Depression and Anxiety in Dialysis Patients

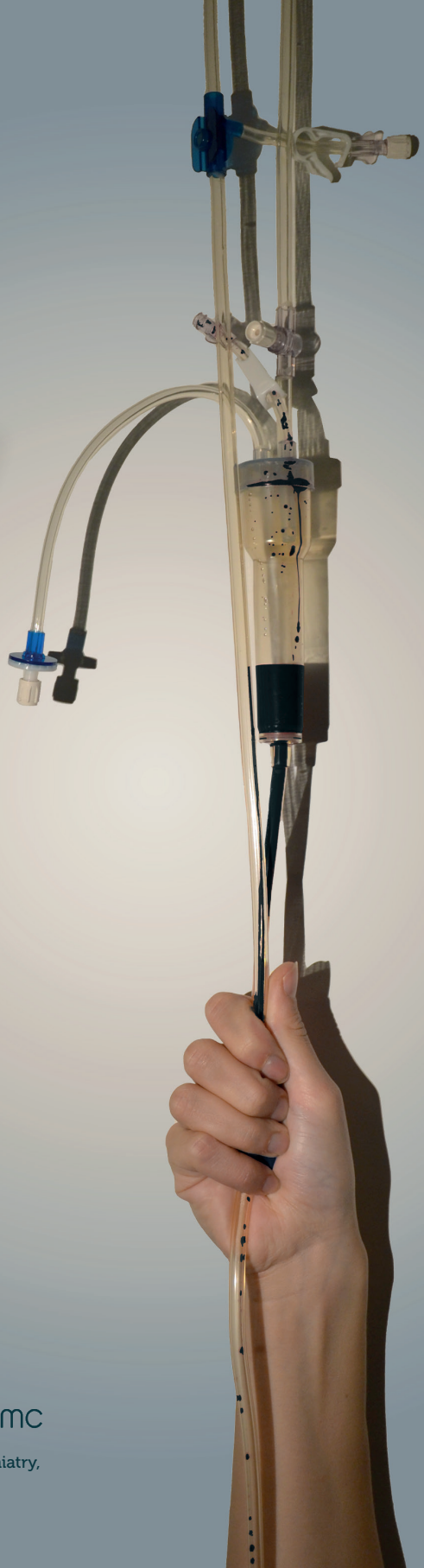
Nadort, Els

2022

document version
Publisher's PDF, also known as Version of record

Depression and Anxiety in Dialysis Patients

Els Nadort



Amsterdam UMC
Universitair Medische Centra
Department of Psychiatry,
location VUmc

Depression and Anxiety in Dialysis Patients

Els Nadort

Colophon
Depression and Anxiety in Dialysis Patients
PhD thesis, Vrije Universiteit, Amsterdam, The Netherlands

This research was funded by:

The printing of this thesis was kindly sponsored by:

Afdeling Onderzoek & Innovatie GGZ inGeest

Stichting Wetenschappelijk Onderzoek olvg

Gerrit Blaauw Fonds
GOED GEVEN–GOED DOEN

Author: Els Nadort
ISBN: 978-94-6416-906-5
Cover design: Yoshi Hoet Design|www.yoshihoetdesign.nl
Layout: Els Nadort, Yoshi Hoet Design, Ridderprint
Printing: Ridderprint | www.ridderprint.nl

VRIJE UNIVERSITEIT

Depression and Anxiety in Dialysis Patients

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor of Philosophy aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. C.M. van Praag,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op woensdag 19 januari 2022 om 13.45 uur
in een bijeenkomst van de universiteit,
De Boelelaan 1105

door

Els Nadort

geboren te Wormer

promotoren:	prof.dr. P.C. van Oppen prof.dr. F.W. Dekker
copromotoren:	dr. C.E.H. Siegert dr. B.F.P. Broekman
Promotiecommissie:	prof.dr. F.J. Bemelman prof.dr. M. Hemmelder prof.dr. J.H. Smit dr. Y. Meuleman dr. A. van Schaik

Table of Contents

Chapter 1

General Introduction

Kidney failure and dialysis treatment

Chronic kidney disease (CKD) is a progressive disease characterized by progressive kidney damage resulting into declining kidney function.(1) CKD has a global prevalence of 9%, which likely will increase over the next few decades due to population aging, and increasing prevalence of diabetes and hypertension.(2, 3) CKD's final stage is kidney failure and CKD is a leading cause of morbidity and mortality worldwide. Patients with kidney failure need kidney replacement therapy (KRT) in order to survive.(4) KRT options are kidney transplantation, hemodialysis and peritoneal dialysis. The individual choice of treatment depends on availability, clinical characteristics and patient's preferences.(4) If KRT is not possible or not preferred by the patient, comprehensive conservative care can be started in which symptoms of kidney failure are treated.(5) In the Netherlands, 17.500 people were receiving KRT in 2018. Although kidney transplantation is the preferred treatment for most patients, this is often not possible due to organ shortages or medical contraindications. These patients are dependent on dialysis therapy, a chronic, intensive and time-consuming treatment with high physical and mental burden.(6-8)

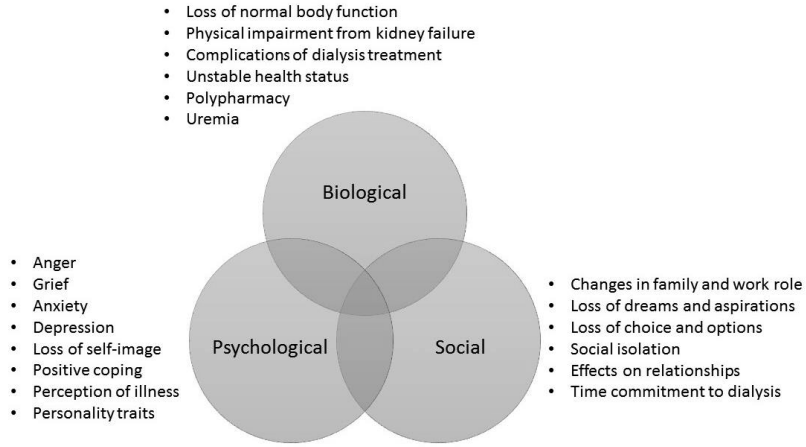
Hemodialysis is a center-based therapy where waste products are removed from the blood by diffusion through a semi-permeable membrane in an extracorporeal artificial kidney.(9) A hemodialysis session has a duration of three to five hours with a frequency of three times a week. Rapid changes in hemodynamic and fluid status often lead to feeling tired after a hemodialysis session.(10) Peritoneal dialysis is a continuous home-based therapy performed by the patients themselves by exchanging dialysate fluid in the peritoneal cavity four to five times a day. Waste products are exchanged from the blood continuously across the abdominal peritoneal, resulting in biochemical and hemodynamic stability compared to hemodialysis.(9, 11) The decision to treat a patient with hemodialysis or peritoneal dialysis is multifactorial and influenced by clinical and socioeconomic factors, such as the cardiovascular ability to tolerate volume shifts, peritoneal dysfunction due to intra-abdominal adhesions, the home situation of the patient and patient's preferences.(11-13)

Kidney failure has a significant impact on daily lives of patients due to the experience of multiple losses, including loss of kidney function, family roles and work roles, time and mobility, defined as being able to walk without limitation or assistance.(14, 15) Impaired quality of life and feelings of loss of control are increased by other stressors like medication effects, dependency on treatment, dietary constraints, fear of death and symptom burden.(16, 17) More than half of the patients on dialysis experience symptoms of pain, fatigue, pruritus and constipation.(18) Other frequent symptoms are loss of appetite, sexual dysfunction, muscle cramps, insomnia, nausea and mental health symptoms like depression and anxiety.(6, 7, 18)

Depression and anxiety in dialysis patients

Psychiatric comorbidities such as depression and anxiety could already be present before onset of kidney failure and dialysis treatment, or could be a consequence of disease and treatment.(19) A depressed mood or feelings of anxiety can be a normal psychological reaction to the burden of kidney failure and dialysis treatment, but becomes problematic when causing significant distress and impairment of functioning with a negative effect on health outcomes. It is also possible that kidney failure, depression and anxiety share pathological pathways in stress-related processes like immune activation and hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis.(20-22) The complexity of depression and anxiety in patients with kidney failure on dialysis therapy is illustrated in the biopsychosocial model in **figure 1**. This model is based on the concept that development of disease is reflected through the complex interplay between biological, psychological and social factors in a patient's life.(23)

Figure 1: The biopsychosocial model in dialysis patients



Note: based on the qualitative analysis in dialysis patients by White and colleagues.(24)

Depression and anxiety are the most common mental health symptoms in dialysis patients, with a prevalence range for depression of 29% to 42% and for anxiety of 27% to 53%.(3, 8, 25, 26) Diagnostic and Statistical Manual of Mental Disorders, fifth Edition (DSM-5) diagnosis of depressive disorder are displayed in **Table 1**.(27) The start of a dialysis lifestyle can contribute to depression, as patients can experience feelings of sadness and grieve about the loss of freedom and flexibility and loss of self-worth due to discontinuation of their usual work or activities. Also, patients can experience loneliness and emotional isolation as a result of spending long periods of time on dialysis, away from family and friends.(16)

Table 1: DSM-5 diagnosis or depressive disorders

Depressive disorder	Characteristics
Major depressive disorder	Definition: five or more depressive symptoms for ≥2 weeks that cause significant distress and impairment • Core symptoms: feelings of sadness or depressed mood and diminished interest or pleasure in most or all activities.
Persistent depressive disorder	A depressed mood plus to other symptoms for at least two years that cause significant distress and impairment.

