently alleviate the disease burden caused by MDD. eHealth interventions have the potential for more reach with fewer resources. Indeed, such interventions might overcome some of the financial, geographic, and time barriers that limit the dissemination and reach of traditional face-to-face interventions. As such, these interventions might have considerable impact at a population level. Moreover, considering the prevalence (21) and impairment

associated with subthreshold depression (22, 23), eHealth has the potential to make meaningful change. Preventive interventions are never likely to produce large individual effects, but when expanded to a population level, the overall impact can be substantial (24).

Our studies have some important implications for clinical practice. First, they add to the existing evidence that psychological interventions for subthreshold depression could result in substantial and clinically significant effects. For example, the post-treatment effect sizes were as large as those shown in a meta-analysis on face-to-face psychotherapy for major depression (25). In the first trial, treatment effects were sustained at 6- and 12-month follow-up. Thus, in contrast to recommendations of current clinical guidelines (i.e., (16)) we found strong evidence for offering psychological interventions to individuals with subthreshold depression. Both studies support the effectiveness of indicated preventive interventions. In addition, the first study adds that reducing the incidence of MDD is also possible using a web-based guided self-help intervention. The number-needed-to-treat (NNTs) of 5.9 found in this study is comparable to NNTs in the treatment of MDD (26). The NNT implies that of those identified with subthreshold depression and participating in the intervention almost 17% would benefit in terms of a prevented episode of MDD within a 12-month period.

Second, while the majority of non-web-based psychological interventions evaluated so far consist of 10 or more sessions (i.e., (3, 4, 27)), we achieved similar effect sizes with a brief intervention consisting of six sessions. This does not only permit treating more individuals for the same or lesser costs, it also reduces opportunity costs for participants (i.e., their time investment). This makes the intervention potentially more attractive for people with subthreshold depression. More attractive and less burdensome interventions are needed as the majority of individuals suffering from depressive symptoms do not seek help (28), and participation rates in face-to-face interventions are low (29).

However, there are some risks that need to be taken into account when translating a web-based guided self-help intervention to a population level. First, according to the standards model published by the Society for Prevention Research and adapted by Flay and colleagues, scale up or country-wide implementation of an intervention depends on the completion of (a) two high quality efficacy trials, (b) two high quality effectiveness trials including (c) information about the intervention's cost-effectiveness, followed by (d) dissemination research that shows that the intervention can be delivered as intended (i.e., with fidelity to the model being tested) (59). We have conducted two pragmatic randomised trials. However, only one study showed that the intervention could effectively prevent the onset of depressive disorders and indicated its likelihood of being more cost-effectiveness than enhanced usual care. Thus, more research is needed to replicate the findings before a nation-wide implementation could be considered.

Second, the individual eCoach feedback provided in this web-based intervention hinders a scale-up. A recent review of randomised controlled trials showed that unguided interventions can also be effective (with lower adherence rates and effects compared to guided interventions (30). Providing guidance may not only affect the outcome and cost-effectiveness of the intervention. In addition, it may influence the target group's willingness to use such an intervention and thereby influencing the intervention effects at population level. Furthermore, there are no guarantees that adherence and (by proxy) effectiveness will be maintained if preventive web-based interventions are scaled up in the population. For example, Christensen and colleagues reported that less than 1% of public registrants using a preventive intervention delivered openly on a website completed all modules (31). Future research need to evaluate the amount and type of guidance that should be provided to achieve clinically meaningful improvements while using as few resources as possible.

Third, cost of IT servers and infrastructure will increase if the intervention is scaled up because more servers are needed. However, these fixed costs are subject to an economies of scale effect. Economies of scale refer to the reduction in the cost per treatment as a result of increasing the number of clients. Economies of scale arise because many of the costs associated with the web-based intervention are fixed and not dependent on the number of clients (i.e., hosting the intervention on a server). Thus increasing the intervention output reduces the fixed cost per treatment. Hence, we assume that the cost of IT infrastructure will be cheaper per additional client if the intervention is offered on a larger scale. Economies of scale might also reduce variable costs (i.e., therapist's support per participant) because therapists become more efficient through better organisation and experience. However, the same technical resources available in the research setting (i.e., reasonable Internet connections) may not be available when the intervention is scaled up. In addition, the applicability of web-based interventions is related to (a) the acceptance of such interventions by the target population (i.e., preferences for different treatment modalities, such as face-to-face interventions) and (b) the availability of technical requirements (i.e., reliable access to the Internet).

