



Universiteit
Leiden
The Netherlands

Internet-based treatment for depressive symptoms in hemodialysis patients: a cluster randomized controlled trial

Nadort, E.; Schouten, R.W.; Boeschoten, R.E.; Smets, Y.; Shaw, P.C.; Vleming, L.J.; ... ; Siegert, C.E.H.

Citation

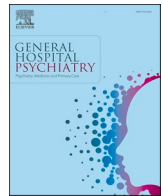
Nadort, E., Schouten, R. W., Boeschoten, R. E., Smets, Y., Shaw, P. C., Vleming, L. J., ... Siegert, C. E. H. (2022). Internet-based treatment for depressive symptoms in hemodialysis patients: a cluster randomized controlled trial. *General Hospital Psychiatry*, 75, 46-53. doi:10.1016/j.genhosppsych.2022.01.008

Version: Publisher's Version

License: [Creative Commons CC BY 4.0 license](https://creativecommons.org/licenses/by/4.0/)

Downloaded from: <https://hdl.handle.net/1887/3564828>

Note: To cite this publication please use the final published version (if applicable).



Internet-based treatment for depressive symptoms in hemodialysis patients: A cluster randomized controlled trial

Els Nadort^{a,b,*}, Robbert W. Schouten^c, Rosa E. Boeschoten^b, Yves Smets^c, Prataap Chandie Shaw^d, Louis Jean Vleming^e, Marijke J.E. Dekker^f, Michiel Westerman^g, Ellen K. Hoogeveen^{h,i}, Willem J.W. Bos^{j,k}, Marcel Schouten^l, Karima Farhat^m, Friedo W. Dekkerⁱ, Patricia van Oppen^b, Birit F.P. Broekman^{a,b}, Carl E.H. Siegert^c

^a Department of Psychiatry, OLVG Hospital, Jan Tooropstraat 164, 1061 AE Amsterdam, the Netherlands

^b Department of Psychiatry, Amsterdam University Medical Centre and GGZ inGeest, Oldenaller 1, 1081, HJ, Amsterdam, the Netherlands

^c Department of Nephrology, OLVG hospital, Jan Tooropstraat 164, 1061 AE Amsterdam, the Netherlands

^d Department of Nephrology, Haaglanden Medisch Centrum, Lijnbaan 32, 2512 VA, The Hague, the Netherlands

^e Department of Nephrology, HagaZiekenhuis, Els Borst-Eilersplein 275, 2545 AA The Hague, the Netherlands

^f Department of Nephrology, Maasstad Ziekenhuis, Maasstadweg 21, 3079 DZ, Rotterdam, the Netherlands

^g Department of Nephrology, Franciscus Gasthuis & Vlietland Ziekenhuis, Kleiweg 500, 3045 PM Rotterdam, the Netherlands

^h Department of Nephrology, Jeroen Bosch Ziekenhuis, Henri Dunantstraat 1, 5223 GZ s-Hertogenbosch, the Netherlands

ⁱ Department of Clinical Epidemiology, Leiden University Medical Centre, Albinusdreef 2, 2333 ZA Leiden, the Netherlands

^j Department of Internal Medicine, St. Antonius Ziekenhuis, Koekoekslaan 1, 3435 CM Nieuwegein, the Netherlands

^k Department of Internal Medicine, Leiden University Medical Centre, Albinusdreef 2, 2333 ZA Leiden, the Netherlands

^l Department of Nephrology, Tergooi Hospital, Van Riebeeckweg 212, 1213 XZ Hilversum, the Netherlands

^m Department of Nephrology, Spaarne Gasthuis, Boerhaavelaan 22, 2035 RC Haarlem, the Netherlands

ARTICLE INFO

Keywords:

Cluster RCT
Depression
Hemodialysis
Internet-based
CBT

ABSTRACT

Objective: To investigate the effectiveness of a guided internet-based self-help intervention for hemodialysis patients with depressive symptoms.

Method: Chronic hemodialysis patients from nine Dutch hospitals with a depression score on the Beck Depression Inventory – second edition (BDI-II) of ≥ 10 , were cluster-randomized into a five modules guided internet-based self-help problem solving therapy intervention or a parallel care-as-usual control group. Clusters were based on hemodialysis shift. The primary outcome depression was measured with the BDI-II. Analysis was performed with linear mixed models.

Results: A total of 190 hemodialysis patients were cluster-randomized to the intervention ($n = 89$) or control group ($n = 101$). Post-intervention measurement was completed by 127 patients (67%) and more than half of the patients (54%) completed the intervention. No significant differences were found on the BDI-II score between the groups (mean difference -0.1 , 95%CI -3.0 ; 2.7 , $p = 0.94$). Per protocol sensitivity analysis showed comparable results. No significant differences in secondary outcomes were observed between groups.

Conclusions: Guided internet-based self-help problem solving therapy for hemodialysis patients with depressive symptoms does not seem to be effective in reducing these symptoms as compared to usual care. Future research should examine how to best design content and accessibility of an intervention for depressive symptoms in hemodialysis patients.

Trial registration: Dutch Trial Register: Trial NL6648 (NTR6834) (prospectively registered 13th November 2017).

* Corresponding author at: OLVG hospital Jan Tooropstraat, 164 1061 AE Amsterdam, the Netherlands.

E-mail addresses: e.nadort@olvg.nl (E. Nadort), r.schouten@olvg.nl (R.W. Schouten), r.boeschoten@ggzingeest.nl (R.E. Boeschoten), y.f.c.smets@olvg.nl (Y. Smets), p.chandieshaw@haaglandenmc.nl (P. Chandie Shaw), l.vleming@hagaziekenhuis.nl (L.J. Vleming), dekkerM2@maasstadziekenhuis.nl (M.J.E. Dekker), m.westerman@franciscus.nl (M. Westerman), e.hoogeveen@jzbz.nl (E.K. Hoogeveen), w.bos@antoniusziekenhuis.nl (W.J.W. Bos), maschouten@tergooi.nl (M. Schouten), kfarhat@spaanegasthuis.nl (K. Farhat), f.w.dekker@lumc.nl (F.W. Dekker), p.vanoppen@ggzingeest.nl (P. van Oppen), b.f.p.broekman@olvg.nl (B.F.P. Broekman), c.siegert@olvg.nl (C.E.H. Siegert).

<https://doi.org/10.1016/j.genhospsych.2022.01.008>

Received 1 November 2021; Received in revised form 17 January 2022; Accepted 24 January 2022

Available online 30 January 2022

0163-8343/© 2022 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Depressive symptoms are common in hemodialysis patients and are associated with adverse clinical outcomes such as decreased quality of life, increased hospitalization and mortality [1–4]. Despite its high prevalence and negative consequences only a minority of dialysis patients with depressive symptoms are diagnosed and treated. This is due to poor recognition of depressive symptoms, unwillingness of patients to seek help and the stigma attached to a diagnosis of depression and its treatment [1,5].