Anxiety is characterized by disruptive and excessive feelings of uncertainty, fear or worrying that can cause clinically significant distress with impairment of functioning.(28) There are several DSM-5 diagnosis of anxiety disorders with variation in presentation, symptoms and duration (**Table 2**).(27) Often, anxiety and worry are accompanied by physical symptoms, including abdominal pain, dyspepsia, chest pain, fatigue, dizziness, insomnia and headache.(29) A multitude of potential triggers for anxiety are present on a dialysis ward. For example, blood-injection-injury phobia can be triggered by cannulation in hemodialysis patients, patients can feel anxious by alarming of the dialysis machine or due to lack of control over treatment management.(16, 30, 31) Behavior of dialysis patients with anxiety disorders can sometimes be perceived as seemingly irrational behavior, that may lead to conflict with health care staff, for example aggressive demands to be treated by a particular technician or the use of a certain machine.(32)

Table 2: DSM-5 diagnosis of anxiety disorders

Anxiety disorder	Characteristics
Panic disorder	An abrupt surge of intensive fear that starts without a clear reason and reaches a peak within minutes.
Social anxiety disorder	Fear of social or performance situations.
Specific phobia	Excessive anxiety triggered by the presence or anticipation of a specific object or situation.
General anxiety disorder (GAD)	Excessive anxiety or worry about a variety of topics, events or activities.

Adverse clinical outcomes

Both symptoms of depression and anxiety have a marked negative impact on self-reported quality of life of dialysis patients.(33-35) Symptoms of depression and anxiety are also associated with adverse clinical outcomes such as hospitalization and mortality. Both a diagnosis as well as symptoms of depression and anxiety are associated with an increased number of hospitalizations as well as the length of stay in the hospital.(33, 36-38) In a meta-analysis of 31 studies on patients with kidney failure, the presence of depressive symptoms

measured by self-report assessment was a significant predictor of mortality with a Hazard Rate (HR) of 1.45 (95%CI 1.27-1.65).(36) Furthermore, an association is known with poor adherence to medication and dietary and fluid restrictions, possibly due to impairment of motivation for self-management, and increased health care utilization.(39-42) In addition, peritoneal dialysis patients with depressive symptoms have an increased risk of peritonitis and technique failure.(43, 44)

Despite its high prevalence and negative consequences, only a minority of dialysis patients with depression and anxiety are diagnosed and treated.(37, 45) Reasons for this under-diagnosis and under-treatment are poor recognition of symptoms of depression and anxiety due to overlap with symptoms of kidney failure and dialysis treatment, unwillingness of patients to seek help and the stigma attached to a diagnosis of depression or anxiety and its treatment.(37, 45) Despite the poor recognition of depression and anxiety, routine psychological evaluation is lacking in dialysis care. Furthermore, it is shown that symptoms of depression and anxiety do not remit spontaneously in a substantial proportion of patients if they are left untreated.(46-48) The under-recognition and under-treatment of depression and anxiety in dialysis patients might have considerable consequences as comorbid depression and anxiety magnify the impact of chronic illness, are associated with adverse clinical outcomes and increase functional disability and health-care usage.(49)

Screening for depression and anxiety

Diagnosing depression and anxiety is challenging among dialysis patients as symptoms of depression and anxiety overlap with symptoms of uremia due to kidney failure, dialysis therapy itself and other common comorbidities such as diabetes or vascular disease.(28, 32, 50) Furthermore, symptoms of depression and anxiety often coexist.(8, 32) The psychological concept of ‘general distress’ includes symptoms of both depression and anxiety and may potentially be useful for screening purposes.(51, 52) Recent evidence shows that a general distress score can be used for screening in chronically ill patients, including a small dialysis cohort.(53) More research into general distress in dialysis patients could aid screening for depression and anxiety in this population.

Depression and anxiety can be assessed by either a DSM diagnosis based on a clinical interview, this is generally seen as a reference standard, or by means of self-report scales on which patients themselves rate the severity and frequency of their symptoms, expressed in a total score on a continuous scale. On self-report scales, cut-offs scores are used to classify patients with clinically significant symptoms or symptom severity (mild, moderate or severe). Self-report scales are generally preferred for screening in both clinical and research settings for pragmatic reasons such as time and costs, although they cannot be used to diagnose a depressive or anxiety disorder.(50, 54) Despite this, screening tools can be helpful by identifying patients who have significant symptoms and may require further evaluation and treatment.(55)

International guidelines suggest routine screening for depression in dialysis patients.(56) Although screening is generally useful, it is important to use accurate tools as diagnostic accuracy of screening tools varies between settings and patient groups. A recent systematic review included 16 studies that examined the performance of various depression screening tools in patients with kidney failure and found that depression can be accurately diagnosed by these tools.(57) However, there is no system-wide screening protocol, leading to variation in the assessment of depression in both research and clinical settings.(57) The burden and impact of anxiety in dialysis patients has gained more awareness recently, however, international nephrology guidelines inadequately address screening for anxiety and no recommendations on frequency and preferred screening tools are proposed.(4, 28, 32) Although various screening tools for anxiety are available, only few have been validated in hemodialysis patients, with inconclusive results.(58-60) The validation of screening tools for anxiety could aid clinicians and researchers in identifying patients who are in need for further assessment and treatment of anxiety symptoms.

Symptom dimensions of depression and anxiety

Studies on screening instruments from the general population have shown that depression and anxiety may consist of several symptom dimensions, in addition to one overall score.(61-65) Insight in symptom dimensions contributes to better understanding of clinical presentation of depression and anxiety and the association with certain clinical outcomes. These symptom dimensions often differ across different patient populations and literature from the dialysis population is scarce.(66, 67) Our research group recently investigated symptom dimensions of depression in dialysis patients with factor analysis and the relationship of these dimensions to adverse clinical outcomes. It was found that, in line with studies from other somatically ill patient groups, only the somatic symptom dimension was associated with all-cause mortality in dialysis patients and both the somatic and cognitive symptom dimensions were associated with increased hospitalization and impaired quality of life.(47) The constructs of symptom dimensions of anxiety in dialysis patients and the association of these dimensions with adverse clinical outcomes have not been thoroughly studied yet.

It is possible that dialysis modality influences the prevalence of anxiety and depression due to differences in autonomy, therapy burden and complications between hemodialysis and peritoneal dialysis treatment, although the existing literature on this topic is inconclusive.(68) Better insight in the clinical presentation of depression and anxiety by looking at symptom dimensions in subgroups of dialysis patients, could aid in de development of more individualized screening and treatment approaches.

Depression, anxiety and COVID-19

In the general population, symptoms of depression, anxiety and stress are common reactions to the COVID-19 pandemic and the impact on mental health is becoming more evident.(69-

72) Meta-analyses on self-reported stress among the general population during the pandemic demonstrated a prevalence of 30-40%.(70, 71) Factors associated with COVID-19 related stress are fear of the contagious disease itself, loss of employment and financial insecurity, deaths of family members, friends, or colleagues, forced quarantine and social isolation.(73) Risk factors for symptoms of depression and anxiety are pre-existent physical or mental health problems and accompanying chronic disease.(74-76)

Although patients with chronic diseases are vulnerable due to pre-existent high levels of physical and mental distress, studies investigating mental health during the COVID-19 pandemic among these patients are limited. Elevated stress levels caused by the pandemic could even further increase the burden of depression and anxiety in dialysis patients. Two cross-sectional studies without comparison to pre-pandemic data show a prevalence of depression of 22-27% and a prevalence of anxiety of 12% in dialysis patients, but these scores are difficult to interpret as symptoms of depression and anxiety were already highly prevalent in dialysis cohorts before the pandemic. (77, 78) More insight in the impact of the COVID-19 pandemic on depression and anxiety in dialysis patients from longitudinally data could aid clinicians in the screening and treatment during pandemics and other major stressful events in the future.

Treatment of depression and anxiety

Evidence regarding safety and efficacy of commonly used pharmacological treatment for depression and anxiety, for example antidepressants and benzodiazepines, is sparse and inconclusive in the dialysis population.(32, 79-81) Also, to avoid medication dosing errors, appropriate dose reduction to account for loss of kidney function, the dialyzability of medications and timing of dialysis sessions is needed when initiating drug therapy.(82, 83) Furthermore, the willingness to modify or initiate antidepressant medication is often lacking in both chronic dialysis patients and renal care providers.(84)

Another treatment for depression and anxiety of proven effectivity in the general population as well as in patients with medical conditions, is cognitive behavioral therapy (CBT).(85-89) Evidence from small trials in dialysis patients shows promising results for CBT in decreasing depressive symptoms as well as improving quality of life but studies on anxiety are lacking.(32, 90-92) However, the ability and willingness of dialysis patients to attend face-to-face psychotherapy may be reduced by kidney failure related physical limitations such as fatigue and the already high burden of health care contacts.(91, 93) Therefore, more research into the optimal delivery methods of CBT in dialysis patients is required.(93)

Internet delivered self-help CBT (ICBT) is a possible alternative for face-to-face treatment for dialysis patients as it is easy accessible and can be followed in one's own limited time.(94) Meta-analysis showed that these ICBT self-help interventions have been proven to be as effective as face-to-face therapy in other populations with chronic somatic conditions, in

terms of the reduction of depressive symptoms and treatment adherence and promising results are shown in feasibility trials on ICBT in dialysis patients .(95-103)

Problem solving therapy (PST) is a commonly used brief and structured psychological intervention to develop sufficient coping skills in patients suffering from depression.(104) PST is based on the assumption that symptoms of depression and anxiety are caused by difficulties patients encounter in their daily lives. Research on PST in other medical settings shows promising results in improving depressive symptoms and a small pilot trial in older dialysis patients showed that PST helped patients to better solve problems and improved their ability to cope with their medical condition.(105, 106) An Internet-based version of PST (IPST) has been developed and has proven to be effective in reducing depressive symptoms in the general population.(107) However, the effect of IPST has not yet been investigated in dialysis patients. Evidence on the effectivity of and innovative treatment such as self-help IPST in dialysis patients could aid clinicians in discussing and initiating treatment for depression and anxiety and improve the quality of care and quality of life of dialysis patients.