Also, dissemination into primary care does not only depend on the target group's willingness to use such intervention and the availability of technical requirements, but also on the willingness of practitioners to refer patients to a web-based intervention. Clinicians may feel threatened that interventions offered via the Internet may take over their work. One task is thus to communicate that a web-based intervention should be seen as a complement to existing interventions rather than a full replacement of those interventions. Hence, diagnostic guidelines and proper training of practitioners are needed to be well established to render appropriate and safe referrals. In addition, dissemination can be hindered by legal and ethical regulations (32). For example, in Germany, providing psychotherapy over the Internet has been regarded

as being inappropriate. Although this is gradually changing (33), more political efforts are needed. Moreover, clinical guidelines need to be developed and evaluated.

Finally, an unanswered question refers to how web-based interventions could be rolled out to the population. A stepped care model, in which the web-based intervention serves as a first step followed by more intensive face-to-face interventions, when needed, could be one possibility to integrate web-based interventions into mental health care. For example, in the UK and the Netherlands, Internet-delivered CBT is already prescribed by GPs (22). In addition, web-based interventions could be promoted independently at the GP's (i.e., promotion videos in the GP's waiting rooms). However, one challenge in depression prevention is that most individuals at risk of developing a major depression do not show up in primary care. Therefore, innovative approaches are needed to reach these groups, for example through a systematic mental health screening of all people in specific settings (i.e., occupational setting or universities) and to motivate those at risk to engage in preventive interventions (i.e., acceptance facilitating interventions (52)). However, such strategies do not guarantee uptake either.

Directions for future research

How much guidance is needed in web-based interventions?

As stated above, the individual eCoach feedback provided in this web-based intervention hinders scaling up this intervention. The role of human support in web-based interventions has been widely discussed. Available evidence suggests that interventions that include some form of support yield better outcomes than unguided treatments (34-36). However, the expertise of therapists in web-based interventions might be less relevant as compared to face-to-face interventions. Hence, the guidance provided in web-based interventions is mainly focussed on supporting participants to engage in the intervention and to assist to solve technical problems.

A systematic review of internet-based interventions for depression showed a linear effect for the role of therapist contact. If there was no contact at all, between-group effect sizes were d = 0.21. Effect sizes increased when there was some therapist contact before (d = 0.44) or during the intervention (d = 0.58). Largest effect sizes were found if there was therapist contact both before and during the intervention (d = 0.76) (37).

Although guided web-based interventions produce larger effect sizes, there are still some unanswered questions about the frequency and form of guidance that should be provided. First, there is no apparent dose-response relationship between the amount of guidance and outcome. Interventions with intensive guidance do not appear to differ from interventions with minimal guidance (i.e., 10 minutes or less per participant and week) (36).

Second, assuming that a web-based intervention is highly structured evidence suggests that clinical outcomes are similar when a professional psychologist or a non-professional provides guidance (38, 39). However, it is unclear whether such clinical outcomes would also be obtained when interventions are less structured. Third, guided interventions are associated with higher costs than unguided interventions and interventions with automated feedback, respectively. From a public health perspective, despite smaller effects, unguided interventions may still produce larger effects at a population level with regard to the reduction of disease burden as more individuals can be reached for comparable lower costs. However, evidence whether unguided interventions are cost-effective is still scarce. Finally, a remaining question relates to therapist factors that are thought to be important in face-to-face treatments (40). Only a few studies have investigated therapist factors in web-based interventions showing no or small effects (41, 42). Some studies have explored therapeutic alliance in web-based interventions (43). Even if therapeutic alliance appears to be high in web-based interventions, there seems to be no association with the outcome (44, 45). However, some evidence suggests that therapeutic alliance could be important in internet-delivered CBT (46). It is important to understand which participants need what type and amount of guidance, delivered by whom and when.

How acceptable are web-based interventions at the population level?

We do not know whether characteristics of participants using a web-based intervention are similar to those accessing traditional face-to-face mental services. Therefore, even if an effective web-based intervention for the prevention of depression is available, we do not know to what extent it will be used in the target group at population level. However, for approximately 60% of participants in our first trial, it was their first time using a psychological intervention indicating that web-based interventions do attract people who may not make use of traditional face-to-face mental health services.