Evidence for the effective treatment of depression in dialysis patients is scarce [6–8]. Therefore, safe and effective treatment of depressive symptoms is needed [5]. Although a recent trial shows a modestly better effect of sertraline in lowering depressive symptoms than psychotherapy, evidence on the safety and effectiveness of antidepressant medication in dialysis patients is sparse and inconclusive [9–11]. Cognitive behavioral therapy (CBT) is an effective treatment for people with depression in general as well as for patients with medical conditions [12–14]. CBT seems promising in decreasing depressive symptoms as well as improving quality of life for dialysis patients based on two meta-analyses who report limited evidence from small trials with per protocol analysis [8,15]. A recent trial comparing the efficacy of CBT and sertraline in hemodialysis patients showed modestly better depression scores but also more frequent adverse events in the sertraline group [11].

A cognitive behavioral method that is commonly used in patients with medical illness and depressive symptoms is problem solving therapy (PST) [16–18]. PST focusses on training problem-solving skills to help individuals to cope better with stressful problems in daily life, to reduce psychopathology and to enhance positive well-being [19]. In patients with cancer attending specialist medical services, PST has shown to improve psychological outcomes like depression and quality of life [20,21]. Two small trials on the effect of PST on depression scores in hemodialysis patients showed significant improvement of these scores in the treatment group compared to the control group [22,23].

CBT treatment protocols are not yet part of routine dialysis care and research regarding optimal delivery methods are required [24]. End-stage renal disease related physical limitations such as fatigue and the high burden of health care contacts of dialysis patients may reduce the ability and willingness of patients to attend face-to-face psychotherapy [24,25]. A possible alternative for face-to-face treatment is Internet-based self-help CBT (ICBT) as it is easily accessible and of proven effectiveness, also in populations with other chronic somatic conditions [26–31]. Two non-controlled feasibility trials on ICBT and Internet-based positive psychological intervention in dialysis patients provide encouragement that this is a feasible and innovative option for effective psychological treatment for depression in these patients [32,33]. A third feasibility trial on ICBT found that ICBT might only be feasible in computer literate patients [34]. An Internet-based version of PST (IPST) has already been developed and is effective in reducing depressive symptoms in the general population [35]. However, the effect of IPST has not yet been investigated in dialysis patients.

This cluster RCT investigates the effectiveness of a guided IPST tailored to hemodialysis patients. The primary outcome is depressive symptoms and secondary outcomes are anxiety symptoms, health-related quality of life (HRQoL) and dialysis symptoms.

2. Materials and methods

2.1. Trial design

This study is a multicenter cluster RCT with an active guided self-help IPST arm and a parallel care-as-usual control arm. Cluster randomization was chosen to prevent contamination between participants from the intervention and control group, which might occur when control participants learn about the intervention and adopt it

themselves. Inclusion ran from January 2017 through March 2020. Eligible and consenting hemodialysis patients were assessed at baseline (T0) and 12 weeks after randomization (T1). An extensive description of the study has been published earlier [36]. The study was approved by the Medical Ethics Committee of MEC-U, Nieuwegein, the Netherlands (registration number: NL58520.100.17). Written informed consent was obtained from all participants. This study was carried out in accordance with the declaration of Helsinki and the CONSORT 2010 statement: extension to cluster randomized trials [37].

2.2. Participants

Hemodialysis patients were recruited from 18 participating dialysis centers affiliated with nine hospitals across the Netherlands. All patients were assessed for eligibility. Adult chronic hemodialysis patients with increased levels of depressive symptoms (score of ≥ 10 on the Beck Depression Inventory – second edition (BDI-II)), who were willing to take part in an IPST self-help course were eligible to participate in the study [38,39]. Chronic hemodialysis is defined as >90 days on treatment. Potential participants were excluded if they were actively suicidal or did not have a sufficient command of the Dutch language necessary to participate in the study. Suicidality was assessed by a study doctor under supervision of a psychiatrist if patients reported suicidal ideations on item 9 of the BDI-II.

2.3. Intervention

All participants in the clusters allocated to the intervention were offered an individual evidence-based guided IPST [35]. The intent and core constructs of the original PST-based intervention, to apply problem solving skills to solve important problems, to worry less about unimportant problems and to accept unsolvable problems, were conserved. To adjust the IPST for use in the hemodialysis population, additional information about psychosocial consequences of kidney failure and hemodialysis treatment were added. To help participants filling out the exercises and to give them a feeling of connection with other people in the same situation, we have provided real-life example cases from dialysis patient focus groups throughout the modules. Furthermore, the large amounts of written information and psychoeducational texts were transformed into easily understandable animations to take reduced concentration and fatigue common in hemodialysis patients into account.

The intervention consisted of five modules with information, examples and assignments and is called ‘Worry Less for Dialysis Patients’ (in Dutch: ‘Minder Zorgen voor Dialyse Patiënten’). Participants had to finish the modules within 10 weeks on tablet-computers during hemodialysis sessions or at home if preferred. In the exercises, patients addressed their own problems that they faced in day-to-day life and were encouraged to put the learned skills into practice the next week. Individual feedback on the patients’ assignments was provided on a weekly basis by a therapist via the online portal. Participants could request support on the use of the tablet-computer. Patients who completed at least three modules were considered to have completed the treatment because the core concepts of the IPST were covered in the first three modules [40].

Patients randomized to the care-as-usual control group received no IPST.

2.4. Patient characteristics and outcomes

At baseline, socio-demographic and clinical data were extracted from the questionnaire and electronic patient files. The primary cause of kidney disease was classified according to the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) coding system [41]. The Davies comorbidity index was used to define the level of comorbidity [42].

The primary outcome depressive symptoms was measured with the BDI-II. The BDI-II contains 21 items, in which respondents are asked how much these symptoms have bothered them in the past two weeks with a total score between 0 and 63 with higher scores indicating more severe depression. A score above 10 means at least mild symptoms of depression [38,43]. The BDI-II has been validated and extensively used in the dialysis setting [44,45]. The minimal clinically important difference of the BDI-II is defined as a 17.5% reduction in BDI-II score [46].

Secondary outcome assessments included anxiety symptoms with the Beck Anxiety Inventory (BAI), consisting of 21 items with a similar scoring system to the BDI-II [47]. HRQoL was measured with the Short Form-12 (SF-12), consisting of 12 items of which a Mental Component Summary score (MCS) and a Physical Component Summary (PCS) score can be calculated on a scale of 0 to 100, where higher scores reflect better HRQoL [48–51]. The prevalence and impact of dialysis symptoms were measured with the Dialysis Symptom Index (DSI), containing 30 items on which patients were asked to report the presence (yes/no) and to which degree the symptom was bothersome using a five-point Likert scale (1 = not at all bothersome to 5 = very bothersome) [52,53].

2.5. Sample size

The power calculation was based on the comparison of T1 minus T0 in the intervention versus the control group. We took the conservative small to medium effect size (Cohen's $d = 0.4$) on the primary outcome measure based on a meta-analysis of Internet-based treatment for adult depression, while using a power 0.80, with alpha set on 0.05 and an attrition rate of 30% (as seen in other internet-based therapies for patients with depressive symptoms) [54]. Therefore, a total set of $N = 99$ patients was required in each arm. The design effect of cluster-randomization was estimated to be 1.04. After adjustment for cluster randomization, sample size was calculated to be $N = 206$ in total, 103 patients per arm.