Aims and outline of this thesis

The overall objective of this thesis is to gain more insight in depression and anxiety in dialysis patients. In particular, the first aim of this thesis is to assess which screening tools can be used to identify hemodialysis patients who are in need for further assessment and treatment of anxiety. **Chapter 2** investigates the concept of a 'general distress score' for depression and anxiety with confirmatory factor analysis in three frequently used self-report questionnaires on depression and anxiety. **Chapter 3** describes the investigation of the diagnostic accuracy of two widely used screening tools for anxiety by a reference standard diagnostic psychiatric interview in hemodialysis patients.

The second aim of this thesis is to assess what symptom dimensions of anxiety can be identified in dialysis patients and how are these symptom dimensions associated with adverse clinical outcomes and dialysis modality. **Chapter 4** describes the investigation of several pre-defined constructs of symptom dimensions of anxiety in dialysis patients with confirmatory factor analysis and the association of these symptom dimensions with adverse clinical outcomes such as decreased quality of life, hospitalization and mortality. **Chapter 5** investigates the association of dialysis modality with the prevalence and symptom dimensions of anxiety and depression.

The third aim of this thesis is to assess the impact of the COVID-19 pandemic on anxiety and depression in hemodialysis patients. **Chapter 6** describes the longitudinal investigation of the impact of the COVID-19 pandemic on anxiety and depression in hemodialysis patients measured with valid screening measures.

The fourth aim of this thesis is to assess the effectivity of treatment of depression in dialysis patients. **Chapter 7** describes a systematic review and meta-analysis of randomized controlled trials (RCTs) with an inactive control group on various treatment options for

patients undergoing maintenance dialysis with a current diagnosis of depression or depressive symptoms above the defined cut-off. **Chapter 8** describes the extensive study protocol of the DIVERS-II study; a large cluster randomized controlled trial on the effectiveness of guided internet-based self-help Cognitive Behavioral Therapy (CBT) for depressive symptoms in hemodialysis patients. The intervention is based on problem solving therapy and has been tailored to the needs and problems of dialysis patients. **Chapter 9** describes the outcomes of the DIVERS-II study on the effectiveness of guided internet-based self-help CBT of depressive symptoms in hemodialysis patients. A total of 190 patients were cluster-randomized to the intervention or usual care control group. The primary outcome was symptoms of depression measured by the BDI-II and secondary outcomes were anxiety symptoms, quality of life and dialysis symptoms.

Finally, **Chapter 10** includes a summary and discussion of the results of the previous chapters. The clinical implications of the research will be outlined and suggestions for future research will be provided.

Data used in this thesis

Loosman-study

For chapter 2, data is used from the Loosman-study.(108) This is a mono-center observational cohort study of chronic hemodialysis and peritoneal dialysis patients from an urban dialysis center in the Netherlands in 2008.

DIVERS-I

For chapters 2, 4 and 5 data is used from the Depression Related Factors and Outcomes in Dialysis Patients With Various Ethnicities and Races Study (DIVERS).(33) This is a multicenter prospective cohort study of chronic hemodialysis and peritoneal dialysis patients from 10 dialysis centers in the Netherlands from 2012 until 2017. Every six months, depression was measured with the BDI-II and anxiety was measured with the BAI. The follow-up had a duration up to four years and outcomes were hospitalization, dialysis withdrawal and mortality.

DIVERS-II: Internet Intervention

For chapters 3, 6, 8 and 9, data is used from the DIVERS-II study. DIVERS-II consists of a cluster randomized controlled trial (RCT) and a parallel observational cohort of chronic hemodialysis patients from 18 dialysis centers in the Netherlands. Inclusion period ran from 2018 to 2020 and follow-up data acquisition is currently ongoing. The RCT of DIVERS-II investigates the effectiveness of an online self-help intervention for depressive symptoms in hemodialysis patients. Patients who were excluded from the randomization because of a low depression score or of insufficient Dutch language skills, were offered to participate in the parallel observational cohort.(11)

References

1. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005;67(6):2089-100.
2. Collaboration GBDCKD. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395(10225):709-33.
3. Liyanage T, Ninomiya T, Jha V, Neal B, Patrice HM, Okpechi I, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. Lancet. 2015;385(9981):1975-82.
4. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International Supplements. 2013;3(1):1-150.
5. Murtagh FE, Burns A, Moranne O, Morton RL, Naicker S. Supportive Care: Comprehensive Conservative Care in End-Stage Kidney Disease. Clin J Am Soc Nephrol. 2016;11(10):1909-14.
6. Almutary H, Bonner A, Douglas C. Symptom burden in chronic kidney disease: a review of recent literature. J Ren Care. 2013;39(3):140-50.
7. van der Willik EM, Hemmelder MH, Bart HAJ, van Ittersum FJ, Hoogendijk-van den Akker JM, Bos WJW, et al. Routinely measuring symptom burden and health-related quality of life in dialysis patients: first results from the Dutch registry of patient-reported outcome measures. Clin Kidney J. 2021;14(6):1535-44.
8. 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.
9. de Jong PE, Koomans HA, Weening JJ. Klinische nefrologie. 4th ed. Amsterdam: Springer Media B.V.; 2011.
10. Brown EA, Johansson L, Farrington K, Gallagher H, Sensky T, Gordon F, et al. Broadening Options for Long-term Dialysis in the Elderly (BOLDE): differences in quality of life on peritoneal dialysis compared to haemodialysis for older patients. Nephrol Dial Transplant. 2010;25(11):3755-63.
11. Eroglu E, Heimburger O, Lindholm B. Peritoneal dialysis patient selection from a comorbidity perspective. Semin Dial. 2020.
12. Devoe DJ, Wong B, James MT, Ravani P, Oliver MJ, Barnieh L, et al. Patient Education and Peritoneal Dialysis Modality Selection: A Systematic Review and Meta-analysis. Am J Kidney Dis. 2016;68(3):422-33.
13. Van Biesen W, Vanholder R, Lameire N. The role of peritoneal dialysis as the first-line renal replacement modality. Perit Dial Int. 2000;20(4):375-83.
14. Kimmel PL, Weihs K, Peterson RA. Survival in hemodialysis patients: the role of depression. J Am Soc Nephrol. 1993;4(1):12-27.
15. Kimmel PL. Psychosocial factors in dialysis patients. Kidney Int. 2001;59(4):1599-613.
16. Nataatmadja M, Evangelidis N, Manera KE, Cho Y, Johnson DW, Craig JC, et al. Perspectives on mental health among patients receiving dialysis. Nephrol Dial Transplant. 2020.
17. Kimmel PL. Depression in patients with chronic renal disease: what we know and what we need to know. J Psychosom Res. 2002;53(4):951-6.

18. Murtagh FE, Addington-Hall J, Higginson IJ. The prevalence of symptoms in end-stage renal disease: a systematic review. Adv Chronic Kidney Dis. 2007;14(1):82-99.
19. Huyse FJ, Stiefel FC. Medical clinics of North America. Integrated care for the complex medically ill. Philadelphia: Elsevier Saunders; 2006. Volume 90, Number4.
20. Gregg LP, Carmody T, Le D, Martins G, Trivedi M, Hedayati SS. A Systematic Review and Meta-Analysis of Depression and Protein-Energy Wasting in Kidney Disease. Kidney Int Rep. 2020;5(3):318-30.
21. Taraz M, Taraz S, Dashti-Khavidaki S. Association between depression and inflammatory/anti-inflammatory cytokines in chronic kidney disease and end-stage renal disease patients: a review of literature. Hemodial Int. 2015;19(1):11-22.
22. Staufenbiel SM, Penninx BW, Spijker AT, Elzinga BM, van Rossum EF. Hair cortisol, stress exposure, and mental health in humans: a systematic review. Psychoneuroendocrinology. 2013;38(8):1220-35.
23. Engel GL. The need for a new medical model: a challenge for biomedicine. Science. 1977;196(4286):129-36.
24. White Y, Grenyer BF. The biopsychosocial impact of end-stage renal disease: the experience of dialysis patients and their partners. J Adv Nurs. 1999;30(6):1312-20.
25. Cukor D, Coplan J, Brown C, Friedman S, Cromwell-Smith A, Peterson RA, et al. Depression and Anxiety in Urban Hemodialysis Patients. Clin J Am Soc Nephrol. 2007;2(3):484-90.
26. Reckert A, Hinrichs J, Pavenstadt H, Frye B, Heuft G. Prevalence and correlates of anxiety and depression in patients with end-stage renal disease (ESRD). Z Psychosom Med Psychother. 2013;59(2):170-88.
27. Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed. Arlington, VA, US: American Psychiatric Publishing, Inc.; 2013. xliv, 947-xliv, p.
28. Kimmel PL, Cukor D. Anxiety Symptoms in Patients Treated With Hemodialysis: Measurement and Meaning. Am J Kidney Dis. 2019;74(2):145-7.
29. Gelenberg AJ. Psychiatric and Somatic Markers of Anxiety: Identification and Pharmacologic Treatment. Prim Care Companion J Clin Psychiatry. 2000;2(2):49-54.
30. Feroze U, Martin D, Kalantar-Zadeh K, Kim JC, Reina-Patton A, Kopple JD. Anxiety and depression in maintenance dialysis patients: preliminary data of a cross-sectional study and brief literature review. J Ren Nutr. 2012;22(1):207-10.
31. Kopple JD, Shapiro BB, Feroze U, Kim JC, Zhang M, Li Y, et al. Hemodialysis treatment engenders anxiety and emotional distress. Clin Nephrol. 2017;88(10):205-17.
32. Cohen SD, Cukor D, Kimmel PL. Anxiety in Patients Treated with Hemodialysis. Clin J Am Soc Nephrol. 2016;11(12):2250-5.
33. 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.
34. Preljevic VT, Osthus TB, Os I, Sandvik L, Opjordsmoen S, Nordhus IH, et al. Anxiety and depressive disorders in dialysis patients: association to health-related quality of life and mortality. Gen Hosp Psychiatry. 2013;35(6):619-24.
35. Olagunju AT, Campbell EA, Adeyemi JD. Interplay of anxiety and depression with quality of life in endstage renal disease. Psychosomatics. 2015;56(1):67-77.