With regard to low uptake rates and high drop-out rates of some web-based interventions for depression (47), it is important to explore in future studies how a better fit between eligible participants and available web-based interventions could be achieved. The potential of web-based interventions very much depends on the acceptance in the target population. Thus, apart from their effectiveness, user acceptance is necessary before such interventions could be widely implemented in existing mental health care (48, 49). Acceptability of web-based interventions is based on positive attitudes towards such interventions. Although most effectiveness studies on web-based interventions do report on acceptability rates, their usefulness is limited because of methodological weaknesses. First, data on user acceptability are commonly based on completers while excluding non-completers. However, participants who are not satisfied might be more likely to drop out. Thus, acceptability rates might be

positively biased. Second, a valid measurement instrument has only recently been developed (50). Previous studies mostly relied on single items (51). However, single-item measures seem to be less reliable and valid as compared to multi-item measures. Third, acceptability of web-based interventions is commonly assessed retrospectively in relation to participants' evaluations of a specific intervention. However, an appraisal of a specific intervention does not disclose much about general attitudes towards web-based interventions.

Future research on attitudes towards psychological web-based interventions could facilitate the development and dissemination of web-based interventions. Eventually, this might help improve the quality of care for people suffering from subthreshold depression (50).

Who benefits most from preventive (web-based) interventions?

An important topic that needs to be addressed in future research is whether specific variables moderate treatment effects of web-based interventions. Gaining knowledge about moderators has practical implications for routine care. Whereas effect sizes may substantiate the average effectiveness of web-based interventions, they do not provide information about for whom it might work. However, this is of considerable interest for both researchers and clinicians since individuals clearly differ in their response to treatments.

For instance, even if two different interventions have found to be equally effective, it may be that one subgroup that shares specific characteristics shows greater response to one of the two intervention options while another intervention might be better suited for another subgroup. Being aware of moderating factors might facilitate the clinician's decision about which intervention option is most likely to reduce depressive symptom severity of a particular patient.

Identifying specific target groups also enables a clinician to customize existing interventions to the particular needs of this specific group. A better fit between eligible participants and interventions will probably lead to higher satisfaction and less dropouts and eventually to better outcomes.

However, there has been limited research on the impact of moderators in (web-based) interventions. Usually, studies lack sufficient statistical power to detect potentially small moderator effects (52). Individual patient data (IPD) meta-analysis could be an approach to overcome this limitation (53). In an IPD meta-analysis, primary data of multiple trials are combined resulting in a large sample size with sufficient power to examine moderators of outcome (54). However, one inherent problem of this approach is that one can only conduct analyses with variables that have been assessed across a sufficient number of trials. Currently, a questionnaire is tested in a pilot study that includes items on predictors on depression onset and treatment outcomes (ICare project). If this questionnaire is used in future prevention

studies, one will be able to pool available data to develop prediction algorithms on who is likely to benefit most from preventive interventions.

What do we know about negative effects of web-based interventions?

Limited evidence is available with respect to negative outcomes of psychotherapy (55, 56). Symptom deterioration is one of the possible negative outcomes. Evidence from uncontrolled trials showed proportions of patients with symptom deterioration ranging from 3% to 14% (57-60). Compared to face-to-face interventions, web-based self-help interventions might be associated with an even greater risk for symptom deterioration. For instance, a self-help intervention might be inappropriate for some patients due to its low intensity (61). Other patients might feel overstrained by applying new techniques into everyday life without guidance from a therapist. This could result in even greater intensifications of feeling hopeless. For example, a recent individual patient data meta-analysis indicated that depressed patients with low education showed a higher risk for symptom deterioration than better educated patients (62).

However, we do not know whether this also apply for participants displaying subthreshold depressive symptoms. In individuals with subthreshold manifestations of depression, lack of treatment response might lead to various negative consequences. For example, participants could become less motivated to engage in other, more intensive psychological treatments. Thus, future studies should evaluate potential negative effects of web-based interventions, especially in non-responders.

How could men be reached?

