Chapter 7

Effectiveness of a web-based self-help intervention with adherence-focussed guidance

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Effectiveness of web- and mobile-based treatment of subthreshold depression with adherence-focused guidance

Under review

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Abstract

Evidence for the impact of psychological Interventions for subthreshold depression (sD) is conflicting. Moreover, human resources to deliver such treatments are limited. This study aimed to evaluate the effectiveness of a web-based intervention with adherence-focused guidance in the treatment of sD.

Participants with sD (CES-D ≥ 16, no Major Depressive Disorder according to DSM-IV criteria, N = 204) recruited via a large health insurance were randomly allocated to a web-based mobile-supported cognitive-behavioural intervention or to a waitlist control condition with unrestricted access to usual care. The primary outcome was the reduction in depressive symptom severity as measured by blind diagnostic raters using the Quick Inventory of Depressive Symptomatology (QIDS) at post-treatment.

There was a statistically significant between-group difference in QIDS scores at post-treatment in favour of the intervention group [$F(1,201) = 11.31$, $p = .001$] corresponding to a medium effect size of $d = 0.40$ (95% CI 0.12 - 0.68) and a NNT of 7 (95% CI 3.7 - 41.2). Significant effects in favour of the intervention group were also found for secondary outcomes such as quality of life, anxiety, and insomnia severity. Web-based self-help interventions with adherence-focused guidance could be an acceptable and effective approach to reduce a range of negative consequences associated with subclinical depression.

Introduction

Subthreshold depression can be defined dimensionally (i.e., scoring above a cut-off level on a validated self-rated depression screening measure while the criteria of a full-blown depressive disorder are not yet met according to a diagnostic interview) or categorically (i.e., fewer than five symptoms of depression according to the DSM-IV, for instance, are present) (1, 2).

Subthreshold depression is a highly prevalent condition (3) related to increased mortality (4), poorer quality of life (5), increased health care service utilisation (6), and vast societal costs (7). From a clinical perspective, subthreshold depression is not only important because it can be a disabling condition, but also due to the associated risk of developing major depression. Subthreshold depression can be regarded as part of the prodromal phase of major depression (8). Almost all individuals who have developed a major depression are assumed to have initially passed through a period of subthreshold depression, underscoring the importance of preventive interventions aimed at the treatment of subthreshold depression and the prevention of major depression.

In contrast to major depressive disorder, however, there are only a few studies on the effectiveness of psychological treatments for subthreshold depression. A recent meta-analysis showed small-to-moderate effect sizes of psychological interventions on depressive symptom severity at post-treatment compared to usual care (1). Notwithstanding, the four studies using clinician-rated outcomes did not indicate significant positive results. As effects of psychological interventions are expected to be small to moderate in size only, cost-effective delivery modes are particularly needed. The Internet offers an opportunity to deliver psychological interventions to a large audience at lower costs than face-to-face interventions, depending on the level of human support involved.

However, while the efficacy of web-based interventions for major depression is very well researched (9, 10), the evidence-base for their usefulness in subthreshold depression is still limited. Recently, our group conducted one of the two randomised controlled trials that have tested the efficacy of web-based interventions in adults with subthreshold depression (11-13). In our trial, the intervention proved to be effective in reducing self-rated depressive symptom severity over a 12-month follow-up period. However, replication of these findings is essential before widespread dissemination is considered. Furthermore, the afore-mentioned study evaluated an intervention that provided participants with substantial professional support (up to 3 hours of guidance per participant from a mental health expert). This amount of intensive guidance clearly places constraints for scaling up this intervention. Therefore, we evaluated the same web-based intervention with minimal guidance (i.e., adherence-focused guidance), as such an intervention may cost less and will be associated with fewer constraints for scaling up.

In the context of adherence-focused guidance, participants are supported to complete the intervention sessions using e-mail reminders. Moreover, feedback is provided only upon request of the intervention users as part of a feedback on demand approach. This format is expected to offer the positive effects of guidance whilst keeping the time spent per participant to a minimum, thus producing a more economic version of the guided web-based intervention.

This study was aimed at testing the hypothesis that the effectiveness of a web-based intervention with adherence-focused guidance for the treatment of subthreshold depression with clinician-rated depressive symptom severity at post-treatment as its main outcome was superior to a waitlist control group with unrestricted access to usual care.

Methods

Design

A two-armed, pragmatic randomised controlled clinical trial was conducted to compare an adherence-focused guided web-based intervention (GET.ON Mood Enhancer) with a waitlist control condition with unrestricted access to care-as-usual. Assessments took place at baseline (diagnostic interviews, online questionnaires), at post-treatment (7 weeks; diagnostic interviews, online questionnaires), and at 3-month follow-up (online questionnaires only; see Figure 1 for a detailed overview of assessments). The study was approved by the Medical Ethics Committee of the University of Lueneburg (reference number Ebert201404_Depr) and registered under DRKS00005973 in the German clinical trial registry.