36. Farrokhi 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.
37. 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.
38. 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.
39. Cukor D, Rosenthal DS, Jindal RM, Brown CD, Kimmel PL. Depression is an important contributor to low medication adherence in hemodialyzed patients and transplant recipients. Kidney Int. 2009;75(11):1223-9.
40. Weisbord SD, Mor MK, Sevick MA, Shields AM, Rollman BL, Palevsky PM, et al. Associations of depressive symptoms and pain with dialysis adherence, health resource utilization, and mortality in patients receiving chronic hemodialysis. Clin J Am Soc Nephrol. 2014;9(9):1594-602.
41. Sensky T, Leger C, Gilmour S. Psychosocial and cognitive factors associated with adherence to dietary and fluid restriction regimens by people on chronic haemodialysis. Psychother Psychosom. 1996;65(1):36-42.
42. Abbas Tavallaii S, Ebrahimnia M, Shamspour N, Assari S. Effect of depression on health care utilization in patients with end-stage renal disease treated with hemodialysis. Eur J Intern Med. 2009;20(4):411.
43. Lin J, Ye H, Yi C, Li J, Yu X, Zhu L, et al. The negative impact of depressive symptoms on patient and technique survival in peritoneal dialysis: a prospective cohort study. Int Urol Nephrol. 2020;52(12):2393-401.
44. Troidle L, Watnick S, Wuerth DB, Gorban-Brennan N, Kliger AS, Finkelstein FO. Depression and its association with peritonitis in long-term peritoneal dialysis patients. Am J Kidney Dis. 2003;42(2):350.
45. 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.
46. 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.
47. Schouten RW, Harmse VJ, Dekker FW, van Ballegooijen W, Siegert CEH, Honig A. Dimensions of Depressive Symptoms and Their Association With Mortality, Hospitalization, and Quality of Life in Dialysis Patients: A Cohort Study. Psychosom Med. 2019;81(7):649-58.
48. Cukor D, Coplan J, Brown C, Peterson RA, Kimmel PL. Course of depression and anxiety diagnosis in patients treated with hemodialysis: a 16-month follow-up. Clin J Am Soc Nephrol. 2008;3(6):1752-8.
49. Stein MB, Cox BJ, Afifi TO, Belik SL, Sareen J. Does co-morbid depressive illness magnify the impact of chronic physical illness? A population-based perspective. Psychol Med. 2006;36(5):587-96.

50. Chilcot J, Wellsted D, Da Silva-Gane M, Farrington K. Depression on dialysis. Nephron Clin Pract. 2008;108(4):c256-64.
51. Clark LA, Watson D. Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. J Abnorm Psychol. 1991;100(3):316-36.
52. Kroenke K, Wu J, Yu Z, Bair MJ, Kean J, Stump T, et al. Patient Health Questionnaire Anxiety and Depression Scale: Initial Validation in Three Clinical Trials. Psychosom Med. 2016;78(6):716-27.
53. Chilcot J, Hudson JL, Moss-Morris R, Carroll A, Game D, Simpson A, et al. Screening for psychological distress using the Patient Health Questionnaire Anxiety and Depression Scale (PHQ-ADS): Initial validation of structural validity in dialysis patients. Gen Hosp Psychiatry. 2018;50:15-9.
54. Hedayati SS, Bosworth HB, Kuchibhatla M, Kimmel PL, Szczech LA. The predictive value of self-report scales compared with physician diagnosis of depression in hemodialysis patients. Kidney Int. 2006;69(9):1662-8.
55. Goh ZS, Griva K. Anxiety and depression in patients with end-stage renal disease: impact and management challenges - a narrative review. Int J Nephrol Renovasc Dis. 2018;11:93-102.
56. National Kidney F. KDOQI Clinical Practice Guideline for Hemodialysis Adequacy: 2015 update. Am J Kidney Dis. 2015;66(5):884-930.
57. Kondo K, Antick JR, Ayers CK, Kansagara D, Chopra P. Depression Screening Tools for Patients with Kidney Failure: A Systematic Review. Clin J Am Soc Nephrol. 2020;15(12):1785-95.
58. Preljevic VT, Osthus TB, Sandvik L, Opjordsmoen S, Nordhus IH, Os I, et al. Screening for anxiety and depression in dialysis patients: comparison of the Hospital Anxiety and Depression Scale and the Beck Depression Inventory. J Psychosom Res. 2012;73(2):139-44.
59. Martin CR, Thompson DR. The hospital anxiety and depression scale in patients undergoing peritoneal dialysis: internal and test–retest reliability. Clin Eff Nurs. 2002;6(2):78-80.
60. Cukor D, Coplan J, Brown C, Friedman S, Newville H, Safier M, et al. Anxiety disorders in adults treated by hemodialysis: a single-center study. Am J Kidney Dis. 2008;52(1):128-36.
61. Steer RA, Ball R, Ranieri WF, Beck AT. Dimensions of the Beck Depression Inventory-II in clinically depressed outpatients. J Clin Psychol. 1999;55(1):117-28.
62. van Loo HM, de Jonge P, Romeijn JW, Kessler RC, Schoevers RA. Data-driven subtypes of major depressive disorder: a systematic review. BMC Med. 2012;10:156.
63. 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.
64. Steer RA, Rissmiller DJ, Ranieri WF, Beck AT. Structure of the computer-assisted Beck Anxiety Inventory with psychiatric inpatients. J Pers Assess. 1993;60(3):532-42.
65. Osman A, Kopper BA, Barrios FX, Osman JR, Wade T. The Beck Anxiety Inventory: reexamination of factor structure and psychometric properties. J Clin Psychol. 1997;53(1):7-14.
66. Chilcot J, Almond MK, Guirguis A, Friedli K, Day C, Davenport A, et al. Self-reported depression symptoms in haemodialysis patients: Bi-factor structures of two common measures and their association with clinical factors. Gen Hosp Psychiatry. 2018;54:31-6.

67. Chilcot J, Norton S, Wellsted D, Almond M, Davenport A, Farrington K. A confirmatory factor analysis of the Beck Depression Inventory-II in end-stage renal disease patients. J Psychosom Res. 2011;71(3):148-53.
68. Ginieri-Coccossis M, Theofilou P, Synodinou C, Tomaras V, Soldatos C. Quality of life, mental health and health beliefs in haemodialysis and peritoneal dialysis patients: investigating differences in early and later years of current treatment. BMC Nephrol. 2008;9:14.
69. Bueno-Notivol J, Gracia-Garcia P, Olaya B, Lasheras I, Lopez-Anton R, Santabarbara J. Prevalence of depression during the COVID-19 outbreak: A meta-analysis of community-based studies. Int J Clin Health Psychol. 2021;21(1):100196.
70. Luo M, Guo L, Yu M, Jiang W, Wang H. The psychological and mental impact of coronavirus disease 2019 (COVID-19) on medical staff and general public - A systematic review and meta-analysis. Psychiatry Res. 2020;291:113190.
71. Salari N, Hosseinian-Far A, Jalali R, Vaisi-Raygani A, Rasoulpoor S, Mohammadi M, et al. Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: a systematic review and meta-analysis. Global Health. 2020;16(1):57.
72. Wang Y, Kala MP, Jafar TH. Factors associated with psychological distress during the coronavirus disease 2019 (COVID-19) pandemic on the predominantly general population: A systematic review and meta-analysis. PLoS One. 2020;15(12):e0244630.
73. Fofana NK, Latif F, Sarfraz S, Bilal, Bashir MF, Komal B. Fear and agony of the pandemic leading to stress and mental illness: An emerging crisis in the novel coronavirus (COVID-19) outbreak. Psychiatry Res. 2020;291.
74. Hossain MM, Tasnim S, Sultana A, Faizah F, Mazumder H, Zou L, et al. Epidemiology of mental health problems in COVID-19: a review. F1000Res. 2020;9:636.
75. Ozdin S, Bayrak Ozdin S. Levels and predictors of anxiety, depression and health anxiety during COVID-19 pandemic in Turkish society: The importance of gender. Int J Soc Psychiatry. 2020:20764020927051.
76. Pieh C, Budimir S, Probst T. The effect of age, gender, income, work, and physical activity on mental health during coronavirus disease (COVID-19) lockdown in Austria. J Psychosom Res. 2020;136:110186.
77. Lee J, Steel J, Roumelioti M-E, Erickson S, Myaskovsky L, Yabes JG, et al. Psychosocial Impact of COVID-19 Pandemic on Patients with End-Stage Kidney Disease on Hemodialysis. Kidney360. 2020;1(12):1390-7.
78. Yeter HH, Gok Oguz E, Akcay OF, Karaer R, Yasar E, Duranay M, et al. The reliability and success of peritoneal dialysis during the COVID-19 pandemic. Semin Dial. 2021;34(2):147-56.
79. 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.
80. 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.
81. 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.