In the first trial, only one-quarter of participants were male. In the second trial, males amounted only to one-fifth of the total sample. It is well established that males hold less favourable attitudes towards psychological interventions for depression and other mental health problems than females (63-65). Gender socialisation seems to play a key role in these findings. For example, help-seeking behaviour and adherence to traditional masculine norms appear to be inversely related (66, 67). In addition, adherence to masculine norms could also contribute to difficulties with therapeutic engagement when attending psychotherapy. Men, who experience depressive symptoms, do not feel comfortable when talking about their problems because they perceive depressive symptoms as incompatible with traditional masculine norms (68). Psychotherapy itself might also been regarded as antimasculine. For example, men who seek help for depressive symptoms were rated as more feminine as those who did not seek help (69).

The above indicates that male-specific adaptations to psychological interventions are needed to improve intervention engagement. Participant evaluations of intervention

components that work could be the basis of how to effectively engage with men in psychological interventions. For example, men could be asked about preferences for and barriers to participation in psychological interventions. Future research is needed on how to reach men for psychological interventions. That is, effective treatments are only of relevance if they are used. Some evidence shows that pre-treatment motivational interventions might increase help-seeking among men (70). However, more studies are needed to further explore how such motivational interventions could also help men be better prepared to engage in psychological interventions.

Conclusion

In summary, both trials have shown that GET.ON Mood Enhancer Prevention is effective in treating subthreshold depression. In addition, the first trial has shown that the web-based intervention is also effective in preventing the onset of major depressive disorder. Moreover, the web-based intervention represented good value for money. The intervention can result in clinically meaningful changes also in the long-term using different guidance concepts. Our studies support recommendations given in clinical guidelines on depression treatment (such as the NICE guideline and the Dutch Multidisciplinary Guideline for Depressive Disorder) that low-intensity psychosocial interventions should be offered to manage (persistent) subthreshold depressive symptoms and mild to moderate depression. Web-based interventions might be a complement to face-to-face mental health services. Large-scale dissemination of web-based preventive interventions might be a promising strategy to alleviate depression's disease burden on a wide scale in an affordable way.

References

1.   Cuijpers P, Koole SL, van Dijke A, Roca M, Li J, Reynolds CF, 3rd. Psychotherapy for subclinical depression: meta-analysis. Br J Psychiatry. 2014; 205(4): 268-74.
2.   Le HN, Perry DF, Stuart EA. Randomized controlled trial of a preventive intervention for perinatal depression in high-risk Latinas. J Consult Clin Psychol. 2011; 79(2): 135-41.
3.   Haringsma R, Engels GI, Cuijpers P, Spinhoven P. Effectiveness of the Coping With Depression (CWD) course for older adults provided by the community-based mental health care system in the Netherlands: a randomized controlled field trial. Int Psychogeriatr. 2006; 18(2): 307-25.
4.   Allart-van Dam E, Hosman CM, Hoogduin CA, Schaap CP. Prevention of depression in subclinically depressed adults: follow-up effects on the 'Coping with Depression' course. Journal of affective disorders. 2007; 97(1-3): 219-28.
5.   Furukawa TA, Horikoshi M, Kawakami N, Kadota M, Sasaki M, Sekiya Y, et al. Telephone cognitive-behavioral therapy for subthreshold depression and presenteeism in workplace: a randomized controlled trial. PLoS One. 2012; 7(4): e35330.
6.   Spek V, Nyklicek I, Smits N, Cuijpers P, Riper H, Keyzer J, et al. Internet-based cognitive behavioural therapy for subthreshold depression in people over 50 years old: a randomized controlled clinical trial. Psychol Med. 2007; 37(12): 1797-806.
7.   Willemse GR, Smit F, Cuijpers P, Tiemens BG. Minimal-contact psychotherapy for sub-threshold depression in primary care. Randomised trial. The British journal of psychiatry 2004; 185: 416-21.
8.   Zhang de X, Lewis G, Araya R, Tang WK, Mak WW, Cheung FM, et al. Prevention of anxiety and depression in Chinese: a randomized clinical trial testing the effectiveness of a stepped care program in primary care. J Affect Disord. 2014; 169: 212-20.
9.   de Jonge P, Hadj FB, Boffa D, Zdrojewski C, Dorogi Y, So A, et al. Prevention of major depression in complex medically ill patients: preliminary results from a randomized, controlled trial. Psychosomatics. 2009; 50(3): 227-33.
10.   Mihalopoulos C, Vos T. Cost-effectiveness of preventive interventions for depressive disorders: an overview. Expert Rev Pharmacoecon Outcomes Res. 2013; 13(2): 237-42.
11.   Lokkerbol J, Adema D, Cuijpers P, Reynolds CF, 3rd, Schulz R, Weehuizen R, et al. Improving the cost-effectiveness of a healthcare system for depressive disorders by implementing telemedicine: a health economic modeling study. Am J Geriatr Psychiatry. 2014; 22(3): 253-62.
12.   Mihalopoulos C, Vos T, Pirkis J, Smit F, Carter R. Do indicated preventive interventions for depression represent good value for money? Aust N Z J Psychiatry. 2011; 45(1): 36-44.
13.   Smit F, Willemse G, Koopmanschap M, Onrust S, Cuijpers P, Beekman A. Cost-effectiveness of preventing depression in primary care patients: randomised trial. Br J Psychiatry. 2006; 188: 330-6.
14.   Van't Veer-Tazelaar P, Smit F, van Hout H, van Oppen P, van der Horst H, Beekman A, et al. Cost-effectiveness of a stepped care intervention to prevent depression and anxiety in late life: randomised trial. Br J Psychiatry. 2010; 196(4): 319-25.
15.   van den Berg M, Smit F, Vos T, van Baal PH. Cost-effectiveness of opportunistic screening and minimal contact psychotherapy to prevent depression in primary care patients. PLoS One. 2011; 6(8): e22884.