2.6. Randomization and blinding

Cluster randomization was performed by an automated computer software program to ensure independent allocation. Clusters were based on the hemodialysis shift, being Monday-Wednesday-Friday and Tuesday-Thursday-Saturday. Baseline measurements were completed for all participants in the cluster prior to randomization. A total number of 36 clusters of average 5.3 patients (range 1–8) were randomized using stratified blocks per participating dialysis center. Cluster size varied among clusters as it was dependent on how many patients agreed to fill out the BDI-II and scored ≥ 10 in a given dialysis shift. Outcome assessors were blinded and data analysts were blinded until all data collection was completed and the first analysis was performed.

2.7. Statistical analysis

Descriptive statistics were used to describe baseline characteristics, treatment adherence and dropout. Differences in BDI-II score and other continuous secondary outcomes between intervention and control group were assessed using linear mixed models. Both crude coefficients, with only baseline scores as a fixed effect factor, as well as adjusted coefficients, with the respective clusters and baseline scores as fixed effect factors and the respective centers as random effects factor in the model, were calculated. When center was added as random intercept in the model, a significant improvement was seen. Treatment effect was incorporated by adding randomization as a fixed effect factor in the model. Treatment effect was estimated from the model by reporting the coefficient for randomization and the respective p -value. Restricted maximum likelihood was used as the method of estimation. The intra-cluster correlation coefficient (ICC) was calculated for the primary outcome (depressive symptoms). Analyses were done per intention-to-treat principle. Per protocol analysis on treatment completers versus

control was done as sensitivity analysis. The analyst was blinded to the treatment group allocation. All statistical analyses were performed using SPSS for Windows, version 27 (IBM Corp).

3. Results

3.1. Participant flow

The participant flow is presented in Fig. 1. In total, 1477 patients were assessed for eligibility of which 30% did not meet the study criteria and 40% refused to participate. A total of 190 patients were cluster-randomized to IPST ($n = 89$) or the control group ($n = 101$) based on hemodialysis shift. No patients had to be excluded because of active suicidality. At T1, dropout rates were somewhat higher in the intervention group ($n = 35$, 39%) than in the control group ($n = 33$, 33%).

3.2. Baseline characteristics

Baseline demographics and clinical characteristics of included patients are shown in Table 1. Patients who were lost to follow-up were more likely to be of migration background (52% versus 39%, $p = 0.09$), to be married (52% versus 35%, $p = 0.14$) and to be on the waiting list for a kidney transplant (38% vs 27%, $p = 0.30$) (Supplemental Table S1).

3.3. Treatment adherence

Of 89 patients in the intervention group, 71 (80%) patients started the allocated intervention and 48 (54%) completed at least three modules and were considered to have completed the treatment (Fig. 1). Thirteen participants (18%) who started the intervention needed assistance with the use of the tablet computer and 32 (45%) also needed help with filling out the exercises. Average duration of the treatment for treatment-completers was 7.3 ± 2.2 weeks. Reasons for not starting the intervention or dropout were health problems or hospitalization ($n = 16$), no motivation ($n = 12$), death or dialysis withdrawal ($n = 4$), receiving a kidney transplant ($n = 4$), dissatisfaction with the treatment ($n = 4$) or cognitive problems ($n = 1$). There were no significant differences between completers and non-completers in baseline characteristics (Supplemental Table S1).

3.4. Improvement on outcome measures

The results of the intention to treat analysis are presented in Table 2. The scores on the BDI-II dropped by approximately 4 points (21%) in both the intervention and control group, but no significant differences were found between the groups (-0.1 , 95%CI -3.0 ; 2.7 , $p = 0.94$). The minimal clinically important difference, defined as 17.5% of the baseline BDI-II score of 19.0, is 3.3 points. Per protocol sensitivity analysis of 48 treatment completers compared to the control group showed comparable results (-1.0 , 95%CI -4.0 ; 1.9 , $p = 0.50$) (Table 3). The secondary outcome scores of symptoms of anxiety, health related quality of life and dialysis symptoms also improved, but differences found between the two study arms at T1 were not significant either.

ICC was 0.029 for the primary outcome depression. The design effect of this study was 1.12 with a calculated effective sample size of $n = 169$.

3.5. Treatment satisfaction

The IPST was rated with an average of 7.4 ± 1.4 on a 10-point scale with 1 being the worst rating and 10 the best rating. Most patients indicated that the IPST was clear (89%) and easy to use (86%). The majority was satisfied with the frequency of feedback (88%) and rated the quality of the feedback as good or excellent (82%).

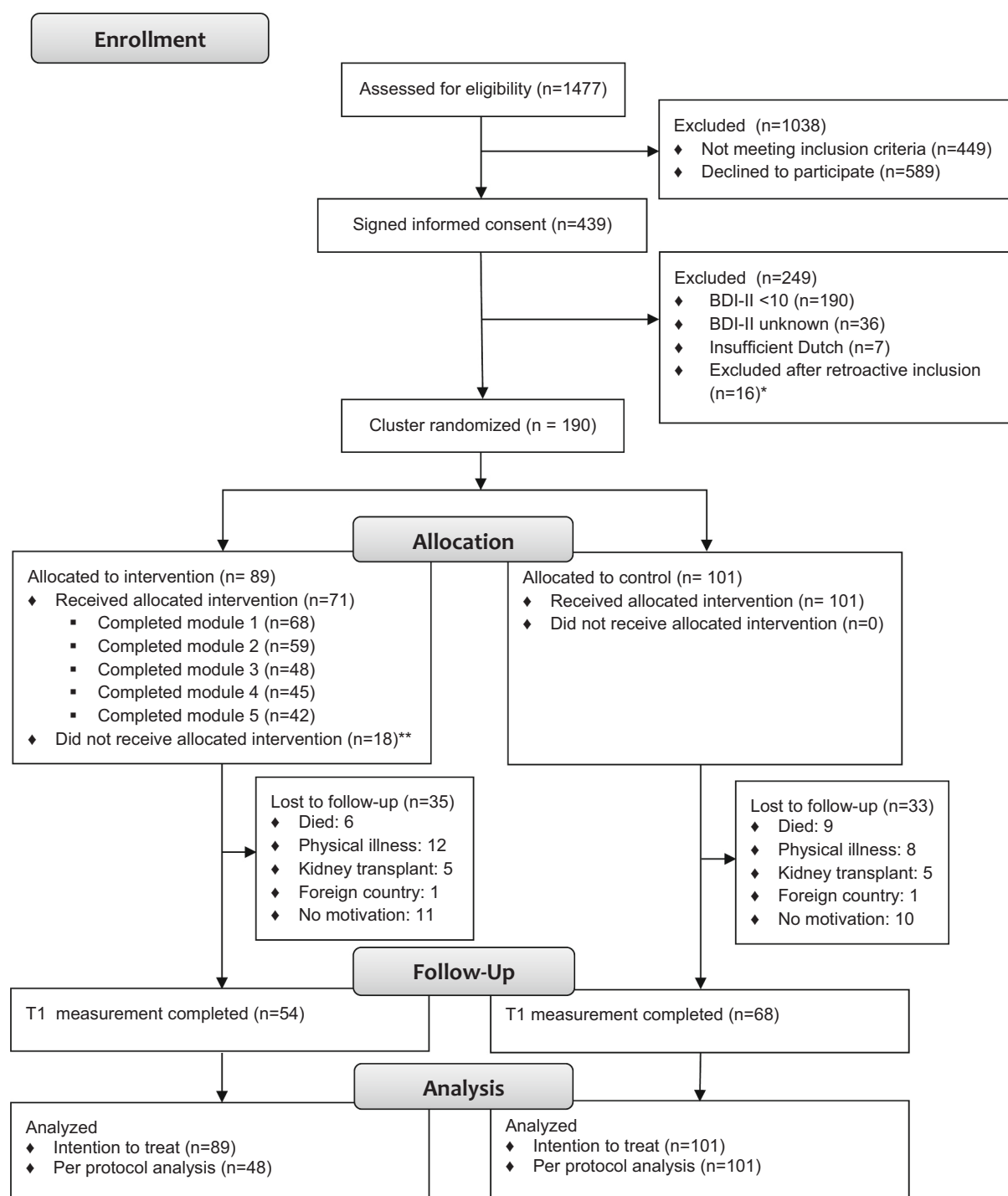


Fig. 1. Consort Flow Diagram.