Study population and recruitment

Study participants were recruited from the general population via a large German health insurance company (BARMER GEK), through newspaper articles, on-air media, and related websites. Referral by a GP was not required. Applicants self-identifying with a diminished mood who (a) screened positive for subthreshold depressive symptoms (Center for Epidemiologic Studies Depression Scale (CES-D) ≥ 16), (b) were aged 18 and above, (c) had Internet access, (d) were not currently receiving or (e) on a waiting list for psychotherapy for any kind of mental health problem, (f) had had no psychotherapy for any kind of mental health disorder in the past six months, and (g) had no notable suicidal risk (BDI item 9 > 1) were scheduled for a semi-structural clinical interview (SCID) conducted by telephone by trainees in psychotherapy to assess final eligibility. Those not meeting DSM-IV criteria for (a) a major depressive episode, (b) bipolar disorder, or (c) psychotic disorder, and (d) not having a history of a major depressive disorder in the past six months according to Kupfer's model (14) were excluded. As we conducted a pragmatic trial, the use of antidepressant medication was allowed as part of care-

as-usual. However, participants needed to be on a stable dose for at least four weeks to be able to enter the study.

Randomisation and masking

Participants passing all inclusion and exclusion criteria who completed the baseline assessment and returned their informed consent form were randomly allocated to study conditions. Randomisation took place at individual level and was conducted centrally by an independent researcher not otherwise involved in the study using an automated computer-generated random numbers table. Block randomization of size twelve was used to ensure equity of sample sizes across study conditions. As usual for psychological intervention trials, study participants knew their allocation.

The research staff conducting the observer-based rating of depressive symptom severity were blind to treatment allocation. Steps to ensure blindness included the following: (a) an explanation to participants why it is important not to inform the interviewer about the condition to which they were assigned; (b) a written reminder in the interview manual for the interviewer to ask participants not to disclose their randomisation status; (c) verbal reminders to participants before the interview; and (d) a documentation after the assessment of whether or not the interviewer was still blind to the treatment condition.

Interventions

All study participants had unrestricted access to routine care (i.e., visits to the GP). According to the German S3-Guideline/National Disease Management Guideline Unipolar Depression, more intensive psychological interventions (i.e., cognitive behavioural therapy) should only be offered if depressive symptoms intensify (i.e., diagnosed major depressive disorder) (15). Following the S3-Guideline, usual care is then subsequently stepped up to more intensive interventions (i.e., psychotherapy or prescription of antidepressant medication). In this pragmatic trial, usual care was not protocolized. Participants in the control condition received access to the web-based intervention 3 months after randomisation.

Web-based intervention

The web-based intervention consists of six 30-minute interactive sessions. However, the duration of sessions might vary across users. Four weeks after finishing the intervention, participants are offered an optional booster session. The aim of this session is to evaluate progress and to strengthen skills acquired during the intervention. Intervention sessions include text, exercises, testimonials, and audio and video clips. Audio sequences introduce relaxation exercises, whereas video clips explain theoretical frameworks in a user-friendly way. Based on

studies suggesting that a higher treatment session frequency might be associated with a better outcome (16), participants were advised to complete two sessions a week, if possible, but a minimum of at least one.

The intervention is based on behaviour therapy (BT) and problem-solving therapy (PST), the content of which has been described in detail elsewhere by Buntrock, et al. (11, 13). During the study, a strong emphasis was placed on homework assignments meant to help the integration of acquired coping skills into daily life. As an optional component, participants could choose to receive a set of roughly 42 standardised text-messages supporting them in this integration.

During the intervention, participants were supported by an e-coach applying an adherence-focused guidance concept. In line with the supportive accountability model (17), it is assumed that adherence to a web-based intervention (and therefore the effectiveness) could be enhanced via human support through accountability to an e-coach who is seen as legitimate, trustworthy, benevolent, and having expertise. The e-coach guidance consisted of two elements: (a) adherence monitoring and (b) feedback on demand. Adherence monitoring included checking whether participants completed intervention sessions and if not, reminding them to do so. The e-coach sent reminders if participants did not complete a session within 7 days. Both personal and automatic reminders have shown to improve adherence to self-guided health promotion and behaviour change interventions (18). However, it is assumed that personal as opposed to automatic reminders from an e-coach are perceived as more benevolent and are, therefore, more effective. Feedback on demand provided the participants with the opportunity to contact the e-coach via the internal messaging function on the platform and to receive individual support/feedback whenever they desired. Within 48 hours, the participants received personalized written feedback. Feedback is not assumed to have a direct influence on the effectiveness of the intervention, rather simply thought to create a sense that the coach is legitimate and has the participant's best interest at heart. Individuals are assumed to respond more positively to adherence demands from an e-coach who is perceived as legitimate (19-21).

Waitlist control condition

Participants who were randomised to the waitlist control condition received access to the web-based intervention after a 3-month waiting period.

Outcomes

Self-report measures were collected at baseline, post-treatment, and 3-month follow-up using a secured online-based assessment system (AES, 256-bit encrypted). The diagnostic interviews at baseline and post-treatment were conducted by telephone.

Primary outcome

Depressive symptom severity

The primary outcome was depressive symptom severity as measured by the 16-item Quick Inventory of Depressive Symptomatology–Clinician-Rating (QIDS-CR16). The QIDS-CR16 evaluates the nine depression criterion symptom domains, as stated in the DSM-IV, during the prior seven days providing a nuanced understanding of the symptom severity. Each item is scored on a scale from 0 to 3, with higher scores indicating higher symptom severity. The QIDS has shown good psychometric properties, such as strong internal consistency ($\alpha = 0.85$), concurrent validity, and sensitivity to symptom change in patients with major depression (22). Cut-off points of 6, 11, 16, and 21 represent the thresholds for mild, moderate, severe, and very severe depressive symptom severity, respectively. Interrater reliability was assessed by rating audiotaped diagnostic interviews by an independent experienced diagnostic rater. Inter-rater reliability based on data of 10% of participants was 0.97.