82. Fanton JH, Germain MJ, Cohen LM. Treatment of Psychiatric Disorders in Chronic Kidney Disease Patients. In: Kimmel PL, Rosenberg ME, editors. Chronic Renal Disease San Diego, CA: Elsevier; 2015. p. 725–37.
83. Velenosi TJ, Urquhart BL. Pharmacokinetic considerations in chronic kidney disease and patients requiring dialysis. Expert Opin Drug Metab Toxicol. 2014;10(8):1131-43.
84. Pena-Polanco JE, Mor MK, Tohme FA, Fine MJ, Palevsky PM, Weisbord SD. Acceptance of Antidepressant Treatment by Patients on Hemodialysis and Their Renal Providers. Clin J Am Soc Nephrol. 2017;12(2):298-303.
85. 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.
86. 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.
87. 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.
88. Dickens C, Cherrington A, Adeyemi I, Roughley K, Bower P, Garrett C, et al. Characteristics of psychological interventions that improve depression in people with coronary heart disease: a systematic review and meta-regression. Psychosom Med. 2013;75(2):211-21.
89. Cuijpers P, Karyotaki E, Reijnders M, Huibers MJH. Who benefits from psychotherapies for adult depression? A meta-analytic update of the evidence. Cogn Behav Ther. 2018;47(2):91-106.
90. Cukor D, Ver Halen N, Asher DR, Coplan JD, Weedon J, Wyka KE, et al. Psychosocial intervention improves depression, quality of life, and fluid adherence in hemodialysis. J Am Soc Nephrol. 2014;25(1):196-206.
91. 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.
92. Lerma A, Perez-Grovas H, Bermudez L, Peralta-Pedrero ML, Robles-Garcia R, Lerma C. Brief cognitive behavioural intervention for depression and anxiety symptoms improves quality of life in chronic haemodialysis patients. Psychol Psychother. 2017;90(1):105-23.
93. Chilcot J, Hudson JL. Is successful treatment of depression in dialysis patients an achievable goal? Semin Dial. 2018.
94. Gellatly J, Bower P, Hennessy S, Richards D, Gilbody S, Lovell K. What makes self-help interventions effective in the management of depressive symptoms? Meta-analysis and meta-regression. Psychol Med. 2007;37(9):1217-28.
95. Barak A, Hen L, Boniel-Nissim M, Shapira Na. 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.
96. 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.

97. 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.
98. 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.
99. Andersson G, Cuijpers P, Carlbring P, Riper H, Hedman E. Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis. World Psychiatry. 2014;13(3):288-95.
100. 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.
101. 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.
102. 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.
103. 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.
104. Mynors-Wallis L. Problem solving treatment for anxiety and depression: A practical guide. New York: Oxford University Press; 2005.
105. 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.
106. 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.
107. 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.
108. 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.

Chapter 2

General distress and symptoms of anxiety and depression: A factor analysis in two cohorts of dialysis patients.

Schouten RW, Nadort E, van Ballegooijen W, Loosman WL, Honig A, Siegert CEH, Meuleman Y, Broekman BFP.

General Hospital Psychiatry; Volume 65, July-August 2020, Pages: 91-99

Abstract

Objective: Depression and anxiety often coexist in patients with end-stage-kidney disease. Recently, studies showed that a composite 'general distress score' which combines depression and anxiety symptoms provides a good fit in dialysis and oncology patients. We aim to investigate if the three most frequently used self-report questionnaires to measure depression and anxiety in dialysis patients are sufficiently unidimensional to warrant the use of such a general distress score in two cohorts of dialysis patients.

Methods: This study includes two prospective observational cohorts of dialysis patients (total n = 749) which measured depression and anxiety using Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and Hospital Anxiety and Depression Scale (HADS). Confirmatory factor analysis was used to investigate both a strictly unidimensional model and a multidimensional bifactor model that includes a general distress, depression and anxiety factor. The comparative fit index (CFI) and The Root Mean Square Error of Approximation (RMSEA) were used as model fit indices.

Results: Factor analysis did not show a good fit for a strictly unidimensional general distress factor for both the BDI/BAI and HADS (CFI 0.690 and 0.699, RMSEA 0.079 and 0.125 respectively). The multidimensional model performed better with a moderate fit for the BDI/BAI and HADS (CFI 0.873 and 0.839, RMSEA 0.052 and 0.102).

Conclusions: This data shows that the BDI/BAI and HADS are insufficiently unidimensional to warrant the use of a general distress score in dialysis patients without also investigating anxiety and depression separately. Future research is needed whether the use of a general distress score might be beneficial to identify patients in need of additional (psychological) support.

Introduction

Chronic kidney disease is an increasingly prevalent disease, with millions of patients worldwide needing dialysis therapy when reaching its end-stage. Patients on dialysis therapy experience high levels of physical and mental distress, (1–3) with depression and anxiety symptoms as most common mental health symptoms (1,2). Both depression and anxiety are known to be associated with an impaired quality of life (QoL), treatment non-adherence and adverse clinical outcomes, such as hospitalization and mortality (4,5). Despite this burden, symptoms of depression and anxiety are often not screened and left untreated in dialysis patients (6). Knowledge on the properties and performance of screening tools in this specific population could aid in the development of screening programs.

The most common self-report questionnaires to measure depressive and anxiety symptoms in dialysis patients are the Hospital Anxiety and Depression Scale (HADS) and the Beck Depression and Anxiety Inventories (BDI and BAI). These questionnaires focus on depression and anxiety as being different entities or symptom domains. However, depression and anxiety often coexist in dialysis patients, and there exists a substantial correlation and possibly overlap between symptoms of depression, anxiety and physical symptoms from the chronic renal failure and the dialysis therapy itself (1,2). Furthermore, treatment options for these mental health symptoms may also overlap. For example: cognitive behavioral therapy is advised to treat anxiety symptoms but also (subclinical) depressive symptoms, without the need for a formal diagnosis (7). Within the field of Psychology, the concept of 'general distress' has been introduced which includes symptoms of both depression and anxiety, and may potentially be beneficial for screening purposes and to guide therapy (8,9).

The concept of general distress has been investigated by testing the unidimensionality or multidimensionality of the depression and anxiety concepts in questionnaires using factor analysis. In 1991, Clark et al. described a tripartite model including a general distress domain besides specific depression and anxiety domains, which provided a good fit for their data (8). More recently, Kroenke et al. investigated a general distress score in three medically ill patient groups and found the 16- item PHQ-ADS 'general distress score' to be a reliable and valid composite measure of depression and anxiety. This composite score could, if validated in other populations, be useful as a single measure for jointly assessing two of the most common psychological conditions in clinical practice and research (9). Chilcot et al. tested this unidimensional general distress model and confirmed these results with the PHQ-ADS in dialysis patients (10). However, these authors also indicated that validation of this general distress score is warranted in a larger sample of dialysis patients. Additionally, it is unknown whether this concept of a general distress score also exists in other, more frequently used self-report questionnaires to assess depression and anxiety (i.e., HADS, BDI and BAI).

In addition to a general distress factor, studies found evidence that Somatic items can be differentiated from Cognitive items in both the BDI and BAI questionnaires (11–13). Given the

large burden of physical symptoms in these chronically ill patients, we hypothesize that there might be an overarching Somatic distress factor and Cognitive distress factor. A previous study among cardiac rehabilitation patients described a 3-factor model including Depression, Subjective Anxiety and Somatic Anxiety using a combination of the BDI and BAI (14). So far, it is unknown how these Somatic-Cognitive models perform in dialysis patients.

This study aims to investigate a general distress score for depression and anxiety by using the BDI/BAI and HADS in two different cohorts of dialysis patients. Evidence for a general distress score will be determined based on the performance of the following three models: 1) strictly unidimensional model that includes a general distress factor, 2) multidimensional model that includes a depression factor and anxiety factor, and 3) tripartite bi-factor model that includes a general distress, depression and anxiety factor. Secondary analyses included the investigation of a Somatic-Cognitive distress model using the extensive 42-item BDI/BAI questionnaires.

Methods

Study design and participants

This study performs analyses in two Dutch cohorts of dialysis patients: the DIVERS-cohort (n = 687) and the Loosman-cohort (n = 73) (11,15). All analyses were performed separately for both cohorts, both the demographic description of the cohorts and the factor analysis. By analyzing two separate cohorts we aimed to generate more results with synchronized methods to better interpret the concept of 'general distress' in dialysis patients.