16. NICE. NICE Clinical Guidelines, No. 90. Depression: The Treatment and Management of Depression in Adults (Updated Edition). British Psychological Society, 2010.

17. Furukawa TA, Noma H, Caldwell DM, Honyashiki M, Shinohara K, Imai H, et al. Waiting list may be a nocebo condition in psychotherapy trials: a contribution from network meta-analysis. Acta Psychiatr Scand. 2014; 130(3): 181-92.

18. Breslau N. Depressive symptoms, major depression, and generalized anxiety: a comparison of self-reports on CES-D and results from diagnostic interviews. Psychiatry Res. 1985; 15(3): 219-29.

19. Batterham PJ, Neil AL, Bennett K, Griffiths KM, Christensen H. Predictors of adherence among community users of a cognitive behavior therapy website. Patient preference and adherence. 2008; 2: 97-105.

20. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380(9859): 2163-96.

21. Cuijpers P, de Graaf R, van Dorsselaer S. Minor depression: risk profiles, functional disability, health care use and risk of developing major depression. Journal of Affective Disorders. 2004; 79(1-3): 71-9.

22. Fergusson DM, Horwood LJ, Ridder EM, Beautrais AL. Subthreshold depression in adolescence and mental health outcomes in adulthood. Arch Gen Psychiatry. 2005; 62(1): 66-72.

23. Oxman TE, Sengupta A. Treatment of minor depression. Am J Geriatr Psychiatry. 2002; 10(3): 256-64.

24. Rose G. Sick individuals and sick populations. Int J Epidemiol. 1985; 14(1): 32-8.

25. Cuijpers P, Berking M, Andersson G, Quigley L, Kleiboer A, Dobson KS. A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. Can J Psychiatry. 2013; 58(7): 376-85.

26. Cookson J, Gilaberte I, Desaiah D, Kajdasz DK. Treatment benefits of duloxetine in major depressive disorder as assessed by number needed to treat. International clinical psychopharmacology. 2006; 21(5): 267-73.

27. Konnert C, Dobson K, Stelmach L. The prevention of depression in nursing home residents: a randomized clinical trial of cognitive-behavioral therapy. Aging Ment Health. 2009; 13(2): 288-99.

28. Mack S, Jacobi F, Gerschler A, Strehle J, Hofler M, Busch MA, et al. Self-reported utilization of mental health services in the adult German population--evidence for unmet needs? Results of the DEGS1-Mental Health Module (DEGS1-MH). Int J Methods Psychiatr Res. 2014; 23(3): 289-303.

29. Cuijpers P, van Straten A, Warmerdam L, van Rooy MJ. Recruiting participants for interventions to prevent the onset of depressive disorders: possible ways to increase participation rates. BMC Health Serv Res. 2010; 10: 181.

30. Baumeister H, Reichler L, Munzinger M, Lin J. The impact of guidance on Internet-based mental health interventions - A systematic review. Internet Interventions. 2014; 1(4): 205-15.

