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General Hospital Psychiatry 98 (2026) 165–171

Contents lists available at ScienceDirect

General Hospital Psychiatry

journal homepage: www.elsevier.com/locate/genhospsych

Research paper

Internet-based problem solving therapy improves depressive and dialysis related physical symptoms in hemodialysis patients under 65 years of age: A post-hoc secondary subgroup analysis of a cluster randomized controlled trial

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ARTICLE INFO

Keywords:
Hemodialysis
Depression
RCT
CBT
PST
Internet-based

ABSTRACT

Background and hypothesis: Patients on hemodialysis therapy often experience a high burden of mental and physical health symptoms. We developed a guided internet-based self-help problem-solving therapy (IPST) targeted on practical daily life issues. While we did not find an effect for all patients, we hypothesized that an internet intervention might be effective in younger patients below 65 years of age. In this post-hoc secondary subgroup analysis we divided our study population based on age to study the effect of our intervention on depressive- and dialysis-related symptoms.

Methods: Chronic hemodialysis patients with a depression score on the Beck Depression Inventory (BDI-II) of ≥10, were randomized into a five modules guided IPST or a care-as-usual control group. The study population was stratified by age (< 65 and ≥ 65 years). The primary outcome was depressive symptoms (BDI-II). Secondary outcomes were anxiety (BAI), health-related quality of life (HRQoL) and dialysis related symptoms (DSI). Analyses were performed using linear mixed models.

Results: 122 out of 190 randomized patients completed post-intervention measurements. In 25 younger patients (age < 65), a significant effect was found in reduction of BDI-II (−30 %, $p = 0.04$) and DSI (presence of symptoms: −27 %, $p = 0.001$; level of distress: −25 %, $p = 0.03$). No effect was seen on BAI or HRQoL. In the older population ($n = 29$), no effect of the intervention was found on any outcomes.

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https://doi.org/10.1016/j.genhosppsych.2025.12.022
Received 18 August 2025; Received in revised form 22 December 2025; Accepted 29 December 2025
Available online 30 December 2025

Conclusion: An easy to implement guided IPST showed a clinically relevant decrease in depressive symptoms and dialysis related physical symptoms in hemodialysis patients aged below 65 years although results should be interpreted cautiously given the post-hoc design.
Trial registration: Dutch Trial Register: Trial NL6648 (NTR6834) (prospectively registered 13th November 2017).

1. Introduction

Patients on dialysis therapy often experience a high burden of mental and physical health symptoms with a negative impact on quality of life [1]. One of the most common mental health problems in hemodialysis patients are depressive symptoms [2,3]. Besides the mental burden, dialysis patients suffer from dialysis-related symptoms such as fatigue, pruritis, nausea and headaches. Research has shown that mental and physical symptoms can interact with each other [4]. Cognitive-behavioral therapy (CBT) is an effective evidence-based psychotherapy that is widely used for depressive symptoms outside the dialysis unit [5]. A few smaller trails show promising results on the effect of CBT like interventions on depression in dialysis patients [2,6,7]. However, there is a lack of adequately powered randomized trials. Lesser-known is the effect of CBT on somatic symptoms in comparison to the effect on depressive symptoms although multiple studies demonstrate positive effects on somatic symptoms [8–15]. To our knowledge, no studies have been conducted on the effects of CBT like interventions on depression in combination with dialysis-related physical symptoms.

Multiple barriers like costs, availability, intensity with extra hospital visits and stigma on mental illness [16] make the implementation of psychotherapy for patients on dialysis challenging and may explain the lack of research on this topic. Internet-based treatment with the guidance of a trained psychologist could tackle these barriers and play an important role in a stepped care program to treat these symptoms. At the same time an internet-based therapy may not be a feasible treatment option for some patient groups that are less familiar with tablet-use and internet programs.