Secondary outcomes

Observer-based depressive symptom severity was also measured with the Hamilton Rating Scale for Depression (($HRSD_{24}$); inter-rater reliability 0.94). The HRSD is a widely used clinician-rated scale for measuring depression with high internal consistency ($\alpha = .88$) and sensitivity to change over time and treatment. The cut-off points of 10, 19, 27, and 35 indicate the thresholds for mild, moderate, severe, and very severe depressive symptom severity, respectively (23). Using the HRSD allowed us for a more detailed comparison with previous research. Other secondary outcomes included self-reported depressive symptom severity (Center for Epidemiologic Studies Depression Scale (CES-D) (24); 20 items, range 0 - 60, $\alpha = .78$), quality of life (Assessment of Quality of Life (AQoL-8D) (25); 35 items, range 0 - 100, $\alpha = .89$), anxiety (anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A) (26); 7 items, range 0 - 21, $\alpha = .67$), problem-solving skills (Social Problem-Solving Inventory-Revised (SPSI-R) (27); positive problem orientation subscale, 5 items, range 0 - 20, $\alpha = .77$; negative problem orientation subscale, 5 items, range 0 - 20, $\alpha = .85$), behavioural activation (BADS-Short Form (BADS-SF) (28); 9 items, range 0 - 56, $\alpha = .68$), mastery (Pearlin Mastery Scale (PSMS) (29); 7 items, range 0 - 21, $\alpha = .72$), worrying (ultra-brief version of the Penn State Worry Questionnaire (PSWQ) (30); 3 items, range 0 - 18, $\alpha = .84$), insomnia severity (Insomnia Severity Index (ISI) (31); 7 items, range 0 - 28, $\alpha = .86$), and alcohol use disorders (Alcohol Use Disorders Identification Test (AUDIT) (32); 10 items, range 0 - 40, $\alpha = .80$).

Sample size

Based on a meta-analysis of psychological treatments for subthreshold depression (1), this trial was powered to detect a mean difference of d = 0.35 in the primary outcome between the groups at post-treatment, with an α of 0.05 and a power of 80% in a one-tailed test. A one-tailed test was applied based on the unidirectional hypothesis that the intervention group is superior compared to the control group. This assumption is supported by the first trial on this intervention (11, 13). Based on the power calculation, we needed to include 204 participants.

Data analyses

All analyses are reported according to the CONSORT statement. Analyses were based on the intention-to-treat (ITT) principle. All analyses were performed with IBM SPSS v. 22. All reported p-values are one-sided with a significance level of 0.05. Missing data were imputed using a Markov Chain Monte Carlo multivariate imputation algorithm (missing data module in SPSS 22) with 10 estimations per missing value. We used analysis of covariance (ANCOVA) to compare outcomes between groups at post-treatment and at 3-month follow-up adjusting for baseline scores. Results were reported as mean within- and between-group differences and as Cohen's d effect sizes (and their 95% CIs according to Hedges and Olkin (33).

Improvements on the primary outcome at individual level were examined by assessing the number of participants who displayed a treatment response and symptom-free status. Response represented significant symptomatic improvement, whereas symptom-free status represented improvement to the point of being asymptomatic within a normal range. On the HRSD and QIDS, response was defined as at least 50% reduction from baseline.

Symptom-free status was defined a priori as a non-pathological score of <6 on the QIDS and of <10 on the $HRSD_{24}$. Numbers needed-to-treat (NNT) (with 95% CI) to achieve one additional response and symptom-free status, respectively, were calculated as the inverse of the risk difference (34).

Results

Participants

Participant characteristics at baseline are shown in Table 1. In brief, participants were predominately female (80.4%), of an average age of 44 years (SD = 11.7), had an above average level of education (A-level or higher: 81.9%), and were employed (86.8%). Four out of ten participants have received psychotherapy at some point in their lives (n = 82; 40.2%). There

were no clinically important differences between treatment conditions in terms of any baseline characteristic indicating that randomisation was successful.

Figure 1 illustrates the enrolment and flow of participants through the study. A total of 204 participants were included in the study. Dropout rates differed between study groups at post-treatment and 3-month follow-up. As can be seen, dropout was higher in the intervention group (HRSD/QIDS interview post-treatment: χ^2 (1, n = 204) = 7.76, p = .005; online questionnaires post-treatment: χ^2 (1, n = 204) = 11.28, p = .001; online questionnaires 3-month follow-up: χ^2 (1, n = 204) = 11.02, p = .001). Study dropout was not associated with baseline depressive symptom severity or any socio-demographic factor.