* Reasons for exclusion after retroactive inclusion: BDI <10 at time of randomization.

**Reasons for not receiving allocated intervention: No motivation (n = 5), physical illness (n = 5), died (n = 3), receiving kidney transplant (n = 2), participating in study in too confronting (n = 2), cognitive problems (n = 1).

4. Discussion

This is the first controlled cluster randomized trial that investigates the effectiveness of a guided self-help IPST tailored to hemodialysis patients with depressive symptoms versus care-as-usual. We found an identical improvement of 4 BDI-II points (21%) in both groups, which exceeds the minimal clinically important difference, but shows no treatment effect. It is concluded therefore, that guided self-help IPST

does not seem to be more effective than care-as-usual in lowering depressive symptoms in hemodialysis patients. No differences were seen between the groups in secondary outcomes: change of symptoms of anxiety, HRQoL or dialysis symptoms.

The fact that we did not find a treatment effect of guided self-help IPST was surprising as evidence exists of its possible effectiveness in other chronic patient populations and because of promising results from feasibility trials in dialysis patients [32,33,40,55]. Furthermore, a recent

Table 1
Patient characteristics of 190 hemodialysis patients at baseline.

Characteristic	All patients (n = 190)	Intervention (n = 89)	Control (n = 101)
Demographic			
Age (year)	64 ± 15	63 ± 15	65 ± 15
Male sex	117 (62%)	57 (64%)	60 (60%)
Immigrant*	83 (44%)	38 (43%)	45 (45%)
Country of birth			
The Netherlands	124 (65%)	61 (69%)	63 (62%)
Social			
Married/in a relationship	78 (41%)	39 (44%)	39 (39%)
Has Children	134 (71%)	63 (71%)	71 (70%)
Education**			
Low	75 (40%)	33 (37%)	42 (42%)
Middle	81 (43%)	45 (51%)	36 (36%)
High	33 (17%)	11 (12%)	22 (22%)
Employed	14 (7%)	7 (8%)	7 (7%)
Renal and dialysis			
Dialysis vintage (months)	26 [8–49]	23 [7.5–43.5]	32 [8.5–56]
Primary kidney disease			
Renal vascular disease	39 (21%)	20 (23%)	19 (19%)
Diabetic nephropathy	56 (30%)	24 (27%)	32 (32%)
Glomerulonephritis	15 (8%)	6 (7%)	9 (9%)
Other	60 (32%)	29 (33%)	31 (31%)
Kt/V _{urea} at baseline	3.9 ± 1.2	3.9 ± 1.2	3.9 ± 1.2
On waiting list for kidney transplant	59 (31%)	28 (32%)	31 (31%)
Residual diuresis of ≥100 ml/24 h	113 (60%)	57 (64%)	56 (55%)
Clinical			
Davies comorbidity score			
Low comorbidity	34 (18%)	16 (18%)	18 (18%)
Moderate comorbidity	114 (60%)	54 (61%)	60 (59%)
High comorbidity	42 (22%)	19 (21%)	23 (23%)
Comorbid conditions			
Diabetes mellitus	98 (52%)	45 (51%)	53 (53%)
Cardiovascular disease***	162 (85%)	73 (82%)	89 (88%)
Laboratory			
Hb (g/dL)	11.2 ± 1.3	10.9 ± 1.2	11.5 ± 1.3
Phosphate (mg/dL)	5.1 ± 1.7	5.1 ± 1.8	5.1 ± 1.7
Albumin (g/L)	3.7 ± 0.5	3.8 ± 0.4	3.6 ± 0.5
PTH (pg/mL)	38 ± 30	39 ± 29	38 ± 32
Psychiatric			
Psychiatric diagnosis in medical history			
None	148 (78%)	67 (75%)	81 (80%)
Major depressive disorder	16 (8%)	6 (7%)	10 (10%)
Anxiety disorder	6 (3%)	5 (6%)	1 (1%)
Other	32 (17%)	18 (20%)	14 (14%)
BDI-II score	19.0 ± 7.7	19.0 ± 7.2	19.0 ± 8.1
BAI score	13.8 ± 10.5	13.0 ± 9.9	14.6 ± 11.0
Current psychotherapy	18 (10%)	12 (14%)	6 (6%)
Current psychopharmac use			
Antidepressants	37 (20%)	20 (23%)	17 (17%)
Benzodiazepine	38 (20%)	21 (24%)	17 (17%)

Note: Values are presented as mean ± standard deviation, median [interquartile range], or frequency (percentage).

Abbreviations: BDI-II, Beck Depression Inventory; BAI, Beck Anxiety Inventory; SSRI, selective serotonin reuptake inhibitor; SNRI, Serotonin and norepinephrine reuptake inhibitors.

* Immigrant status is based on country of birth of both patient and biological parents of patient.

** Education: Low = primary education, middle = secondary education, high = higher professional education and university.

*** CVD = acute coronary syndrome, angina pectoris, percutaneous coronary angioplasty, coronary artery bypass surgery, heart failure, peripheral arterial vascular disease, stroke, hypertension.

systematic review shows statistically significant improvements in depression scores of CBT, including PST, in comparison with depression scores of control groups [15]. The improvement in our control group suggests that the improvement in both groups may be explained by spontaneous recovery, regression to the mean, a possible therapeutic advantage for patients in the care-as-usual arm associated with involvement in a trial (Hawthorne effect) or a combination of a sample more favorable to recovery in the control arm than the treatment arm [5].

Both self-help and internet-based therapies have shown to be effective in various cohorts of chronic somatically ill patients [29–31]. The main potential benefits of internet-based therapies compared to conventional face-to-face therapy are better access to psychological support and overcoming barriers like direct cost, time, distance and mobility limitation [32,34]. It is possible that Internet-based interventions are less effective in the dialysis population compared to other chronically ill patient populations due to older age, the large treatment and illness burden of patients with kidney failure on dialysis therapy and high unemployment rates, which may decrease the acceptance and usage skills associated with the Internet [26,34]. As we did not assess which aspect of the IPST was too complex, the content itself or the access on tablet-computers, we cannot answer this question based on our results. However, our experience was that the majority of the patients needed assistance with filling out the exercises due to cannulation of the dominant arm or computer illiteracy and not with explanation of the exercises, which might be an indication that the accessibility of IPST is a problem in the dialysis population and not the content of the intervention itself. More research on the effectivity of the various IPST aspects is necessary before any conclusions can be drawn and more research is needed on how the accessibility and design of the content of an intervention can be optimized, with the purpose to develop an effective treatment available for all hemodialysis patients.