In a previous report on this trial we did not observe an effect of a guided internet-based problem solving therapy (IPST), a CBT method, on depressive symptoms in hemodialysis patients compared to usual care at a group level (intervention $n = 54$, usual care $n = 68$,1, 95 %CI -3.0; 2.7, $p = 0.94$) [17]. We observed that younger patients were more proficient in tablet-use and computer based interventions (unpublished data). Literature suggests a negative effect of age on guided internet-delivered CBT for depression and anxiety [18]. As such, we hypothesized that IPST for hemodialysis patients would be more effective in the subpopulation of patients <65 years of age. In this study we performed a post-hoc subgroup analysis dividing our study population based on age and study the effect of our intervention on both depressive- and dialysis symptoms.

2. Methods

2.1. Trial design

This study consists of a multicenter cluster RCT with an active guided self-help IPST arm and a parallel care-as-usual control arm. Clusters were based on the hemodialysis shift (the scheduled day and time of the patient's hemodialysis treatment) and were 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. An extensive description of the study has been published earlier [17]. Inclusion ran from January 2017 through March 2020. Eligible and consenting hemodialysis patients were assessed at baseline (T0) and 12 weeks after randomization (T1). 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 [19]. This post-hoc secondary subgroup analysis was not part of the main analysis in the original trial protocol. This post-hoc analyses was considered as we observed a trend during the trial that younger patients were more familiar with tablet-based interventions, which led to the hypothesis that age could influence treatment outcomes, a factor not previously explored in the literature and relevant for clinical practice. We did not do any other secondary analyses.

2.2. Study population

Adult chronic hemodialysis patients (>90 days on dialysis treatment) with sufficient Dutch language skills and an increased level of depressive symptoms (score of ≥10 on the Beck Depression Inventory – second edition (BDI-II)), who were willing to take part in an guided IPST, were recruited from 18 participating dialysis centers affiliated with nine hospitals across the Netherlands. Potential participants were excluded if they were actively suicidal or did not have sufficient command of the Dutch language to enable participation in the study. To study the effect of age on outcome we divided the study population by age using a cut-off point based on the Organisation for Economic Co-operation and Development (OECD), who defines the elderly population as 65 years and over [20].

2.3. Intervention

All participants in the clusters allocated to the intervention were offered an individual guided internet-based problem-solving therapy (IPST) that was specifically tailored to hemodialysis patients [21]. IPST is a cognitive-behavioral therapy (CBT) intervention that focuses on training in the adoption and effective application of adaptive problem-solving attitudes and skills [22]. The intent and core constructs of the original evidence-based problem solving therapy intervention, to apply problem solving skills to solve important problems and to learn to worry less about unimportant issues [23,24], were conserved, but additional information about psychosocial consequences of kidney failure and hemodialysis treatment were added. The intervention consisted of five modules. 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. For more details on the intervention we refer to our previous publication [17]. Patients randomized to the care-as-usual control group received no IPST.

2.4. Outcome measurements

Depressive symptoms were 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 [25]. The BDI-II has been validated and extensively used in the dialysis setting [26–28]. The minimal clinically important difference of the BDI-II is defined as a 17.5 % reduction in BDI-II score [29]. Anxiety symptoms were measured with the Beck Anxiety Inventory (BAI), consisting of 21 items with a similar scoring system to the BDI-II [30]. Health-related quality of life (HRQoL) was measured with the Short Form-12 (SF-12), consisting of 12 items of which a Mental Component Summary (MCS) score and a Physical Component Summary (PCS) score can be calculated

on a scale of 0 to 100, where higher scores reflect better HRQoL [31,32]. 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 of the dialysis related symptom (yes/no) and the distress experienced by the dialysis related symptom (to which degree the symptom was bothersome using a five-point Likert scale, 1 = not at all bothersome to 5 = very bothersome) [33].