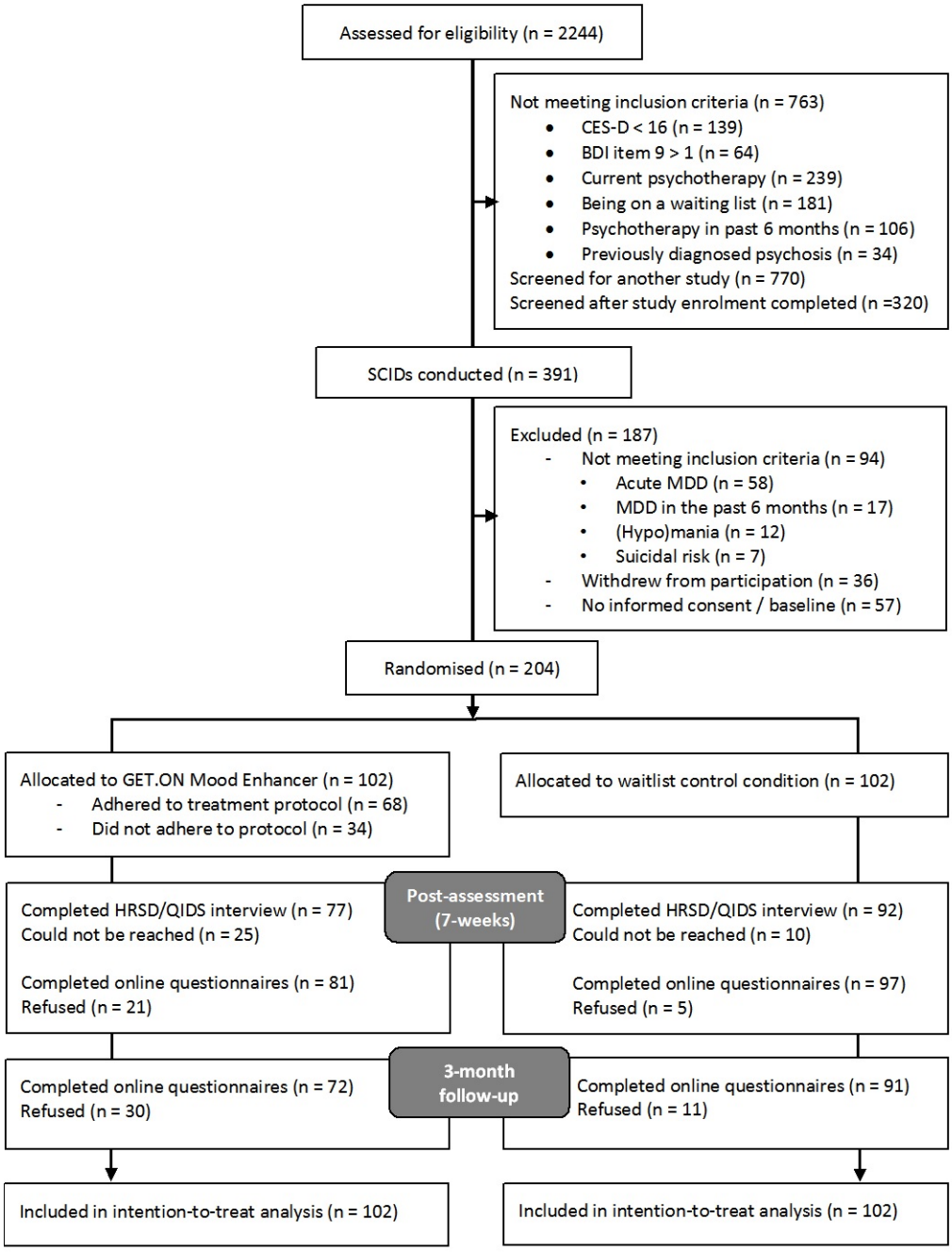

Figure 1. Study flow

Table 1. Baseline characteristics according to study group

Characteristic	Intervention group (n = 102)	Control group (n = 102)	Total sample (N = 204)
QIDS sum score, mean (SD)	8.17 (3.62)	8.11 (3.90)	8.14 (3.75)
HRSD sum score, mean (SD)	13.72 (6.20)	14.63 (6.81)	14.17 (6.52)
CES-D sum score, mean (SD)	26.67 (6.50)	27.73 (7.50)	27.20 (7.02)
Use of antidepressants, n (%)	7 (6.9)	6 (5.9)	13 (6.4)
Age, mean (SD)	44.66 (11.65)	43.75 (11.84)	44.20 (11.73)
Gender, n (%)			
Male	20 (19.6)	20 (19.6)	40 (19.6)
Female	82 (80.4)	82 (80.4)	164 (80.4)
Relationship, n (%)			
Single	27 (26.5)	28 (27.5)	55 (27.0)
Married or cohabiting	65 (63.7)	53 (52.0)	118 (57.8)
Divorced or separated	9 (8.8)	20 (19.6)	29 (14.2)
Widowed	1 (1.0)	1 (1.0)	2 (1.0)
Ethnicity, n (%)			
Caucasian	79 (77.5)	81 (79.4)	160 (78.4)
Not reported	23 (22.5)	21 (20.6)	44 (21.6%)
Level of education, n (%)			
Low (primary)	2 (2.0)	3 (2.9)	5 (2.5)
Middle (secondary)	16 (15.7)	16 (15.7)	32 (15.7)
High (A-level or higher)	84 (82.4)	83 (81.4)	167 (81.9)
Employment status, n (%)			
Employed	90 (88.3)	87 (85.3)	177 (86.8)
Unemployed or seeking work	2 (2.0)	4 (3.9)	6 (2.9)
On sick leave	0 (0)	2 (2.0)	2 (1.0)
Non-working	10 (9.8)	9 (8.8)	19 (9.3)
Income in Euro[a], n (%)			
Low (< 10.000)	9 (8.8)	25 (24.5)	34 (16.7)
Middle (10 - 60.000)	70 (68.6)	59 (57.8)	129 (63.2)
High (> 60.000)	14 (13.7)	10 (9.8)	24 (11.8)
Not reported	9 (8.8)	8 (7.8)	17 (8.3)

Abbreviations: QIDS, Quick Inventory of Depressive Symptomatology – Clinical-rated; SD, standard deviation; HRSD, Hamilton Rating Scale for Depression; CES-D, Center for Epidemiologic Studies Depression Scale

[a] Gross annual income

Intervention usage, reminders, and content feedbacks

The average treatment duration was 7 weeks (SD = 3.17) and participants completed on average 5 sessions (SD = 2.25). Out of the 102 participants who were initially assigned to the intervention, 68 (66.7%) were intervention completers. Of those, 63 (92.6%) adhered to all six sessions. The booster session was completed by 40 (39.2%) participants. Of the 34 participants (33.3%) not completing 80% of the intervention, 6 participants never started the intervention (5.9%).