The DIVERS-study is an observational, prospective cohort study among dialysis patients from 10 urban dialysis centers in The Netherlands. The cohort consists of both prevalent and incident hemodialysis and peritoneal dialysis patients, included between June 2012 and October 2016, as described in detail elsewhere (5). Patients were offered questionnaires in Dutch, English, Arabic and Turkish. To promote generalizability, all patients on chronic dialysis therapy (> 90 days on dialysis therapy) were considered eligible. If needed, patients received assistance in filling in the questionnaires.

The Loosman-study is an observational, prospective cohort study in 1 urban dialysis center in Amsterdam, The Netherlands. All patients with chronic kidney disease who were treated with either hemodialysis or peritoneal dialysis in the St. Lucas Andreas hospital (currently OLVG) between February 2008 and June 2008 were eligible for participation in this study, as described in detail elsewhere (15). Patients who were unable to read or understand the Dutch language were excluded.

Ethical Approval of the Medical Ethnic Committee was obtained. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and

its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Demographic, social and clinical data

At baseline, the following socio-demographic and clinical data were collected from electronic medical records in both cohorts: age, gender, dialysis modality and vintage, primary cause of kidney disease, routine laboratory measures (e.g., hemoglobin and albumin) and status on the transplantation waiting list. Incident patients on chronic dialysis therapy were defined as new patients who started renal replacement therapy (> 90 days and < 180 days). Primary cause of kidney disease was classified according to the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) coding system and divided into 3 groups: diabetic nephropathy, renal vascular disease and other cause (16).

We collected the following characteristics through self-report questionnaires: ethnicity (defined as immigrant status based on the country of birth), marital status, children, educational level, working status, current smoking, alcohol use and previous diagnosis of depression. No data was available on previous anxiety diagnoses.

Assessment of symptoms of depression and anxiety

The DIVERS-cohort used the Beck Depression Inventory-II edition (BDI) and the Beck Anxiety Inventory (BAI) (17,18). Respondents were asked to rate how much each of the 21 symptoms had bothered them in the past week on a scale ranging from 0 (not at all) to 3 (severely). The total score ranges from 0 to 63. Both the BDI and the BAI include many items assessing physical symptoms. The BDI has been validated in dialysis patients using a depression diagnosis as reference with good sensitivity and specificity (15). The BAI has not been validated in dialysis patients using a formal anxiety diagnosis as reference, however, the BAI has been validated in a large variety of cohorts, including cohorts with somatically ill patients (14,19–22).

The Loosman-cohort used the Hospital Anxiety and Depression Scale (HADS) (23). The HADS consists of seven items to assess anxiety symptoms (HADS-A) and seven items to assess depressive symptoms (HADS-D). Respondents were asked to rate how much each of the symptoms bothered them from 0 (not present) to 3 (considerable). The item scores are summed to provide sub scores on the HADS-A and HADS-D, with scores ranging from 0 to 21 for either anxiety or depression. The HADS items are primarily based on psychological aspects of anxiety and depression with no items assessing physical symptoms, thus the HADS may be especially useful for screening for anxiety and depression in somatically ill patients. The anxiety items concentrate on general anxiety, with five out of 7 items that resemble the diagnostic criteria for generalized anxiety disorder. The depressive items concentrate primarily on anhedonia. The HADS has been validated in dialysis patients using the DSM diagnosis for depression as reference with good sensitivity and specificity (15,24).

Statistical analysis

Standard descriptive statistics were used to present baseline patient characteristics for both cohorts separately. The factor structure of the BDI/BAI and the HADS-D/HADS-A was analyzed using confirmatory factor analysis (CFA) with robust full information maximum likelihood (FIML) estimation as the primary method. FIML estimation is robust for missing data and non-normally distributed data (25). Missing items on the questionnaires will be included in this estimation method.

The models were identified using the marker-item approach, which means that the loading of the first item of every subscale is fixed to 1 and its intercept is set to 0. Model fit was interpreted by inspecting fit indices, employing the following rules of thumb: the comparative fit index (CFI) indicates acceptable fit above 0.900 and good fit above 0.950; the root mean squared error of approximation (RMSEA) indicates good fit below 0.060 (26). These fit indices should be considered in combination, so a good fit meets all these criteria (26). The best fitting model was obtained by means of an iterative process, starting with factor models found in the literature (9,14) and, if necessary, adapting the model until adequate model fit was obtained. The following constructs were evaluated using CFA:

- strictly unidimensional model that includes a general distress factor
- multidimensional model that includes a depression factor and anxiety factor
- tripartite bi-factor model that includes a general distress, depression and anxiety factor.

Secondly, besides the performance indices, factor loadings were inspected to judge the amount of correlation between the items and the general factor, where an R2 above 0.60 as a marker for a relatively high explained common variance.

In the bifactor models, the correlations between the factors were fixed on zero and the variances of the general factor and the other factors together were set to be equal.

Secondary analyses included the investigation of a construct containing a Somatic general distress factor based on the Somatic items in the BDI and BAI, and a Cognitive general distress factor based on the Cognitive items of the BDI and BAI. Furthermore, a construct by Clark et al. containing a 3-factor Depression, Subjective Anxiety and Somatic Anxiety factor model was investigated (11,19). Constructs that were evaluated using CFA for this secondary analysis include:

- Two-factor model including Somatic distress and Cognitive distress
- A bifactor model including Somatic, Cognitive and a general distress factor
- Three-factor model including Depression, Subjective Anxiety and Somatic anxiety

Sensitivity analyses

To be able to directly compare our results with the existing literature, we have included analyses using a weighted least square mean and variance adjusted (WLSMV) estimation in the CFA, in concordance with the analyses by Kroenke and Chilcot, (9,10) This WLSMV method is specifically designed for ordinal data and uses full information data, in contrast to the main analyses in this paper using FIML estimation which may be more appropriate to use in this setting with missing data.

All analyses were performed in R (R Core Team), using the package lavaan (27). The complete R code used for the factor analyses can be found in Supplementary file S1.

Results

Baseline patient characteristics

A total of 687 patients were included in the DIVERS-cohort and 73 patients in the Loosman-cohort. **Table 1** describes the baseline patient characteristics of the two cohorts. The mean age was 65 years and both cohorts had relatively large proportions of immigrant patients, which is explained by the urban setting. Primary causes of kidney disease were mostly diabetic nephropathy or renal vascular disease in both cohorts. Hemodialysis and peritoneal dialysis patients were included in both cohorts, with most of the patients being prevalent dialysis patients. The median dialysis vintage was 13 months (4–47) in the DIVERS-cohort and 41 months (23–64) in the Loosman-cohort.

Table 1: Baseline characteristics of the 2 dialysis cohorts.

Characteristic	DIVERS-cohort (n = 687)	Loosman-cohort (n = 73)
Demographic		
Mean age, years	65 ± 15	64 ± 15
Male sex	424 (62%)	39 (53%)
Ethnicity		
Native Dutch	387 (52%)	38 (52%)
Immigrant	300 (48%)	35 (48%)
Social		
Married	316 (52%)	29 (40%)
Has Children	474 (78%)	–
Low education[a]	127 (22%)	–
Not employed	534 (89%)	70 (96%)
Renal and dialysis		
Incident dialysis patients[b]	240 (36%)	3 (4%)
Median vintage of prevalent group, months	13 [4–47]	41 [23–64]
Treatment modality		
Hemodialysis	592 (88%)	51 (70%)
Peritoneal dialysis	80 (12%)	11 (30%)
Primary kidney disease		
Diabetic nephropathy	155 (24%)	15 (21%)
Renal vascular disease	163 (26%)	23 (32%)
Other cause	317 (50%)	35 (48%)

Table 1 (continued)

Characteristic	DIVERS-cohort (n = 687)	Loosman-cohort (n = 73)
AVG or AVF[c]	435 (65%)	–
Residual diuresis > 100 ml/24 h	475 (71%)	–
On waiting list for kidney transplantation		
Yes	201 (30%)	6 (8%)
No	471 (70%)	67 (92%)
Laboratory parameters		
Mean hemoglobin (mmol/l)	7.1 ± 0.8	7.1 ± 1.0
Mean albumin (g/l)	37.0 ± 5.3	40.2 ± 4.3
Clinical		
Current smoking	108 (18%)	5 (7%)
Current alcohol use	161 (27%)	14 (19%)
Comorbidities		
Diabetes mellitus	284 (42%)	21 (29%)
Chronic heart disease	111 (17%)	23 (32%)
Peripheral vascular disease	84 (13%)	8 (11%)
Davies co-morbidity score		
Low comorbidity	183 (27%)	–
Moderate comorbidity	370 (55%)	–
Severe comorbidity	119 (18%)	–
Psychiatric and quality of life		
Depression and anxiety		
Previous diagnosis of depression	27 (4%)	8 (11%)
Mean BDI depression score	12.9 ± 9.6	8.7 ± 7.2
Mean BAI anxiety score	10.3 ± 10.1	–
Mean HADS-D depression score	–	6.5 ± 3.8
Mean HADS-A anxiety score	–	5.8 ± 4.0
Health-related quality of life (SF-12)		
Mean physical component summary	38.1 ± 11.1	–
Mean mental component summary	48.9 ± 10.8	–

Values are presented as mean ± SD, median [IQR] or frequency (percentage).
[a] Low education: highest level of education is high school or less.
[b] < 180 days on dialysis.
[c] Arteriovenous Graft (AVG) or Fistula (AVF), for HD patients only.