2.5. Statistical analysis

Normally distributed variables are expressed as mean ± SD, non-normally distributed variables as median (IQR). Differences in baseline characteristics between different age groups and different treatment arms were calculated with a Chi-square test for categorical data, and for continuous data with a Student's *t*-test or a Mann-Whitney *U* test in case of non-normally distributed data. Differences in BDI-II score and other continuous outcomes between intervention and control group were assessed using linear mixed models. Coefficients with baseline scores as a fixed effect factor were calculated. Treatment effect was incorporated by adding randomization as a fixed effect factor in the model. Clusters were based on dialysis shifts and were included in the random effects model. Treatment effect was estimated from the model by reporting the mean difference (MD) with 95 % confidence interval (CI) 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). To test the effect of intervention on separate dialysis symptoms, next to the DSI score, scores on baseline and after intervention were compared using a Wilcoxon signed-rank test. All analyses were intention-to-treat analyses. Therefor we included all patients of whom follow-up data were available, regardless of the amount of modules they had completed. Per protocol sensitivity analyses were performed including only patients who completed at least 3 modules. All statistical analyses were performed using SPSS for Windows, version 27 (IBM Corp).

3. Results

3.1. Participant flow

In total 1477 patients were assessed for eligibility of which 30 % did not meet the study criteria and 40 % declined participation. A total of 190 patients were cluster randomized to intervention ($n = 89$) or control group ($n = 101$). Follow-up data was available of 122 patients, 54 patients in the intervention group and 68 patients in the control group. Twenty-five patients in the intervention group and 29 patients in the control group were aged below 65 years. Thirteen patients in the intervention group (of which 7 < 65 years) did not finish the required modules of the intervention but were included in the assessment as this study consists of an intention-to-treat analysis.

3.2. Baseline characteristics

Table 1 shows the baseline characteristics of the included 122 patients. To further improve the ability to judge the generalizability of this trial, we included a description of patients who were excluded due to missing follow-up data (Supplementary Table 1). Baseline characteristics of both groups (included versus excluded) were mostly similar. The only significant difference was seen in quality of life (HRQoL), specifically the mental component summary of the questionnaire ($p = 0.01$). However, no difference was seen in BDI-II, BAI or DSI. The study population was stratified by age with a cutoff point of 65 years to explore differences between a relative younger and older population. In the younger group, 19 out of 25 patients (76 %) finished at least three modules and were considered to have completed the treatment. In the younger group, 7 out of 25 (28 %) patients needed help during the intervention with the use of tablet-computers or to carry out the

Table 1
Patient characteristics of 122 hemodialysis patients at baseline.

	Total	Intervention		Control	
Baseline characteristics	*N* = 122	<65 (*n* = 25)	≥65 (*n* = 29)	<65 (n = 29)	≥65 (*n* = 39)
Demographic					
Age, y	65 ± 14	51 ± 10*	74 ± 6	53 ± 8*	76 ± 7
Male sex	78 (64 %)	15 (60 %)	23 (79 %)#	18 (62 %)	22 (56 %)
Immigrant+	48 (39 %)	14 (56 %)*	8 (28 %)	19 (66 %)*	7 (18 %)
Born in The Netherlands	82 (67 %)	15 (60 %)	21 (72 %)	14 (48 %)*	32 (82 %)
Social					
Married/in a relationship	43 (36 %)	7 (28 %)	13 (45 %)	8 (29 %)*	15 (39 %)
Children	82 (68 %)	17 (68 %)	20 (69 %)	15 (54 %)*	30 (77 %)
Employed	11 (9 %)	4 (16 %)	1 (3 %)	6 (21 %)*	0 (0 %)
Voluntary work	6 (5 %)	2 (8 %)	1 (3 %)	1 (4 %)	2 (5 %)
Help needed during the intervention					
- No help needed	–	17 (71 %)*	3 (12 %)	–	–
- Help needed with usage of tablet	–	1 (4 %)	7 (27 %)	–	–
- Help needed to do the assignments online	–	6 (25 %)	16 (62 %)	–	–
Renal and dialysis					
Dialysis vintage (months)	26 [9–50]	23 [10–70]	20 [5–45]	32 [8–63]	29 [9–53]
Kt/V_{urea} at baseline	3.9 ± 1.2	4.0 ± 1.4	3.7 ± 1.0	4.3 ± 1.2*	3.7 ± 1.1
Residual diuresis of ≥100 ml/24 h	75 (61 %)	16 (64 %)	18 (64 %)	16 (55 %)	25 (64 %)
On waiting list for Tx	33 (27 %)	15 (60 %)*#	4 (14 %)	8 (30 %)	6 (16 %)
Dialysis symptoms (DSI)					
- Presence score	15 ± 6	19 ± 7*#	13 ± 7	15 ± 6	15 ± 5
- Bothersome score	45 ± 23	54 ± 23*	35 ± 22#	47 ± 24	46 ± 22
Cardiovascular	122 (100 %)	25 (100 %)	29 (100 %)	29 (100 %)	39 (100 %)
- Diabetes	60 (49 %)	10 (40 %)	13 (45 %)	13 (45 %)	24 (62 %)
- Hypertension	76 (62 %)	17 (68 %)	17 (59 %)	14 (48 %)*	28 (72 %)
- Hypercholesterolemia	18 (15 %)	3 (12 %)	5 (17 %)	4 (14 %)	6 (15 %)
- Angina Pectoris	12 (10 %)	2 (8 %)	4 (14 %)	1 (3 %)	5 (13 %)
- MI/ACS	17 (14 %)	1 (4 %)	1 (3 %)#	6 (21 %)	9 (23 %)
- PTCA/CABG	25 (21 %)	6 (24 %)*	0 (0 %)#	5 (17 %)	14 (36 %)
- Heatfailure	35 (29 %)	4 (16 %)*	13 (45 %)	7 (24 %)	11 (28 %)
- Peripheral vascular disease	25 (21 %)	3 (12 %)	6 (21 %)	5 (17 %)	11 (28 %)
- TIA/CVA	22 (18)	3 (12 %)	5 (17 %)	5 (17 %)	9 (23 %)
Psychiatric					
Psychiatric diagnosis in medical history					
- None	93 (76 %)	15 (60 %)*	27 (93 %)	18 (62 %)*	33 (85 %)