The e-coaches spent on average 30 minutes on each participant. In total, the e-coaches sent 301 reminders corresponding to a mean of 3.07 reminders per participant (range: 0 - 9, SD = 2.08). Interestingly, only a few participants (n = 6, 5.88%) requested feedback, resulting in 15 content feedbacks for the entire sample. This corresponds to an average of 0.15 feedback demands per participant (range: 0 - 5, SD = 0.71). Thus, most time spent per participant was related to checking adherence and providing reminders.

Primary intervention outcome

Table 2 shows means, standard deviations, and between-group effect sizes of the clinical outcomes based on the intention-to-treat sample. Both study groups displayed statistically significant reductions in depressive symptom severity as indicated by changes in baseline to post-treatment scores in the QIDS (Table 2).

Based on the QIDS, corresponding within-group Cohen's d effect sizes were 0.95 (95% CI 0.66 - 1.24) for the intervention group and 0.52 (95% CI 0.24 - 0.80) for the control group, respectively. As hypothesised, there was a statistically significant between-group difference in QIDS scores at post-treatment in favour of the intervention group [$F(1,201) = 11.31$, $p = .001$]. This difference in QIDS scores corresponded to a medium between-group effect size of 0.40 (95% CI 0.12 - 0.68).

Secondary outcomes

We found a statistically significant between-group difference in HRSD scores at post-treatment in favour of the intervention group [HRSD: $F(1, 201) = 7.36$, $p=.007$]. This difference in HRSD scores corresponded to a small-to-medium between-group effect size of 0.35 (95% CI 0.07 - 0.62). There were significant between-group differences for secondary outcomes favouring the intervention group except for mastery (Pearlin Mastery Scale; $p = .18$), negative problem-orientation (subscale of the SPSI; $p = .36$), and alcohol use (AUDIT; $p = .10$). The effect sizes of the secondary outcomes ranged from $d = 0.45$ (95% CI 0.17 - 0.73) (PSWQ) to $d = 0.84$ (95% CI 0.55 - 1.13) (CES-D) (Table 2).

Response and symptom-free status

Based on the QIDS and HRSD, a positive response from baseline to post-treatment in depressive symptom severity was seen significantly more often in participants of the intervention group (QIDS: 37/102 = 36.3%; HRSD: 34/102 = 33.3%) as compared to the control group (QIDS: 22/102 = 21.6%; χ^2 (1, n = 204) = 5.365, p = .015; HRSD: 19/102 = 18.6%; χ^2 (1, n = 204) = 5.735, p = .012). This resulted in a NNT of 7 for both QIDS (95% CI 3.7 - 41.2) and the HRSD (95% CI 3.8 - 35.2), respectively, in order to achieve one additional treatment response as compared to the control group.

Based on the QIDS and the HRSD, significantly more participants in the intervention group met the criteria for symptom-free status (QIDS: 63/102, 61.8% v. 44/102, 43.1%; χ^2 (1, n = 204) = 7.095, p = .006; HRSD: 65/102, 63.7% v. 46/102, 45.1%; χ^2 (1, n = 204) = 7.124, p = .006). The corresponding NNT was 6 for both the QIDS (95% CI 3.1 - 19.4) and the HRSD (95% CI 3.1 - 19.2), respectively.

Longer-term effects

In both study groups, the reduction in self-reported depressive symptom severity found at post-treatment was sustained at the 3-month follow-up [intervention group: t(101) = -0.654, p = .51; control group: t(101) = .100, p = 0.92], resulting in a statistically significant between-group difference in CES-D scores at follow-up favouring the intervention group [F(1, 201) = 34.80, p < .001]. This difference corresponded to an effect size of 0.81 (95% CI 0.52 - 1.09). Between-group differences for secondary outcomes were still significant at the 3-month follow-up except for negative problem-orientation (subscale of the SPSI; p = .82) and alcohol use disorders (AUDIT; p = .12).

Table 2. Means, SD and effect sizes (95% CIs) for the clinical outcomes based on the imputed data set (N = 204)