4.1. Strengths and limitations

The strength of our study is that it is the first randomized controlled trial with an intention to treat analysis on a ICBT intervention in hemodialysis patients. Other strengths are the development of an innovative, accessible, tailor-made, waiting-list free internet-based intervention focused on practical daily life issues for hemodialysis patients and the embedding of a mental health intervention in routine hemodialysis care. A final strength is the relatively large sample size for a study on a psychosocial intervention in hemodialysis patients.

This study has several limitations. First, the substantial non-adherence to the intervention and the large number of drop-outs at T1 may lead to biased results and may leave the study underpowered. Dropout rates of 30% are seen in other internet-based intervention studies in patients with elevated depression [16], and the additional non-adherence and dropouts in our study are most likely due to physical limitations imposed by chronic renal failure and dialysis treatment and possible stigma. To account for this issue we used linear mixed model analysis, which takes dropout into account by estimating the individual slope based both on the measurements of that individual and on complete observed data of other similar individuals in the data set. We can, however, not exclude residual confounding due to non-random dropout from treatment and/or follow-up.

Second, despite our best efforts, we have a lower-than-expected enrollment rate and we underestimated the design effect of cluster randomization which lowers our effective sample size to 169. Although this might leave the study underpowered, it is not likely that a different effect size will be found with an additional inclusion of 50 patients.

Third, we used a cutoff on the BDI-II of ≥10 to include patients with elevated symptoms of depression instead of confirming a diagnosis of major depression disorder with a clinical interview or combining the BDI-II score with other depression scales to assess depressive symptoms more comprehensively. Although this is common practice in other

Table 2

Intention to treat Linear Mixed Model analyses of primary and secondary outcomes for the intervention and control group.

		Intervention T0: n = 89 T1: n = 54	Control T0: n = 101 T1: n = 68	Crude MD (95%CI)* n = 190	p-value	Adjusted MD (95%CI)** n = 190	p-value
Primary outcome							
Depression (BDI-II)	T0	19.0 ± 7.2	19.0 ± 8.1	−0.2 (−2.8;2.4)	0.87	-0.1 (−3.0;2.7)	0.94
	T1	14.7 ± 8.5	15.2 ± 7.7				
Secondary outcomes***							
Anxiety (BAI)	T0	13.0 ± 9.9	14.6 ± 11.0	2.0 (−0.5;4.5)	0.12	2.1 (−0.7;4.8)	0.15
	T1	11.9 ± 9.0	11.2 ± 8.5				
HRQoL (SF-12), PCS	T0	27.0 ± 7.9	28.4 ± 9.2	−1.0 (−4.0;2.0)	0.50	−1.3 (−4.7;2.1)	0.45
	T1	33.4 ± 8.6	34.2 ± 9.7				
HRQoL (SF-12), MCS	T0	48.5 ± 10.0	49.0 ± 10.1	1.0 (−2.4;4.4)	0.55	0.1 (−3.7;3.9)	0.96
	T1	50.2 ± 9.4	48.0 ± 9.4				
Dialysis symptoms (DSI), Presence score	T0	15.5 ± 6.6	14.6 ± 5.9	−1.4 (−3.2;0.5)	0.14	−1.2 (−3.2;0.8)	0.24
	T1	13.9 ± 7.3	14.7 ± 5.6				
Dialysis symptoms (DSI), Bothersome score	T0	46.0 ± 23.6	44.6 ± 22.5	−1.4 (−7.5;4.7)	0.65	−1.3 (−7.9;5.4)	0.71
	T1	39.5 ± 24.2	42.0 ± 18.3				

Note: Values are presented as mean ± standard deviation.

Note: A positive MD represents a higher value in the intervention group, a negative MD represents a lower value in the intervention group.

Note: BDI-II and BAI score range 0–63, SF-12 score range 0–100, DSI symptom score range 0–30, DSI bothering score range 0–150.

Abbreviations: MD, mean difference; CI, confidence interval; BDI-II; Beck Depression Inventory – Second edition, BAI; Back Anxiety Inventory, HRQoL, health-related quality of life; SF-12, 12-Item Short Form Health Survey; PCS, Physical Component Summary; MCS, Mental Component Summary; DSI, Dialysis Symptom Index.

* Crude Linear mixed model analysis with baseline scores as a fixed effect factor in the model. Treatment effect was incorporated by adding randomization as fixed effect factor in the model. Treatment effect was estimated from the model by reporting the coefficient for randomization and the respective p-value. Restricted maximum likelihood was used as the method of estimation. Analyses were performed using SPSS for Windows, version 27 (IBM Corp).

** Adjusted linear mixed model analysis with the respective clusters and baseline scores as fixed effect factors and the respective centers as random effects factor in the model. A significant improvement was seen after adding center as a random intercept. Treatment effect was incorporated by adding randomization as fixed effect factor in the model. Treatment effect was estimated from the model by reporting the coefficient for randomization and the respective p-value. Restricted maximum likelihood was used as the method of estimation. Analyses were performed using SPSS for Windows, version 27 (IBM Corp).

*** Naïve model without random intercept for center because convergence was not achieved.

Table 3

Per protocol Linear Mixed Model sensitivity analyses of primary and secondary outcomes for the intervention and control group.

		Intervention T0: n = 48 T1: n = 41	Control T0: n = 101 T1: n = 68	Crude MD (95%CI)* n = 149	p-value	Adjusted MD (95%CI)** n = 149	p-value
Primary outcome							
Depression (BDI-II)	T0	18.1 ± 6.0	19.0 ± 8.1	−0.9 (−3.5;1.8)	0.53	−1.0 (−4.0;1.9)	0.50
	T1	13.4 ± 8.4	15.2 ± 7.7				
Secondary outcomes***							
Anxiety (BAI)	T0	12.8 ± 10.9	14.6 ± 11.0	1.5 (−1.2; 4.3)	0.27	1.5 (−1.5; 4.6)	0.32
	T1	11.5 ± 9.1	11.2 ± 8.5				
HRQoL (SF-12), PCS	T0	28.9 ± 7.5	28.4 ± 9.2	−0.4 (−3.7; 3.0)	0.83	−0.5 (−4.2; 3.2)	0.79
	T1	34.8 ± 8.8	34.2 ± 9.7				
HRQoL (SF-12), MCS	T0	48.0 ± 9.6	49.0 ± 10.1	1.4 (−2.3; 5.1)	0.46	0.4 (−3.7; 4.5)	0.85
	T1	50.6 ± 9.7	48.0 ± 9.4				
Dialysis symptoms (DSI), Presence score	T0	15.9 ± 7.3	14.6 ± 5.9	−1.5 (−3.5; 0.5)	0.13	−1.2 (−3.4; 0.9)	0.55
	T1	13.9 ± 7.4	14.7 ± 5.6				
Dialysis symptoms (DSI), Bothersome score	T0	46.2 ± 25.6	44.6 ± 22.5	−1.8 (−8.4; 4.8)	0.58	−1.6 (−8.8; 5.6)	0.67
	T1	39.6 ± 24.3	42.0 ± 18.3				

Note: Values are presented as mean ± standard deviation.