(*continued on next page*)

Table 1 (*continued*)

Baseline characteristics	Total	Intervention		Control	
	N = 122	<65 (*n* = 25)	≥65 (*n* = 29)	<65 (n = 29)	≥65 (*n* = 39)
- Major depressive disorder	12 (10 %)	4 (16 %)*	0 (0 %)	6 (21 %)*	2 (5 %)
- Anxiety disorder	3 (2 %)	2 (8 %)	0 (0 %)	1 (3 %)	0 (0 %)
- Other	22 (18 %)	8 (32 %)*	2 (7 %)	8 (28 %)	4 (10 %)
BDI-II score	19 ± 7	21 ± 6*	16 ± 5	19 ± 9	19 ± 7
BAI score	14 ± 10	14 ± 10	11 ± 9	15 ± 11	15 ± 10
HRQoL (SF-12)					
- Physical component summary	28 ± 8	28 ± 7	29 ± 9	30 ± 9	27 ± 9
- Mental component summary	47 ± 9	44 ± 6	52 ± 9	45 ± 11	48 ± 9
Consultation with psychiatrist/ psychologist++	16 (13 %)	9 (36 %)*#	4 (14 %)	2 (7 %)	1 (3 %)
Current psychopharmic use					
- Antidepressants	23 (19 %)	8 (32 %)*	5 (17 %)	5 (17 %)	5 (13 %)
- Benzodiazepines	19 (16 %)	3 (12 %)	8 (28 %)	(14 %)	4 (10 %)

Note: Values are presented as mean ± standard deviation, median [interquartile range], or frequency (percentage).
Abbreviations: ACS, Acute Coronary Syndrome; BDI-II, Beck Depression Inventory; BAI, Beck Anxiety Inventory; CABG: coronary artery bypass graft surgery; CVA: cerebrovascular accident; MI, myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; SSRI, selective serotonin reuptake inhibitor; SNRI, Serotonin and norepinephrine reuptake inhibitors; TIA: transient ischemic attack.
+ Immigrant status is based on country of birth of both patient and biological parents of patient.
++ Consultation with a psychiatrist or a psychologist 3 months prior to inclusion.
* Significant difference ($p < 0.05$) between age groups in the intervention or control group.
# Significant difference ($p < 0.05$) between intervention and control group in the age group < 65 year or > 65 year.