	Pre-assessment		**Post-assessment**		**3-month FU**		**Between-group effect size Cohen's d (95% CI)**	
	mean	SD	mean	SD	mean	SD	pre-post	pre-3-month FU
$HRSD_{24}$							0.35 (0.07 - 0.62)	
INT	13.72	6.21	9.60	5.60				
CTR	14.62	6.81	11.59	5.86				
QIDS-C							0.40 (0.12 - 0.68)	
INT	8.18	3.62	4.98	3.11				
CTR	8.11	3.89	6.25	3.22				
CES-D							0.84 (0.55 - 1.13)	0.81 (0.52 - 1.09)
INT	26.67	6.50	17.79	7.03	17.32	8.33		
CTR	27.73	7.50	24.06	7.85	24.29	8.90		
AQoL total score	61.66	7.81	67.53	7.57	69.09	8.58	0.58 (0.30 - 0.86)	0.63 (0.35 - 0.91)
INT	61.03	9.87	62.43	9.81	62.99	10.55		
CTR								
AQoL MCS							0.52 (0.24 - 0.80)	0.65 (0.36 - 0.93)
INT	62.18	7.68	67.27	7.40	69.18	8.47		
CTR	61.91	10.01	62.80	9.70	63.23	9.90		
AQoL PCS							0.63 (0.35 - 0.92)	0.55 (0.27 - 0.83)
INT	60.40	9.65	68.17	9.30	68.86	9.96		
CTR	58.90	11.04	61.52	11.55	62.37	13.26		
HADS-A							0.22 (-0.06 - 0.49)	0.44 (0.17 - 0.72)
INT	9.63	3.14	8.10	2.98	7.23	3.20		
CTR	9.38	3.20	8.78	3.20	8.72	3.52		
BADS-SF							0.49 (0.21 - 0.77)	0.31 (0.03 - 0.58)
INT	25.70	7.89	32.37	7.34	31.87	7.65		
CTR	26.80	6.69	28.65	7.75	29.43	8.31		
SPSI-NPO							0.15 (-0.12 - 0.43)	0.06 (-0.22 - 0.33)
INT	7.26	4.54	6.54	4.30	5.92	3.93		
CTR	6.83	4.82	5.87	4.44	5.69	4.13		

Table 2. Means, SD and effect sizes (95% CIs) for the clinical outcomes based on the imputed data set (N = 204) (continued)

	Pre-assessment		**Post-assessment**		**3-month FU**		**Between-group effect size Cohen's d (95% CI)**	
	mean	SD	mean	SD	mean	SD	pre-post	pre-3-month FU
SPSI-PPO							0.22 (-0.05 - 0.50)	0.18 (-0.10 - 0.45)
INT	9.45	3.94	10.69	3.54	10.68	3.44		
CTR	9.71	3.71	9.83	3.62	10.02	4.04		
PSWQ							0.45 (0.17 - 0.73)	0.51 (0.23 - 0.79)
INT	9.78	3.92	6.98	3.49	7.00	3.83		
CTR	9.77	4.04	8.75	4.32	9.15	4.51		
ISI							0.22 (-0.05 - 0.50)	0.35 (0.08 - 0-63)
INT	12.73	5.46	10.11	5.41	9.40	5.36		
CTR	11.92	6.02	11.36	5.89	11.29	6.18		
PSMS							0.04 (-0.23 – 0.32)	0.30 (0.03 - 0.58)
INT	18.71	3.36	19.54	3.21	20.44	3.46		
CTR	19.06	3.15	19.41	3.38	19.36	3.67		
AUDIT							0.07 (-0.20 - 0.34)	0.10 (-0.17 - 0.38)
INT	4.39	4.28	3.68	3.73	3.57	3.60		
CTR	4.34	4.43	3.97	4.53	4.00	4.66		

Abbreviations: SD, Standard deviation; CI, confidence interval; FU, follow-up; INT, intervention group (n = 102); CTR, control group (n = 102); $HRSD_{24}$, Hamilton Rating Scale for Depression; QIDS-C, Quick Inventory of Depressive Symptomatology – Clinician rating; CES-D, Center for Epidemiologic Depression Scale; AQoL, Assessment of Quality of Life; HADS - A, Hospital Anxiety and Depression Scale; BADS-SF, Behavioural Activation for Depression Scale Short Form; SPSI – NPO, Social Problem-Solving Inventory - negative problem orientation; SPSI – PPO, Social Problem-Solving Inventory - positive problem orientation; PSWQ, Penn State Worrying Questionnaire (ultra brief version); ISI, insomnia Severity Index; PSMS, Pearlin Mastery Scale; AUDIT, Alcohol Use Disorders Identification Test

Discussion

Results of the present study support the primary hypothesis that the intervention effectively reduces depressive symptom severity in participants with subthreshold depression. This finding was replicated both in self-reported and in two observer-based ratings of depressive symptom severity. Effects were also found for a number of relevant secondary outcomes such as health-related quality of life, worrying, behavioural activation, anxiety, and sleep problems. No effects were found for mastery, negative problem orientation, and comorbid problematic alcohol use.

The effects observed in the present study are in line with findings of another recent meta-analysis on psychological interventions for subthreshold depression (1). Moreover, the current study extends these findings by showing that a psychological intervention can have clinically relevant effects on observer-rated depressive symptom severity. Remarkably, the effect sizes for most secondary outcomes were similar to those found in the first RCT evaluating this novel web-based intervention (11, 13). While in the first RCT the intervention was delivered with substantial human support from a psychologist (approximately 3 hours per participant), the present study found clinically meaningful effects without providing individual written feedback on each session. The observed difference between self-report and observer-based depressive symptom severity is in line with previous research (1). However, a meta-analysis on self-reported versus clinician-rated symptoms of depression showed a higher effect size for clinician-rated instruments as compared to self-report instruments (35). 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.

Other key findings of our study can be summarised as follows. First, effects on self-reported depression severity were large in size, which further supports the potential benefits of treating depressive symptoms at a very early disease stage. However, it might also indicate the methodological bias when participants cannot be blinded to the psychological intervention they receive in a trial, as illustrated by the difference between self-report and observer-rated depressive symptom severity. Studies on the prevention of depression indicate that the treatment of subthreshold depression may not only reduce symptom severity, but may also help to prevent further deterioration of symptoms and prevent the onset of a full-blown major depression (13, 36).