Factor analysis on general distress

Multiple a priori defined factor models were investigated in both cohorts. **Table 2** shows the performance of these dimensional models for the BDI/BAI combination and HADS-D/HADS-A combination.

First, a unidimensional general distress model with only one factor was investigated. This model showed poor performances in the BDI/BAI and the HADS-D/HADS-A questionnaires with a CFI of 0.737 and 0.699, and a RMSEA of 0.062 and 0.125, respectively.

Second, a 2-factor model with only a depression factor and an anxiety factor was investigated. This model showed a moderate performance in the BDI/BAI questionnaires with a CFI of 0.823 and a RMSEA of 0.060. For the HADS-A/HADS-D combination, the model fit was good, with a CFI of 0.956 and a RMSEA of 0.052.

Last, a tripartite bi-factor model included a general distress factor besides the depression and anxiety factors. This model showed a better fit compared to the 2-factor or unidimensional model in the BDI/BAI (CFI 0.873, RMSEA 0.052). For the HADS-A/HADS-D combination, the inclusion of a general factor did not improve the performance (CFI 0.839, RMSEA 0.102). A visual representation of this model, including its factor loadings is shown in **Fig. 1** for the BDI/BAI and in **Fig. 2** for the HADS. The factor loadings on the general distress factor in the BDI/BAI cohort were low and often negative, indicating that the general factor does not seem to be appropriate for these questionnaires. Furthermore, the R2 (explained variance) of the general and anxiety factors were low compared to the depression factor. The factor loadings on the general factor for the HADS questionnaires were better, however the model performance indicated a better fit without a general factor.

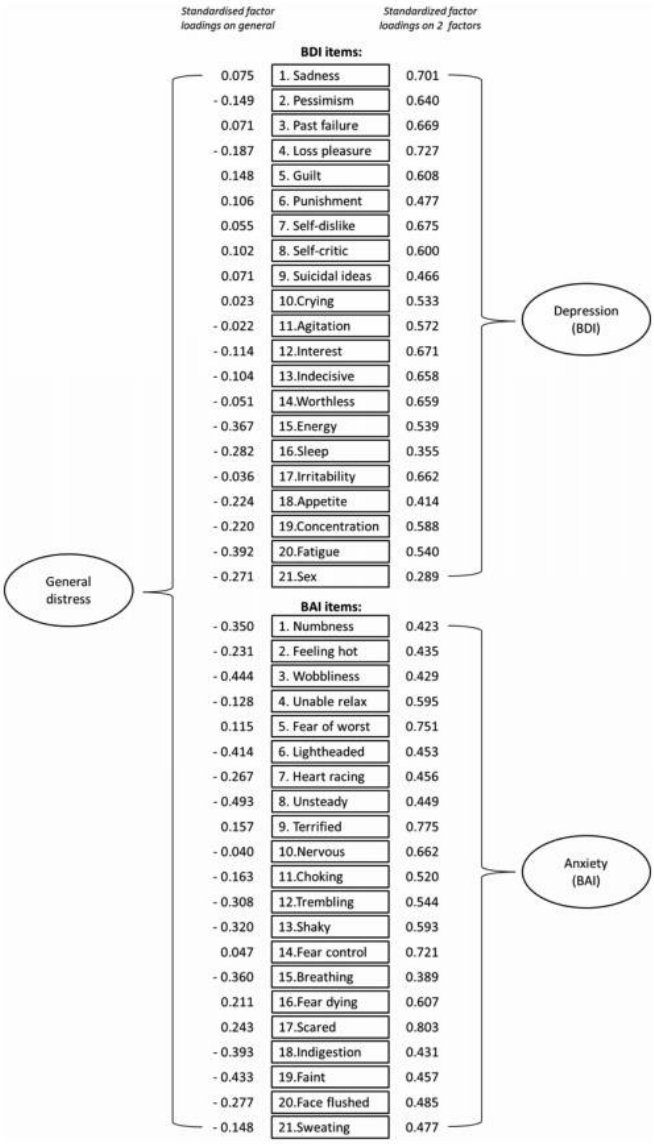
A sensitivity analysis which uses an ordinal model with weighted least squares (WLSMV) showed similar results, with all three models showing better fit indices compared to the main analyses. The bi-factor model for the BDI/BAI and HADS showed a CFI of 0.988 and 0.997, and a RMSEA of 0.022 and 0.021 respectively, as **Supplementary Table S2**.

Table 2: Performance of dimension models with a general factor using confirmatory factor analysis in 2 cohorts.

Dimension model and cohort	CFI	RMSEA
DIVERS-cohort*	0.737	0.062
1-factor: General distress	0.823	0.060
2-factor: BDI + BAI	0.873	0.052
Tripartite bi-factor: BDI + BAI + general distress		
Loosman-cohort**		
1-factor: General distress	0.699	0.125
2-factor: HADS-A + HADS-D	0.956	0.048
Tripartite bi-factor: HADS-A + HADS-D + general distress	0.839	0.102

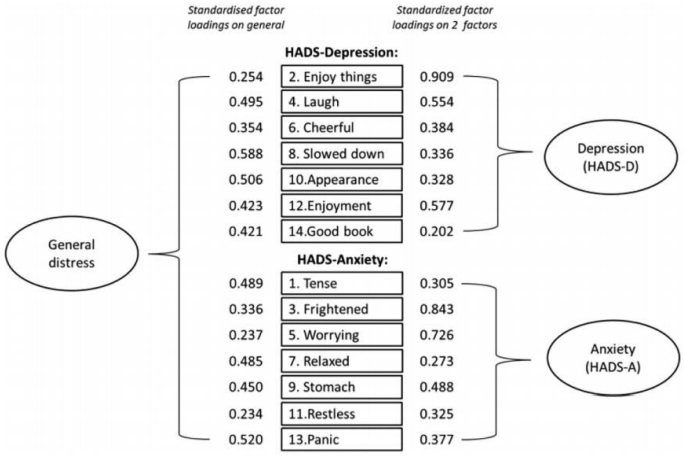
CFI > 0.900 indicates adequate (or okay) fit and CFI > 0.950 indicates good fit.
Root Mean Square Error of Approximation (RMSEA) < 0.06 is considered to demonstrate good fit.
*The chi-square P-value for the BDI/BAI factor models were: P < 0.001 for all models. The ωh and coefficients for the BAI/BDI using 3 factors: Alpha: 0.97, G.6: 0.99, Omega Hierarchical: 0.66, Omega H asymptotic: 0.67, Omega Total 0.98.
**The chi-square P-value for the HADS factor models were: P < 0.001 for the 1-factor model, P = 0.196 for the 2-factor model, and P < 0.001 for the bifactor model. The ωh and coefficients for the HADS using 3 factors: Alpha: 0.83, G.6: 0.89, Omega Hierarchical: 0.53, Omega H asymptotic: 0.60, Omega Total 0.89

Figure 1: Factor loadings in tripartite bifactor model including general distress, Depression and Anxiety using the BDI/BAI



Standardized factor loadings using a tripartite bifactor model. The items of the BDI and BAI load onto both the general factor and on either depression or anxiety (bifactor model). Factor loadings > 0.5 indicate a good fit.

Figure 2: Factor loadings in tripartite bifactor model including general distress, Depression and Anxiety using the HADS



Standardized factor loadings using a tripartite bifactor model. The items of the HADS load onto both the general factor and on either depression or anxiety (bi-factor model). Factor loadings > 0.5 indicate a good fit.

Somatic and cognitive distress

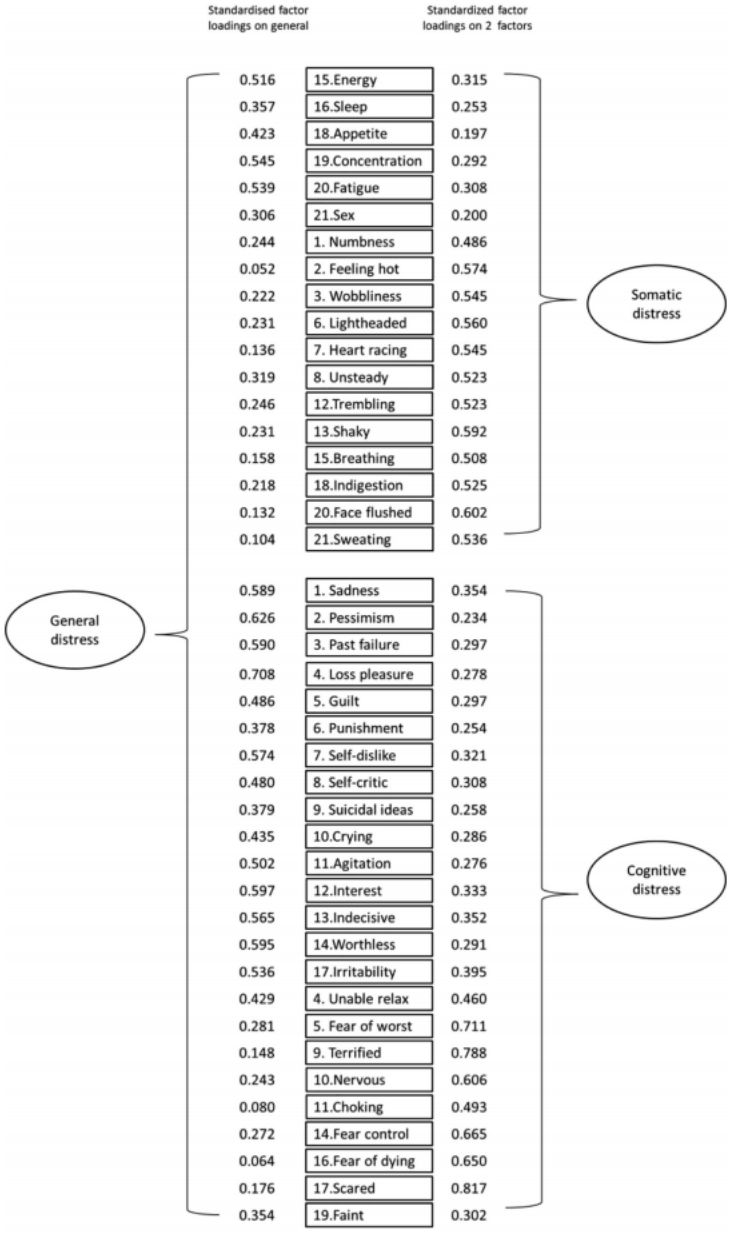
The performance of these models is described in **Table 3.** The Somatic-Cognitive model did not show a good performance with a CFI of 0.785 and a RMSEA of 0.066. When a general distress factor was added to this model, the model improved to a moderate fit with a CFI of 0.879 and a RMSEA of 0.051. A visual representation of this model, including factor loadings, is shown in **Fig. 3.** The factor loadings for the Somatic and Cognitive factors show a better fit compared to the relatively low factor loadings on a general factor. This is especially the case for the anxiety symptoms. The model from Clark et al. showed a similar performance with a CFI of 0.839 and a RMSEA of 0.057.