31. Christensen H, Griffiths KM, Korten AE, Brittliffe K, Groves C. A comparison of changes in anxiety and depression symptoms of spontaneous users and trial participants of a cognitive behavior therapy website. J Med Internet Res. 2004; 6(4): e46.

32.   Dever Fitzgerald T, Hunter PV, Hadjistavropoulos T, Koocher GP. Ethical and legal considerations for internet-based psychotherapy. Cogn Behav Ther. 2010; 39(3): 173-87.

33.   Berger T, Andersson G. [Internet-based psychotherapies: characteristics and empirical evidence]. Psychotherapie, Psychosomatik, medizinische Psychologie. 2009; 59(3-4): 159-66; quiz 67-70.

34.   Richards D, Richardson T. Computer-based psychological treatments for depression: A systematic review and meta-analysis. Clin Psychol Rev. 2012; 32(4): 329-42.

35.   Spek V, Cuijpers P, Nyklicek I, Riper H, Keyzer J, Pop V. Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis. Psychol Med. 2007; 37(3): 319-28.

36.   Palmqvist B, Carlbring P, Andersson G. Internet-delivered treatments with or without therapist input: does the therapist factor have implications for efficacy and cost? Expert Rev Pharmacoecon Outcomes Res. 2007; 7(3): 291-7.

37.   Johansson R, Andersson G. Internet-based psychological treatments for depression. Expert review of neurotherapeutics. 2012; 12(7): 861-9; quiz 70.

38.   Robinson E, Titov N, Andrews G, McIntyre K, Schwencke G, Solley K. Internet treatment for generalized anxiety disorder: a randomized controlled trial comparing clinician vs. technician assistance. PLoS One. 2010; 5(6): e10942.

39.   Titov N, Andrews G, Davies M, McIntyre K, Robinson E, Solley K. Internet treatment for depression: a randomized controlled trial comparing clinician vs. technician assistance. PLoS One. 2010; 5(6): e10939.

40.   Ahn H, Wampold B. Where oh where are the specific ingredients? A meta-analysis of component studies in counseling and psychotherapy. J Counsel Psychol. 2001; 48: 251–7.

41.   Almlov J, Carlbring P, Kallqvist K, Paxling B, Cuijpers P, Andersson G. Therapist effects in guided internet-delivered CBT for anxiety disorders. Behav Cogn Psychother. 2011; 39(3): 311-22.

42.   Almlov J, Carlbring P, Berger T, Cuijpers P, Andersson G. Therapist factors in Internet-delivered cognitive behavioural therapy for major depressive disorder. Cogn Behav Ther. 2009; 38(4): 247-54.

43.   Sucala M, Schnur JB, Constantino MJ, Miller SJ, Brackman EH, Montgomery GH. The therapeutic relationship in e-therapy for mental health: a systematic review. J Med Internet Res. 2012; 14(4): e110.

44.   Andersson G, Paxling B, Wiwe M, Vernmark K, Felix CB, Lundborg L, et al. Therapeutic alliance in guided internet-delivered cognitive behavioural treatment of depression, generalized anxiety disorder and social anxiety disorder. Behav Res Ther. 2012; 50(9): 544-50.

45.   Knaevelsrud C, Maercker A. Does the quality of the working alliance predict treatment outcome in online psychotherapy for traumatized patients? J Med Internet Res. 2006; 8(4): e31.

46.   Bergman Nordgren L, Carlbring P, Linna E, Andersson G. Role of the working alliance on treatment outcome in tailored internet-based cognitive behavioural therapy for anxiety disorders: randomized controlled pilot trial. JMIR research protocols. 2013; 2(1): e4.

47. Christensen H, Griffiths KM, Farrer L. Adherence in internet interventions for anxiety and depression. J Med Internet Res. 2009; 11(2): e13.

48. Ebert DD, Berking M, Cuijpers P, Lehr D, Portner M, Baumeister H. Increasing the acceptance of internet-based mental health interventions in primary care patients with depressive symptoms. A randomized controlled trial. J Affect Disord. 2015; 176: 9-17.

49. Gun SY, Titov N, Andrews G. Acceptability of Internet treatment of anxiety and depression. Australasian psychiatry : bulletin of Royal Australian and New Zealand College of Psychiatrists. 2011; 19(3): 259-64.