Second, our study shows that clinically important results can be achieved in a less intensive guidance format. Instead of providing detailed feedback after each completed session, the e-coach simply monitored the adherence to the intervention and only provided feedback on the content on request of participants. Surprisingly few participants asked for content feedback: 15 in 102 participants, averaging at 0.15 feedbacks per participant. The e-coaches spent on

average 30 minutes on each participant, and most of the resources spent for coaching were utilized to monitor the adherence to the intervention. Hence, the question arises whether or not automated reminders, in combination with feedback on demand, have a similar effect while requiring even fewer resources. Although three hours of psychological support per participant is already much less than in individual face-to-face CBT interventions, even more patients with subthreshold depression could be treated for the same costs if meaningful results are achieved using less therapists' time.

Third, the large effects found in the present study are in line with the assumption that higher effect sizes frequently found for guided vs. unguided self-help interventions (37) are attributable to the adherence-promoting factor of human support. This has also been stated previously in the supportive accountability model of human support in Web-based intervention (17). However, randomized controlled trials that compare adherence-focused guidance format with regular content feedbacks are needed to support such an assumption and to determine whether or not adherence-focused guidance formats result in outcomes equivalent to those of more intensive content-focused guidance formats. Even if a less intensive guidance format should yield lower effects in direct comparisons, their potential on a population level might still be higher, as such interventions can be distributed to more participants for a given budget of health care resources. On the other hand, it may very well be the case that patients with subthreshold depression are less willing to participate in interventions in which no regular content-feedback from a health care provider is offered, which would result in a lower reach and thus lower overall effects in the target population. Thus, future studies should compare the acceptability, effectiveness, cost-effectiveness, and reach of different guidance formats for subthreshold depression.

This study has the following limitations. First, we cannot rule out a potential selection bias while recruiting participants. Future studies that apply different recruitment strategies for the evaluation of web-based interventions for subthreshold depression, i.e. with referral from general practitioners, are needed.

Second, the study may have benefited from an inclusion of physiological measures. Future studies could consider complementing self-reports and observer-based instruments with objective measurements (such as inflammatory markers).

Third, although the current study replicated the results of the first RCT on this newly developed intervention, future studies are needed to reliably estimate the potential effects of web-based interventions for subthreshold depression in different target populations, e.g. in individuals with comorbid chronic conditions or problematic substance use (38).

Fourth, although patients in the control group had full access to treatment as usual, we cannot rule out a potential nocebo effect in the control condition (39).

Finally, although the majority of the participants reached a symptom-free status during the trial, a substantial number of participants did not. Hence, future studies should investigate whether these participants would profit from other forms of treatments, such as face-to-face psychotherapy or antidepressant medication, and whether it is possible to identify these individuals on an individual level on the basis of a multivariate set of baseline predictors (40, 41). The use of scalable web-based interventions based on recent advancements advantages in machine-learning techniques may help to obtain large enough sample sizes that are necessary to overcome the statistical power problem in the development of such prediction algorithms.

In conclusion, the present study adds to the growing evidence that psychological interventions can result in substantial benefits for individuals with subthreshold depressive symptoms. Moreover, the present study further adds to the growing evidence-base that web-based guided self-help has a high potential for delivering effective low-threshold mental health interventions. Results of the present study also indicate that web-based interventions for subthreshold depression can be delivered with limited human support without a substantial loss of effects, thus potentially reaching a much greater population at the same cost as interventions with more intensive human support.

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. Baumeister H. Inappropriate prescriptions of antidepressant drugs in patients with subthreshold to mild depression: time for the evidence to become practice. J Affect Disord. 2012; 139(3): 240-3.
3. 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.
4. Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW. Differential mortality rates in major and subthreshold depression: meta-analysis of studies that measured both. Br J Psychiatry. 2013; 202(1): 22-7.
5. Rucci P, Gherardi S, Tansella M, Piccinelli M, Berardi D, Bisoffi G, et al. Subthreshold psychiatric disorders in primary care: prevalence and associated characteristics. J Affect Disord. 2003; 76(1-3): 171-81.
6. Goldney RD, Fisher LJ, Dal Grande E, Taylor AW. Subsyndromal depression: prevalence, use of health services and quality of life in an Australian population. Soc Psychiatry Psychiatr Epidemiol. 2004; 39(4): 293-8.
7. Cuijpers P, Smit F, Oostenbrink J, de Graaf R, Ten Have M, Beekman A. Economic costs of minor depression: a population-based study. Acta Psychiatr Scand. 2007; 115(3): 229-36.
8. Eaton WW, Badawi M, Melton B. Prodromes and precursors: epidemiologic data for primary prevention of disorders with slow onset. Am J Psychiatry. 1995; 152(7): 967-72.
9. Ebert DD, Zarski AC, Christensen H, Stikkelbroek Y, Cuijpers P, Berking M, et al. Internet and computer-based cognitive behavioral therapy for anxiety and depression in youth: a meta-analysis of randomized controlled outcome trials. PLoS One. 2015; 10(3): e0119895.
10. Hedman E, Ljotsson B, Lindefors N. Cognitive behavior therapy via the Internet: a systematic review of applications, clinical efficacy and cost-effectiveness. Expert Rev Pharmacoecon Outcomes Res. 2012; 12(6): 745-64.
11. Buntrock C, Ebert D, Lehr D, Riper H, Smit F, Cuijpers P, et al. Effectiveness of a Web-Based Cognitive Behavioural Intervention for Subthreshold Depression: Pragmatic Randomised Controlled Trial. Psychother Psychosom. 2015; 84(6): 348-58.
12. 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.
13. Buntrock C, Ebert DD, Lehr D, Smit F, Riper H, Berking M, et al. Effect of a Web-Based Guided Self-help Intervention for Prevention of Major Depression in Adults With Subthreshold Depression: A Randomized Clinical Trial. Jama. 2016; 315(17): 1854-63.
14. Kupfer DJ. Long-term treatment of depression. J Clin Psychiatry. 1991; 52 Suppl: 28-34.
15. Bundesärztekammer, Bundesvereinigung K, Fachgesellschaften AdWM. German S3-Guideline/National Disease Management Guideline Unipolar Depression. 2011. http://www.depression.versorgungsleitlinien.de/.