assignments online. In the older population, 23 out of 29 (79 %) completed the treatment and 27 out of 29 (93 %) needed help. There were no significant differences between completers and non-completers in baseline characteristics. In the intervention group, the younger population in comparison to the older population needed less help with the use of electronic devices, was more often immigrant, was more often on the waiting list for kidney transplantation, experienced more dialysis symptoms (higher DSI score, both presence and bothersome score), was more likely to have a history of mental disorders, particularly depression, experienced more symptoms of depression (higher BDI-II score), used antidepressants more frequently and more often consulted a psychiatrist or psychologist 3 months prior to inclusion.

3.3. Improvement on outcome measures

We performed a linear mixed model to investigate the effect of the intervention on the primary outcome BDI-II score stratified by age. In the younger population the intervention had a significant effect on primary outcome BDI-II score with a decrease in depressive symptoms (MD -3.7 (−7.2;-0.2), $p = 0.04$). The average drop in BDI-II score was 6 points (20.8 ± 5.9 to 14.6 ± 9.2, −30 %). Because the younger intervention group more often used antidepressants or consulted a psychiatrist or psychologist 3 months prior to inclusion, the linear mixed models were controlled for use of antidepressants or consultation of a psychiatrist/psychologist. Adding use of antidepressants or consultation did not have a significant effect on the model. Both adjusted models yielded similar results with a positive effect of the intervention on BDI-II score in the younger population (MD -3.9 (−7.5;-0.3), $p = 0.03$; MD -4.1 (−7.9; −0.3), p = 0.04, respectively). In the older population no effect of intervention was seen on BDI-II score (Tables 2 and 3).

We performed a similar linear mixed model to investigate the effect of the intervention on secondary outcome of dialysis symptoms (DSI). In the younger population we found a decrease in the amount of symptoms (presence, MD -3.4 (−7.8;-2.1), $p = 0.001$) and a decrease in the experienced distress of symptoms (bothersome, MD -10.6 (−20.4;-0.9), $p = 0.03$) (Table 2). Adjustment for use of antidepressants or consultation with a psychiatrist/psychologist 3 months prior to inclusion did not have a significant effect on these models. No effect of intervention was seen in the older population on DSI scores (Tables 2 and 3). When looking at the different dialysis symptoms within the DSI, the presence of the following symptoms reduced significantly after intervention in the younger population: nausea ($p = 0.02$), shortness of breath ($p = 0.01$), bone/joint pain (p = 0.01), muscle soreness ($p = 0.003$), worrying (p = 0.01), insomnia (p = 0.03) and total DSI presence score ($p < 0.001$). The total bothersome score, which depicts the level of distress of all these different symptoms together, decreased significantly in the younger population ($p = 0.005$). The bothersome scores of the different symptoms separately

Table 2
Intention-to-treat Linear Mixed Model analysis of primary and secondary outcomes for the intervention and control group in <65 year population.

		Intervention n = 25	Control n = 29	MD (95 % CI)* *n* = 54	p-value
Primary outcome					
Depression (BDI-II)	T0 T1	20.8 ± 5.9 14.6 ± 9.2	19.4 ± 9.0 17.0 ± 8.9	−3.7 (−7.2;-0.2)	0.04
Secondary outcomes**					
Anxiety (BAI)	T0 T1	14.1 ± 10.4 14.0 ± 9.4	14.7 ± 11.4 13.1 ± 10.5	1.3 (−2.6;5.1)	0.51
HRQoL (SF-12), PCS	T0 T1	27.6 ± 6.9 32.7 ± 8.1	29.7 ± 8.9 36.2 ± 7.9	−2.5 (−6.7;1.6)	0.23
HRQoL (SF-12), MCS	T0 T1	44.3 ± 6.3 49.6 ± 11.6	45.4 ± 11.2 46.4 ± 8.9	2.5 (−3.0;8.1)	0.36
Dialysis symptoms (DSI), Presence score	T0 T1	18.8 ± 6.6 13.8 ± 7.9	15.2 ± 5.8 15.8 ± 6.1	−3.4 (−7.8;-2.1)	0.001
Dialysis symptoms (DSI), Bothersome score	T0 T1	53.8 ± 23.4 40.1 ± 27.0	47.4 ± 23.7 46.0 ± 21.9	-10.6 (−20.4;-0.9)	0.03