50. Schroder J, Sautier L, Kriston L, Berger T, Meyer B, Spath C, et al. Development of a questionnaire measuring Attitudes towards Psychological Online Interventions-the APOI. J Affect Disord. 2015; 187: 136-41.

51. Mohr DC, Siddique J, Ho J, Duffecy J, Jin L, Fokuo JK. Interest in behavioral and psychological treatments delivered face-to-face, by telephone, and by internet. Annals of behavioral medicine : a publication of the Society of Behavioral Medicine. 2010; 40(1): 89-98.

52. Brookes ST, Whitely E, Egger M, Smith GD, Mulheran PA, Peters TJ. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. J Clin Epidemiol. 2004; 57(3): 229-36.

53. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. Bmj. 2010; 340: c221.

54. Cooper H, Patall EA. The relative benefits of meta-analysis conducted with individual participant data versus aggregated data. Psychological methods. 2009; 14(2): 165-76.

55. Barlow DH. Negative effects from psychological treatments: a perspective. The American psychologist. 2010; 65(1): 13-20.

56. Emmelkamp PM, David D, Beckers T, Muris P, Cuijpers P, Lutz W, et al. Advancing psychotherapy and evidence-based psychological interventions. Int J Methods Psychiatr Res. 2014; 23 Suppl 1: 58-91.

57. Smith ML, Glass GV. Meta-analysis of psychotherapy outcome studies. The American psychologist. 1977; 32(9): 752-60.

58. Mohr D. Negative outcome in psychotherapy: a critical review. Clinical Psychology: Science and Practice. 1995; 2: 1-27.

59. Hansen N, Lambert M, Forman E. The psychotherapy dose-response effect and its implications for treatment delivery services. Clinical Psychology: Science and Practice. 2006; 9: 329-43.

60. Lambert M, Whipple J, Hawkins E, Vermeersch D, Nielsen S, Smart D. Is it time for clinicians to routinely track patient outcome? A meta-analysis. Clinical Psychology: Science and Practice. 2006; 10: 288-301.

61. Kiluk BD, Sugarman DE, Nich C, Gibbons CJ, Martino S, Rounsaville BJ, et al. A methodological analysis of randomized clinical trials of computer-assisted therapies for psychiatric disorders: toward improved standards for an emerging field. Am J Psychiatry. 2011; 168(8): 790-9.

62. Ebert DD, Donkin L, Andersson G, Andrews G, Berger T, Carlbring P, et al. Does Internet-based guided-self-help for depression cause harm? An individual participant data meta-analysis on deterioration rates and its moderators in randomized controlled trials. Psychol Med. 2016; 46(13): 2679-93.

63. Chan R, Hayashi K. Gender roles and helpseeking behaviour: Promoting professional help among Japanese men. Journal of Social Work. 2010; 10: 243-62.

64. Curtis C. Youth perceptions of suicide and help-seeking: They'd think I was weak or "mental". Journal of Youth Studies. 2010; 13: 699-715.

65. Moller-Leimkuhler AM. Barriers to help-seeking by men: a review of sociocultural and clinical literature with particular reference to depression. J Affect Disord. 2002; 71(1-3): 1-9.

66. Berger J, Addis M, Green J, Mackowiak C, Goldberg V. Men's reactions to mental health labels, forms of help-seeking, and sources of help-seeking advice. Psychology of Men & Masculinities. 2013; 14(4): 433-43.

67. Berger J, Levant R, McMillan K, Kelleher W, Sellers A. Impact of gender role conflict, traditional masculinity ideology, alexithymia and age on men's attitudes toward psychological help seeking. Psychology of Men & Masculinity. 2005; 6(1): 73-8.

68. Rochlen AB, Paterniti DA, Epstein RM, Duberstein P, Willeford L, Kravitz RL. Barriers in diagnosing and treating men with depression: a focus group report. American journal of men's health. 2010; 4(2): 167-75.

69. McCusker M, Galupo M. The impact of men seeking help for depression on perceptions of masculine and feminine characteristics. Psychology of Men & Masculinity. 2011; 12: 275-84.

70. Syzdek M, Addis M, Green J, Whorley M, Berger J. A pilot trial of gender-based motivational interviewing for help-seeking and internalizing symptoms in men. Psychology of Men & Masculinity. 2013; 15: 90-4.