Note: A positive MD represents a higher value in the intervention group, a negative MD represents a lower value in the intervention group.

Note: BDI-II and BAI score range 0–63, SF-12 score range 0–100, DSI symptom score range 0–30, DSI bothering score range 0–150.

Abbreviations: MD, mean difference; CI, confidence interval; BDI-II; Beck Depression Inventory – Second edition, BAI; Back Anxiety Inventory, HRQoL, health-related quality of life; SF-12, 12-Item Short Form Health Survey; PCS, Physical Component Summary; MCS, Mental Component Summary; DSI, Dialysis Symptom Index.

* Crude Linear mixed model analysis with baseline scores as a fixed effect factor in the model. Treatment effect was incorporated by adding randomization as fixed effect factor in the model. Treatment effect was estimated from the model by reporting the coefficient for randomization and the respective p-value. Restricted maximum likelihood was used as the method of estimation. Analyses were performed using SPSS for Windows, version 27 (IBM Corp).

** Adjusted linear mixed model analysis with the respective clusters and baseline scores as fixed effect factors and the respective centers as random effects factor in the model. A significant improvement was seen after adding center as a random intercept. Treatment effect was incorporated by adding randomization as fixed effect factor in the model. Treatment effect was estimated from the model by reporting the coefficient for randomization and the respective p-value. Restricted maximum likelihood was used as the method of estimation. Analyses were performed using SPSS for Windows, version 27 (IBM Corp).

*** Naïve model without random intercept for center because convergence was not achieved.

clinical trials on online psychotherapy, this may have led to misclassification bias of depression and dilution of the treatment effect. A recent systematic review on depression screening tools in dialysis patients advises a higher cutoff of ≥ 16 on the BDI-II for diagnosis of major depressive disorder. The use of a lower cutoff could potentially lead to

overdiagnosis of depression due to overlap between symptoms of kidney failure and depression. However, when this higher cutoff of 16 was used on our data ($n = 110$), no trend was seen in favor of the intervention.

Fourth, we considered participants who completed at least three modules to have completed the treatment, as is common practice in this

IPST intervention in other medical populations [40]. However, as we did not conduct a BDI-II assessment after the first three modules due to practical reasons, there is no certainty that the effect of completing only the first three modules is the same as completing all five modules.

Fifth, the per protocol sensitivity analysis hampers randomization because of afterwards selection on intervention completers, which should be considered as a weakness. If a treatment effect would have been found, this might have been invalid.

Sixth, the majority of the participants reported the intervention to be easy to use and clear, however, this is likely biased due to dropouts at T1.

4.2. Conclusion

To the best of our knowledge, this is the first RCT that examines the effect of guided self-help IPST for depressive symptoms in hemodialysis patients. In both the intervention and control group a decrease in depression scores of 21% over time was found. However, we did not find a significant difference in improvement of depressive symptoms between the intervention and control group. Although recruitment rates were low, dropout rates were high and there were no differences in outcomes between the intervention and control group, this trial adds to the limited evidence on treatment of depression in hemodialysis patients. Future research should examine how to best design content and accessibility of an intervention for depressive symptoms in hemodialysis patients.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.genhosppsych.2022.01.008>.

Disclosures

None.

Authors' contributions

EN, RWS, FWD, PvO and CEHS have contributed to the study design and all authors have contributed to the preparation of this manuscript. EN, RWS, YS, PCS, LJW, MJED, MW, EKH, WJWB, MAS, KF and CEHS included the patients and contributed to data acquisition. REB and PvO supervised the feedback given by the therapists during the intervention. EN performed suicidality assessments under supervision of BFPB. EN performed the statistical analysis under supervision of RWS and FWD. EN wrote the first draft of this manuscript; all co-authors critically reviewed and revised the initial draft and approved the final version of the manuscript.

Funding

This trial is supported by ZonMW [grant number: 843001 804], Stichting Zabawas [grant number G2016/221] and OLVG. ZonMW has peer-reviewed and approved a previous version of this study protocol in the context of the grant application process, but had no role in data collection, data analysis and drafting or approving the present manuscript. ZonMW can be contacted via doelmatigheidsonderzoek@zonmw.nl.

Data availability statement

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

CRediT authorship contribution statement

Elis Nadort: Conceptualization, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Visualization, Project

administration. **Robbert W. Schouten:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing – review & editing, Supervision. **Rosa E. Boeschoten:** Investigation, Resources, Writing – review & editing, Supervision. **Yves Smets:** Investigation, Resources, Writing – review & editing. **Prataap Chandie Shaw:** Investigation, Resources, Writing – review & editing. **Louis Jean Vleming:** Investigation, Resources, Writing – review & editing. **Marijke J.E. Dekker:** Investigation, Resources, Writing – review & editing. **Michiel Westerman:** Investigation, Resources, Writing – review & editing. **Ellen K. Hoogeveen:** Investigation, Resources, Writing – review & editing. **Willem J.W. Bos:** Investigation, Resources, Writing – review & editing. **Marcel Schouten:** Investigation, Resources, Writing – review & editing. **Karima Farhat:** Investigation, Resources, Writing – review & editing. **Friedo W. Dekker:** Conceptualization, Methodology, Formal analysis, Writing – review & editing, Supervision. **Patricia van Oppen:** Conceptualization, Methodology, Investigation, Resources, Writing – review & editing, Supervision. **Birit F.P. Broekman:** Investigation, Resources, Writing – review & editing, Supervision. **Carl E.H. Siegert:** Conceptualization, Methodology, Investigation, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Data availability

The data that has been used is confidential.

Acknowledgements

The authors are grateful to the participating dialysis centers and the trial team for their precious work.