Note: All patients with follow-up, regardless of the amount of modules of CBT completed, are included in these intention to treat analysis.
Note: Values are presented as mean ± standard deviation.
Note: A positive mean difference (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: BAI; Back Anxiety Inventory, BDI-II; Beck Depression Inventory – Second edition, CI, confidence interval; DSI, Dialysis Symptom Index; HRQoL, health-related quality of life; MCS, Mental Component Summary; MD, Mean difference; PCS, Physical Component Summary; SF-12, 12-Item Short Form Health Survey.
* Linear Mixed Model analysis with baseline scores as covariate.

Table 3
Intention-to-treat Linear Mixed Model analysis of primary and secondary outcomes for the intervention and control group in ≥ 65 year population.

		Intervention T1: $n = 29$	Control T1: n = 39	MD (95 % CI)* $n = 58$	p-value
Primary outcome					
Depression (BDI-II)	T0 T1	16.1 ± 4.8 14.7 ± 8.1	18.6 ± 7.0 13.8 ± 6.4	1.4 (−2.1;5.0)	0.43
Secondary outcomes***					
Anxiety (BAI)	T0 T1	10.7 ± 8.5 10.4 ± 8.4	14.9 ± 10.3 9.7 ± 6.3	2.2 (−1.0;5.5)	0.17
HRQoL (SF-12), PCS	T0 T1	29.0 ± 8.6 34.1 ± 9.1	27.3 ± 9.3 32.9 ± 10.9	0.08 (−4.5;4.7)	0.97
HRQoL (SF-12), MCS	T0 T1	51.6 ± 8.8 50.9 ± 7.0	47.7 ± 9.2 49.5 ± 9.9	−0.8 (−5.2–3.6)	0.71
Dialysis symptoms (DSI), Presence score	T0 T1	12.8 ± 6.7 14.0 ± 6.9	15.0 ± 5.4 13.9 ± 5.3	1.3 (−1.0;3.7)	0.26
Dialysis symptoms (DSI), Bothersome score	T0 T1	35.4 ± 22.2 38.9 ± 21.8	45.9 ± 21.7 39.2 ± 15.3	4.9 (−3.0;12.8)	0.22

Note: All patients with follow-up, regardless of the amount of modules of CBT completed, are included in these intention to treat analysis.
Note: Values are presented as mean ± standard deviation.
Note: A positive mean difference (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: BAI; Back Anxiety Inventory, BDI-II; Beck Depression Inventory – Second edition, CI, confidence interval; DSI, Dialysis Symptom Index; HRQoL, health-related quality of life; MCS, Mental Component Summary; MD, Mean difference; PCS, Physical Component Summary; SF-12, 12-Item Short Form Health Survey.
* Linear Mixed Model analysis with baseline scores as covariate.

did not decrease significantly in the younger population.

Linear mixed models did not show an effect on anxiety (BAI score) or quality of life (HRQoL) in either the younger or the older population.

Supplementary Table 2 shows baseline characteristics of completers versus non-completers in the intervention group. Per protocol sensitivity analysis, in which non-completers were excluded, yielded similar results to all outcome measures. In the population aged below 65 years, both BDI-II and DSI scores significantly improved after intervention (BDI-II: MD -4.4 (−8.3;-0.4), $p = 0.03$; DSI presence score: MD -5.5 (−8.5;-2.5), $p < 0.001$); DSI bothersome score: MD -11.1 (−21.9;-0.3), $p = 0.04$). In the older population these effects were not seen. No effect was seen in the younger or the older population on anxiety (BAI score) or quality of life (HRQoL).