16. Cuijpers P, Huibers M, Ebert DD, Koole SL, Andersson G. How much psychotherapy is needed to treat depression? A metaregression analysis. J Affect Disord. 2013; 149(1-3): 1-13.
17. Mohr DC, Cuijpers P, Lehman K. Supportive accountability: a model for providing human support to enhance adherence to eHealth interventions. J Med Internet Res. 2011; 13(1): e30.
18. Titov N, Dear BF, Johnston L, Lorian C, Zou J, Wootton B, et al. Improving adherence and clinical outcomes in self-guided internet treatment for anxiety and depression: randomised controlled trial. PLoS One. 2013; 8(7): e62873.
19. Tyler TR. The psychology of legitimacy: a relational perspective on voluntary deference to authorities. Personality and social psychology review : an official journal of the Society for Personality and Social Psychology, Inc. 1997; 1(4): 323-45.
20. Zarski AC, Lehr D, Berking M, Riper H, Cuijpers P, Ebert DD. Adherence to Internet-Based Mobile-Supported Stress Management: A Pooled Analysis of Individual Participant Data From Three Randomized Controlled Trials. J Med Internet Res. 2016; 18(6): e146.
21. Ebert DD, Lehr D, Heber E, Riper H, Cuijpers P, Berking M. Internet- and mobile-based stress management for employees with adherence-focused guidance: efficacy and mechanism of change. Scandinavian journal of work, environment & health. 2016; 42(5): 382-94.
22. Trivedi MH, Rush AJ, Ibrahim HM, Carmody TJ, Biggs MM, Suppes T, et al. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. Psychol Med. 2004; 34(1): 73-82.
23. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biological psychiatry. 2003; 54(5): 573-83.
24. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. Applied Psychological Measurement. 1977; 1(3): 385-401.
25. Richardson J, Iezzi A, Khan MA, Maxwell A. Validity and reliability of the Assessment of Quality of Life (AQoL)-8D multi-attribute utility instrument. The patient. 2014; 7(1): 85-96.
26. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983; 67(6): 361-70.
27. D'Zurilla TJ, Nezu AM, Maydeu-Olivares A. Social Problem-Solving Inventory-Revised (SPSI-R). MHS, 2002.
28. Manos RC, Kanter JW, Luo W. The behavioral activation for depression scale-short form: development and validation. Behav Ther. 2011; 42(4): 726-39.
29. Pearlin LI, Schooler C. The structure of coping. J Health Soc Behav. 1978; 19(1): 2-21.
30. Berle D, Starcevic V, Moses K, Hannan A, Milicevic D, Sammut P. Preliminary validation of an ultra-brief version of the Penn State Worry Questionnaire. Clin Psychol Psychother. 2011; 18(4): 339-46.
31. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2001; 2(4): 297-307.

32. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction (Abingdon, England). 1993; 88(6): 791-804.
33. Hedges L, Olkin I. Statistical methods for meta-analysis. Academic Press, 1985.
34. Kraemer HC, Kupfer DJ. Size of treatment effects and their importance to clinical research and practice. Biological psychiatry. 2006; 59(11): 990-6.
35. Cuijpers P, Li J, Hofmann SG, Andersson G. Self-reported versus clinician-rated symptoms of depression as outcome measures in psychotherapy research on depression: a meta-analysis. Clin Psychol Rev. 2010; 30(6): 768-78.
36. van Zoonen K, Buntrock C, Ebert DD, Smit F, Reynolds CF, 3rd, Beekman AT, et al. Preventing the onset of major depressive disorder: a meta-analytic review of psychological interventions. Int J Epidemiol. 2014; 43(2): 318-29.
37. 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.
38. Schaub MP, Blankers M, Lehr D, Boss L, Riper H, Dekker J, et al. Efficacy of an internet-based self-help intervention to reduce co-occurring alcohol misuse and depression symptoms in adults: study protocol of a three-arm randomised controlled trial. BMJ open. 2016; 6(5): e011457.
39. 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.
40. Kessler RC, van Loo HM, Wardenaar KJ, Bossarte RM, Brenner LA, Ebert DD, et al. Using patient self-reports to study heterogeneity of treatment effects in major depressive disorder. Epidemiology and psychiatric sciences. 2016: 1-15.
41. Kessler RC, van Loo HM, Wardenaar KJ, Bossarte RM, Brenner LA, Cai T, et al. Testing a machine-learning algorithm to predict the persistence and severity of major depressive disorder from baseline self-reports. Molecular psychiatry. 2016.