References

- [1] Hedayati SS, Grambow SC, Szczech LA, Stechuchak KM, Allen AS, Bosworth HB. Physician-diagnosed depression as a correlate of hospitalizations in patients receiving long-term hemodialysis. *Am J Kidney Dis* 2005;46(4):642–9. <https://doi.org/10.1053/j.ajkd.2005.07.002>.
- [2] Palmer S, Vecchio M, Craig JC, Tonelli M, Johnson DW, Nicolucci A, et al. Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. *Kidney Int* 2013;84(1):179–91. <https://doi.org/10.1038/ki.2013.77>.
- [3] Farrokh F, Abedi N, Beyene J, Kurdyak P, Jassal SV. Association between depression and mortality in patients receiving long-term dialysis: a systematic review and meta-analysis. *Am J Kidney Dis* 2014;63(4):623–35. <https://doi.org/10.1053/j.ajkd.2013.08.024>.
- [4] Lopes AA, Bragg J, Young E, Goodkin D, Mapes D, Combe C, et al. Depression as a predictor of mortality and hospitalization among hemodialysis patients in the United States and Europe. *Kidney Int* 2002;62(1):199–207. <https://doi.org/10.1046/j.1523-1755.2002.00411.x>.
- [5] Hackett ML, Jardine MJ. We need to talk about depression and Dialysis: but what questions should we ask, and does anyone know the answers? *Clin J Am Soc Nephrol* 2017;12(2):222–4. <https://doi.org/10.2215/CJN.13031216>.
- [6] Schouten RW, Haverkamp GL, Loosman WL, Chandie Shaw PK, van Ittersum FJ, Smets YFC, et al. Anxiety symptoms, mortality, and hospitalization in patients receiving maintenance Dialysis: a cohort study. *Am J Kidney Dis* 2019. <https://doi.org/10.1053/j.ajkd.2019.02.017>.
- [7] Soykan A, Boztas H, Kutlay S, Ince E, Aygor B, Ozden A, et al. Depression and its 6-month course in untreated hemodialysis patients: a preliminary prospective follow-up study in Turkey. *Int J Behav Med* 2004;11(4):243–6. <https://doi.org/10.1207/s15327558ijbm1104.8>.
- [8] Natale P, Palmer SC, Ruospo M, Saglimbene VM, Rabindranath KS, Strippoli GF. Psychosocial interventions for preventing and treating depression in dialysis patients. *Cochrane Database Syst Rev* 2019;12:CD004542. <https://doi.org/10.1002/14651858.CD004542.pub3>.
- [9] Friedli K, Guirguis A, Almond M, Day C, Chilcot J, Da Silva-Gane M, et al. Sertraline versus placebo in patients with major depressive disorder undergoing hemodialysis: a randomized, controlled feasibility trial. *Clin J Am Soc Nephrol* 2017;12(2):280–6. <https://doi.org/10.2215/CJN.02120216>.
- [10] Palmer SC, Natale P, Ruospo M, Saglimbene VM, Rabindranath KS, Craig JC, et al. Antidepressants for treating depression in adults with end-stage kidney disease treated with dialysis. *Cochrane Database Syst Rev* 2016;5:CD004541. <https://doi.org/10.1002/14651858.CD004541.pub3>.
- [11] Mehrotra R, Cukor D, Unruh M, Rue T, Heagerty P, Cohen SD, et al. Comparative efficacy of therapies for treatment of depression for patients undergoing maintenance hemodialysis: a randomized clinical trial. *Ann Intern Med* 2019;170(6):369–79. <https://doi.org/10.7326/M18-2229>.