4. Discussion

This study demonstrated a significant effect of guided internet-based problem-solving therapy (IPST), a cognitive-behavioral therapy (CBT) method, on the primary outcome BDI-II score with a decrease in depressive symptoms in a subpopulation of hemodialysis patients with age below 65 years. This improvement is clinically relevant with an average drop of 6 points (−30 %) in BDI-II score [29]. Moreover, the intervention showed effect on dialyses related symptoms with a decrease in the presence of symptoms (−27 %) and experienced distress of these symptoms (−25 %). No effect of intervention was seen on anxiety or quality of life. In the older population no effect of intervention was seen on any outcome.

The positive effect of IPST on depressive symptoms in hemodialysis patients found in this study is in line with several previously published CBT studies. A systematic review and meta-analysis (2019) combined eight smaller randomized controlled trials to study the effect of CBT and CBT like interventions, including PST, on depression scores of hemodialysis patients. Although studies were small, underpowered and possibly affected by publication bias, they showed improvement in depressive symptoms [34]. However, these studies identified multiple barriers that makes implementation of psychotherapy like CBT for patients on dialysis difficult, like costs, availability, intensity with extra hospital visits and stigma on mental illness [16]. Our internet-based PST with guidance of a trained psychologist was developed to make psychotherapy more accessible and less burdensome. Literature shows that internet-delivered CBT can be as effective as face-to-face interventions for depression in patients with chronic somatic conditions, especially when guided by a therapist [35]. In dialysis patients, research with internet-based CBT is scarce. Only two small single-arm studies were previously published and showed promising effects of an internet-delivered CBT on depression in hemodialysis patients [36,37]. Our randomized controlled trial is an addition to the singe-arm studies and confirms these previous results in a subpopulation of patients with age below 65 years.

The difference in effect of our internet delivered CBT between younger and older patients in our study is in concordance with a recently published meta-analysis including 154 RCT's, which showed that older age was related to diminished efficacy of guided internet-delivered CBT on depression and anxiety [18]. Notably, most studies investigating online treatment interventions in hemodialysis patients have a younger population in comparison to our study. The web-based nature of the intervention has been identified as a possible contribution to this phenomenon [38]. Moreover, it has been previously published that younger age seems to be a predictor for online treatment adherence [39]. Our study served an older population, since its age distribution mirrored the distribution in the average dialysis population in the Netherlands. In our study most patients above 65 years needed help during the intervention with the use of tablet-computers and to perform online assignments. Despite these findings, the satisfaction rates of our treatment was high in both younger and elderly patients. Patients found the intervention clear and easy to use and the quality of feedback was rated as good or excellent [17]. Even when hurdles in the use of tablet-computers are taken away, elderly patients may experience less comfort with technology and online content and perhaps have less ability transforming online exercises to daily offline practice. Developing an effective online intervention for elderly will be a challenge but should be addressed in further studies as the dialysis population is still ageing with improvement of life expectancy.

CBT is often used to treat psychiatric symptoms like depression [4]. However, multiple studies also demonstrate positive effects on somatic symptoms like chronic pain, headaches and distress of somatic symptoms in general [8–15]. In hemodialysis patients, up to date, most studies have been conducted on the effect of CBT on insomnia and fatigue in dialysis patients. However, convincing evidence on effectiveness is still lacking [40–44]. The CBT in our trial aimed at developing coping skills to address (practical) problems, and did not target somatic symptoms per se. Nevertheless, our intervention showed a significant decrease in both the amount and distress of dialysis symptoms, specifically nausea, shortness of breath, bone/joint pain, muscle soreness and insomnia in the younger subgroup. A possible explanation can be found in the connection between physical symptoms and depression as these are often intertwined [4]. Physical symptoms are commonly seen in depressive patients [45]. In general, depression in patients with physical symptoms has a more severe course in severity and duration of symptoms in comparison to patients without physical symptoms [46,47].

Furthermore, there is evidence that the depressive symptoms in the dialysis population have a higher somatic symptom burden compared to other populations [48]. To our knowledge this is the first study that investigated the effect of an intervention on both depressive symptoms and various dialysis related symptoms.

No effect of the intervention was found on anxiety, possibly because the intervention was designed for depressive symptoms. We did not find a significant effect on health-related quality (QoL) of life either. This pattern aligns with previous research in hemodialysis patients, where CBT effects on depression are generally greater and more consistent than on QoL. Studies in dialysis populations [34,49,50] suggest that improvements in QoL often occur later and are (partially) mediated by earlier symptom reduction. The relatively short follow-up period and limited power for QoL outcomes in our study may have contributed to the inability to detect an effect of CBT on QoL at this stage.

Our study has several limitations. First, this study consists of a post-hoc subpopulation analysis which introduces a risk for false positive findings due to multiple testing. This type of study design is suboptimal and should be interpreted carefully. Only after the original design of the study, during the implementation of the trial, we took interest in the effect of age on treatment outcome as we noticed that younger patients were more experienced in tablet-use and computer based interventions. Because our findings could be clinically relevant and provide insight for future research, publication of this post-hoc study is justifiable. Second, stratifying the population based on age, together with the large number of drop-outs at follow-up may have left the study underpowered which can lead to false positive or false negative findings. However, the extent of decrease on both BDI-II and DSI-score does not imply a false positive finding. Third, although our study was randomized, at baseline patients aged below 65 years reported more depressive and dialysis related symptoms in comparison to patients aged above 65 years. This could have influenced the efficacy of the intervention although literature suggests a neutral or a negative impact of the severity of depression on therapy outcome adherence [39,51]. Fourth, younger patients more often used antidepressants or received psychotherapy 3 months prior to inclusion which could have influenced the effect of intervention. We therefor controlled the mixed linear models for use of antidepressants or psychotherapy which yielded in similar results. We concluded that the effect seen in the younger population could not be explained by antidepressants or psychotherapy. Fifth, a large group was excluded due to missing follow-up data which could have created bias. However, both included and excluded patients showed comparable baseline characteristics. Lastly, a cutoff on the BDI-II of $\geq$10 was used to include patients with elevated symptoms of depression but we were not able to confirm a diagnosis of major depression disorder. We choose this cutoff score because a study performed in a population similar to our population, elderly dialysis patients, showed the best diagnostic accuracy at this cutoff point [28]. Also, in other medical ill populations a threshold of 10 has been used [52,53]. Although we consider a BDI cutoff 10 significant as a sensitive screening threshold in somatic medical patients, we do agree it is a conservative threshold as also higher cutoff scores have been published [26,27], and may warrant confirmatory diagnostic evaluation. Nevertheless, in our study most patients had a BDI score well above 10 as the average BDI was 19 $\pm$ 7. We therefor do not expect this relatively low cutoff included many patients without actual depressive symptoms.

Our study has also multiple strengths. First of all, this study consists of a randomized controlled trial with an intention to treat analysis on an internet-based PST intervention in hemodialysis patients which is a valuable addition to existing literature. Also, this study investigates not only the effect of an internet-based PST intervention on depressive symptoms but also dialysis related symptoms. Moreover, our intervention is an innovative, accessible, tailor-made, waiting-list free internet-based intervention addressing practical daily life issues for hemodialysis patients. As a consequence, it has the potential for easy implementation in routine hemodialysis care [2] and could play an important role in a stepped care program to treat depressive and dialyses related symptoms.

In conclusion, our study shows a significant effect of guided internet-based problem solving CBT with a decrease in both depressive and dialysis related symptoms in a subpopulation of hemodialysis patients with age below 65 years. This finding should be confirmed in a subsequent trial as this study consists of a post-hoc analysis which should be interpreted with caution. Moreover, developing an effective (online) intervention for elderly aged above 65 years of age should be addressed in further studies.

Authors' Contribution

EN, RWS, FWD, PvO and CEHS have contributed to the study design of the original trial and DZ, RWS, BFPB and CEHS has contributed to this subpopulation study design and all authors have contributed to the preparation of this manuscript. EN, RWS, YS, PCS, LJV, 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. DZ performed the statistical analysis under supervision of RWS and FWD. DZ 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.

CRediT authorship contribution statement

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

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

Acknowledgements

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2025.12.022.

Data availability

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

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