- [12] Richards SH, Anderson L, Jenkinson CE, Whalley B, Rees K, Davies P, et al. Psychological interventions for coronary heart disease: Cochrane systematic review and meta-analysis. *Eur J Prev Cardiol* 2018;25(3):247–59. <https://doi.org/10.1177/2047487317739978>.
- [13] van Straten A, Geraedts A, Verdonck-de Leeuw I, Andersson G, Cuijpers P. Psychological treatment of depressive symptoms in patients with medical disorders: a meta-analysis. *J Psychosom Res* 2010;69(1):23–32. <https://doi.org/10.1016/j.jpsychores.2010.01.019>.
- [14] Beltman MW, Voshaar RC, Speckens AE. Cognitive-behavioural therapy for depression in people with a somatic disease: meta-analysis of randomised controlled trials. *Br J Psychiatry* 2010;197(1):11–9. <https://doi.org/10.1192/bjp.bp.109.064675>.
- [15] Ng CZ, Tang SC, Chan M, Tran BX, Ho CS, Tam WW, et al. A systematic review and meta-analysis of randomized controlled trials of cognitive behavioral therapy for hemodialysis patients with depression. *J Psychosom Res* 2019;126:109834. <https://doi.org/10.1016/j.jpsychores.2019.109834>.
- [16] Warmerdam L, van Straten A, Twisk J, Riper H, Cuijpers P. Internet-based treatment for adults with depressive symptoms: randomized controlled trial. *J Med Internet Res* 2008;10(4):e44. <https://doi.org/10.2196/jmir.1094>.
- [17] Mynors-Wallis L. *Problem solving treatment for anxiety and depression: A practical guide*. New York: Oxford University Press; 2005.
- [18] Cuijpers P, de Wit L, Kleiboer A, Karyotaki E, Ebert DD. Problem-solving therapy for adult depression: an updated meta-analysis. *Eur Psychiatry* 2018;48:27–37. <https://doi.org/10.1016/j.eurpsy.2017.11.006>.
- [19] Bell AC, D'Zurilla TJ. Problem-solving therapy for depression: a meta-analysis. *Clin Psychol Rev* 2009;29(4):348–53. <https://doi.org/10.1016/j.cpr.2009.02.003>.
- [20] Hopko DR, Armento ME, Robertson SM, Ryba MM, Carvalho JP, Colman LK, et al. Brief behavioral activation and problem-solving therapy for depressed breast cancer patients: randomized trial. *J Consult Clin Psychol* 2011;79(6):834–49. <https://doi.org/10.1037/a0025450>.
- [21] Strong V, Waters R, Hibberd C, Murray G, Wall L, Walker J, et al. Management of depression for people with cancer (SMaRT oncology 1): a randomised trial. *Lancet* 2008;372(9632):40–8. [https://doi.org/10.1016/S0140-6736\(08\)60991-5](https://doi.org/10.1016/S0140-6736(08)60991-5).
- [22] Erdley SD, Gellis ZD, Bogner HA, Kass DS, Green JA, Perkins RM. Problem-solving therapy to improve depression scores among older hemodialysis patients: a pilot randomized trial. *Clin Nephrol* 2014;82(1):26–33. <https://doi.org/10.5414/CN108196>.
- [23] Kucuk L, Isil Ö. The Effects of Problem Solving Education on Depression Level and Problem Solving Skills on Dialysis Patients. 2009. p. 1638–49.
- [24] Chilcot J, Hudson JL. Is successful treatment of depression in dialysis patients an achievable goal? *Semin Dial* 2018. <https://doi.org/10.1111/sdi.12755>.
- [25] Duarte PS, Miyazaki MC, Blay SL, Sesso R. Cognitive-behavioral group therapy is an effective treatment for major depression in hemodialysis patients. *Kidney Int* 2009;76(4):414–21. <https://doi.org/10.1038/ki.2009.156>.
- [26] Barak A, Hen L, Boniel-Nissim M, Shapira N. A comprehensive review and a meta-analysis of the effectiveness of internet-based psychotherapeutic interventions. *Journal of Technology in Human Services* 2008;26(2–4):109–60. <https://doi.org/10.1080/15228830802094429>.
- [27] Beatty L, Lambert S. A systematic review of internet-based self-help therapeutic interventions to improve distress and disease-control among adults with chronic health conditions. *Clin Psychol Rev* 2013;33(4):609–22. <https://doi.org/10.1016/j.cpr.2013.03.004>.
- [28] Carlbring P, Andersson G, Cuijpers P, Riper H, Hedman-Lagerlof E. Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: an updated systematic review and meta-analysis. *Cogn Behav Ther* 2018;47(1):1–18. <https://doi.org/10.1080/16506073.2017.1401115>.
- [29] Ebert DD, Nobis S, Lehr D, Baumeister H, Riper H, Auerbach RP, et al. The 6-month effectiveness of internet-based guided self-help for depression in adults with type 1 and 2 diabetes mellitus. *Diabet Med* 2017;34(1):99–107. <https://doi.org/10.1111/dme.13173>.
- [30] Matcham F, Rayner L, Hutton J, Monk A, Steel C, Hotopf M. Self-help interventions for symptoms of depression, anxiety and psychological distress in patients with physical illnesses: a systematic review and meta-analysis. *Clin Psychol Rev* 2014;34(2):141–57. <https://doi.org/10.1016/j.cpr.2014.01.005>.
- [31] van Beugen S, Ferwerda M, Hoeve D, Rovers MM, Spillekom-van Koulil S, van Middendorp H, et al. Internet-based cognitive behavioral therapy for patients with chronic somatic conditions: a meta-analytic review. *J Med Internet Res* 2014;16(3):e88. <https://doi.org/10.2196/jmir.2777>.
- [32] Chan R, Dear BF, Titov N, Chow J, Suranyi M. Examining internet-delivered cognitive behaviour therapy for patients with chronic kidney disease on haemodialysis: a feasibility open trial. *J Psychosom Res* 2016;89:78–84. <https://doi.org/10.1016/j.jpsychores.2016.08.012>.
- [33] Hernandez R, Burrows B, Wilund K, Cohn M, Xu S, Moskowitz JT. Feasibility of an internet-based positive psychological intervention for hemodialysis patients with symptoms of depression. *Soc Work Health Care* 2018;1-16. <https://doi.org/10.1080/00981389.2018.1523268>.
- [34] Hudson JL, Moss-Morris R, Norton S, Picariello F, Game D, Carroll A, et al. Tailored online cognitive behavioural therapy with or without therapist support calls to target psychological distress in adults receiving haemodialysis: a feasibility randomised controlled trial. *J Psychosom Res* 2017;102:61–70. <https://doi.org/10.1016/j.jpsychores.2017.09.009>.
- [35] van Straten A, Cuijpers P, Smits N. Effectiveness of a web-based self-help intervention for symptoms of depression, anxiety, and stress: randomized controlled trial. *J Med Internet Res* 2008;10(1):e7. <https://doi.org/10.2196/jmir.954>.
- [36] Nadort E, Schouten RW, Dekker FW, Honig A, van Oppen P, Siegert CEH. The (cost) effectiveness of guided internet-based self-help CBT for dialysis patients with symptoms of depression: study protocol of a randomised controlled trial. *BMC Psychiatry* 2019;19(1):372. <https://doi.org/10.1186/s12888-019-2363-5>.
- [37] Campbell MK, Piaggio G, Elbourne DR, Altman DG, Group C. Consort 2010 statement: extension to cluster randomised trials. *BMJ* 2012;345:e5661. <https://doi.org/10.1136/bmj.e5661>.
- [38] Beck AT, Steer RA, Brown GK. *The Beck depression inventory. Second edition ed*. San Antonio: Psychological Corp; 1996.
- [39] Beck AT, Steer RA, Brown GK. *Does AJWvd. BDI-II Manual: The Dutch Version of the Beck Depression Inventory. 2nd edition ed*. Enschede: Ipskamp; 2002.
- [40] Boeschoten RE, Dekker J, Uitdehaag BM, Beekman AT, Hoogendoorn AW, Collette EH, et al. Internet-based treatment for depression in multiple sclerosis: a randomized controlled trial. *Mult Scler* 2017;23(8):1112–22. <https://doi.org/10.1177/1352458516671820>.
- [41] van Dijk PC, Jager KJ, de Charro F, Collart F, Cornet R, Dekker FW, et al. Renal replacement therapy in Europe: the results of a collaborative effort by the ERA-EDTA registry and six national or regional registries. *Nephrol Dial Transplant* 2001;16(6):1120–9. <https://doi.org/10.1093/ndt/16.6.1120>.
- [42] Davies SJ, Phillips L, Naish PF, Russell GI. Quantifying comorbidity in peritoneal dialysis patients and its relationship to other predictors of survival. *Nephrol Dial Transplant* 2002;17(6):1085–92. <https://doi.org/10.1093/ndt/17.6.1085>.
- [43] Balogun RA, Turgut F, Balogun SA, Holroyd S, Abdel-Rahman EM. Screening for depression in elderly hemodialysis patients. *Nephron Clin Pract* 2011;118(2):c72–7. <https://doi.org/10.1159/000320037>.
- [44] Loosman WL, Siegert CE, Korzec A, Honig A. Validity of the hospital anxiety and depression scale and the Beck depression inventory for use in end-stage renal disease patients. *Br J Clin Psychol* 2010;49(Pt 4):507–16. <https://doi.org/10.1348/014466509X477827>.
- [45] Chilcot J, Wellsted D, Farrington K. Screening for depression while patients dialyse: an evaluation. *Nephrol Dial Transplant* 2008;23(8):2653–9. <https://doi.org/10.1093/ndt/gfn105>.
- [46] Button KS, Kounali D, Thomas L, Wiles NJ, Peters TJ, Welton NJ, et al. Minimal clinically important difference on the Beck Depression Inventory–II according to the patient's perspective. *Psychol Med* 2015;45(15):3269–79. <https://doi.org/10.1017/S0033291715001270>.
- [47] Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* 1988;56(6):893–7. <https://doi.org/10.1037/0022-006x.56.6.893>.
- [48] Ware Jr J, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34(3):220–33. <https://doi.org/10.1097/00005650-199603000-00003>.
- [49] Loosman WL, Hoekstra T, van Dijk S, Terwee CB, Honig A, Siegert CE, et al. Short-form 12 or short-form 36 to measure quality-of-life changes in dialysis patients? *Nephrol Dial Transplant* 2015;30(7):1170–6. <https://doi.org/10.1093/ndt/gfv066>.
- [50] Clark JM, Marszalek JM, Bennett KK, Harry KM, Howarter AD, Eways KR, et al. Comparison of factor structure models for the Beck anxiety inventory among cardiac rehabilitation patients. *J Psychosom Res* 2016;89:91–7. <https://doi.org/10.1016/j.jpsychores.2016.08.007>.
- [51] Muntin AD, van der Feltz-Cornelis CM, van Marwijk HW, Spinhoven P, Penninx BW, van Balkom AJ. Is the Beck anxiety inventory a good tool to assess the severity of anxiety? A primary care study in the Netherlands study of depression and anxiety (NESDA). *BMC Fam Pract* 2011;12:66. <https://doi.org/10.1186/1471-2296-12-66>.
- [52] Weisbord SD, Fried LF, Arnold RM, Rotondi AJ, Fine MJ, Levenson DJ, et al. Development of a symptom assessment instrument for chronic hemodialysis patients: the Dialysis symptom index. *J Pain Symptom Manage* 2004;27(3):226–40. <https://doi.org/10.1016/j.jpainsymman.2003.07.004>.
- [53] van der Willik EM, Meuleman Y, Prantl K, van Rijn G, Bos WJW, van Ittersum FJ, et al. Patient-reported outcome measures: selection of a valid questionnaire for routine symptom assessment in patients with advanced chronic kidney disease - a four-phase mixed methods study. *BMC Nephrol* 2019;20(1):344. <https://doi.org/10.1186/s12882-019-1521-9>.
- [54] Andersson G, Cuijpers P. Internet-based and other computerized psychological treatments for adult depression: a meta-analysis. *Cogn Behav Ther* 2009;38(4):196–205. <https://doi.org/10.1080/16506070903318960>.
- [55] Heller HM, Hoogendoorn AW, Honig A, Broekman BFP, van Straten A. The effectiveness of a guided internet-based tool for the treatment of depression and anxiety in pregnancy (MamaKits online): randomized controlled trial. *J Med Internet Res* 2020;22(3):e15172. <https://doi.org/10.2196/15172>.