Table 3: Performance of dimension models with a combination of BDI and BAI in the DIVERS cohort using confirmatory factor analysis.

Dimension model and cohort	CFI	RMSEA
3-factor: Depression-somatic anxiety-subjective anxiety (Clark)	0.839	0.057
2-factor: Somatic-Cognitive BAI + BDI	0.785	0.066
Bi-factor: general-somatic-cognitive BAI + BDI	0.879	0.051

CFI > 0.900 indicates adequate (or okay) fit and CFI > 0.950 indicates good fit.
Root Mean Square Error of Approximation (RMSEA) < 0.06 is considered to demonstrate good fit.

Figure 3: Factor loadings in model including a somatic, cognitive and general factor using the BAI/BDI



Standardized factor loadings using a tripartite bifactor model. The items of the BDI and BAI load onto both the general factor and on either a somatic factor or a cognitive factor (bi-factor model). Factor loadings > 0.5 indicate a good fit.

Discussion

This study aimed to investigate the performance of a general distress factor model in dialysis patients using the BDI/BAI and HADS. We found no evidence to warrant the use of a unidimensional general distress score in these questionnaires. We did find evidence for a tripartite model using the BDI/BAI which includes a general distress factor in addition to the separate constructs for anxiety and depression. The HADS performed best with only a 2-factor model including only depression and anxiety. Furthermore, we found a moderate performance for overarching Somatic and Cognitive dimensions of the BDI/BAI.

A direct comparison of our results to existing literature is somewhat difficult due to the use of different questionnaires and differences in cohort characteristics. The only other study that performed a confirmatory factor analysis in dialysis patients is Chilcot et al. investigating general distress (10). This study was based on a study by Kroenke et al. in three cohorts of oncology patients (9). Both Kroenke and Chilcot found a good performance for both the bi-factor and unidimensional model for general distress (CFI 0.99 and 0.967 in 182 dialysis patients). The present study did not find a good performance for the unidimensional general distress model and only found a moderate performance of the bi-factor model. Several factors may play a role in the conflicting results. First, the present study investigated the 42-item BDI/BAI and 14-item HADS questionnaires, while other existing studies on general distress used the 16-item PHQ-ADS questionnaire (9,10). Despite the fact that all questionnaires measure the same concept of core symptoms of depression and (generalized) anxiety, there are several differences, such as the absence of physical symptoms in the HADS. Second, other studies used weighted least squares (WLSMV) estimation in their factor analyses, while the present study used maximum likelihood estimation (ML) which may be more applicable to handle missing data. A sensitivity analysis using WLSMV estimation showed an overall better performance of the models, however, similar results were found regarding the performance of the unidimensional general distress model.

While the present study found no evidence for a unidimensional use of the BDI/BAI or HADS, evidence was found for a tripartite general distress model, hereby confirming that such a composite ‘general distress’ construct may be used in dialysis patients when using other questionnaires (e.g., PHQ-ADS).

Furthermore, this study showed that an overarching Somatic Cognitive distress model provided a moderate fit (CFI 0.879, RMSEA 0.051). Such a dimensional model has been described previously for both the BDI and the BAI separately (11,12). This adds to the existing knowledge on factor models and possible clinically relevant symptom domains in dialysis patients. In previous research we found that somatic and cognitive symptoms of depression are differentially related to important clinical outcomes like mortality in dialysis patients, were the somatic symptoms of depression are more strongly associated with subsequent mortality. (11) Future research should investigate if somatic and cognitive distress measured with the

BDI and BAI are also clinically relevant in relation to the effect of treatment of these symptoms or if the different symptom dimensions need other treatment options.

Strengths and limitations

This study has several strengths. First, this is the first study to investigate the concept of general distress in dialysis patients using the most frequently used questionnaires to assess anxiety and depressive symptoms, namely: BDI/BAI and HADS. Besides being relevant for dialysis patients, a factor analysis on general distress in the BDI/BAI and HADS questionnaires may also be relevant for other (chronically ill) patient populations. Second, in contrast to trial data often used in other studies on this topic, this study uses a prospective cohort design which may promote the generalizability of the present study (9,10). Finally, the sample size of the DIVERS-cohort is substantially larger compared to the only other study in dialysis patients on this topic (687 versus 182 patients) (10).

While interpreting the results of this study, one should take the following limitations into account. First, while the sample size of the BDI/BAI cohort was large (n = 687), the sample size of the HADS cohort was small (n = 73), which may increase the possibility of a type II error. Second, we included both incident and prevalent dialysis patients, creating a difference in baseline characteristics. However, the combination of both incident and prevalent patients improves the generalizability of our results to the entire dialysis population in clinical practice. Finally, as a result of using self-report questionnaires, there are missing values. Although this is common across literature, there is a possible selection bias of patients who are able and willing to fill in questionnaires.

Future studies are needed to further unravel and specify the concept and hierarchal models of general distress in relation to symptom domains of anxiety and depression in specific patient groups (28).

Clinical implications

There may be several potential advantages of using a general distress score. First, patients could suffer from depressive and anxiety symptoms below the cut-off score for each disorder, while a composite general distress score may be able to identify these patients who are also in need for additional (psychological) support. Second, the use of a single composite score might be an easy to understand and practical solution to the implementation of screening for depression and anxiety, which has been advocated for years but has not yet been implemented into daily nephrological care. Literature on the barriers and facilitators of implementing screening for depression and anxiety in dialysis patients is scarce. More research is needed to better understand these barriers to improve screening and outcomes.

Despite the possible benefits of using a general distress score, this study did not find evidence to warrant the use of a general distress score to describe both depression and anxiety for the BDI/BAI or the HADS. The present study does provide evidence for a tripartite model when

using the BDI/BAI that includes a general distress score, in addition to depression and anxiety. In practice, this could mean that a general distress score could be used as a first step to screen patients for depressive and anxiety symptoms, with the second step being the identification of depression and anxiety to identify if additional treatment options need to be considered for these particular disorders. We believe these results show that both anxiety and depressive symptoms provide a meaningful addition to only measuring a (shorter) general distress questionnaire or score. Additionally, a distinction between a Somatic distress domain and a Cognitive distress domain could be of added value in the choice of treatment options. However, it remains difficult to translate the result of factor analyses to clinical practice, since factor analysis cannot formally investigate whether a concept is clinically meaningful. More research on the association between the symptom dimensions of depression and anxiety and (adverse) clinical outcomes could aid in identifying clinically relevant dimensions.

Psychotherapy, such as cognitive behavioral therapy show promising results in reducing depressive symptoms in dialysis patients. However, there is still a lack of adequately powered randomized controlled trials for both depression and anxiety in dialysis patients. Future research is needed to gain insight in the effectiveness of screening and treatment programs for these symptoms in dialysis patients.

Conclusion

Results suggests that the BDI/BAI and HADS do not show a sufficiently unidimensional structure to warrant the use of such a general distress score without investigating anxiety and depression separately. The results from this study do not support the use of a general distress score to identify anxiety and depressive symptoms. Future research is needed whether the use of a general distress score might be beneficial to identify patients in need of additional (psychological) support.

References

1. 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.
2. Cohen SD, Cukor D, Kimmel PL. Anxiety in patients treated with hemodialysis. Clin J Am Soc Nephrol 2016;11(12):2250–5.
3. Cukor D, Coplan J, Brown C, Friedman S, Cromwell-Smith A, Peterson RA, et al. Depression and anxiety in urban hemodialysis patients. Clin J Am Soc Nephrol 2007;2(3):484–90.
4. Farrokhi 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.
5. 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;74(2):158–66. https://doi.org/10.1053/j.ajkd.2019.02.017. Published online April 23.
6. Cukor D, Coplan J, Brown C, Peterson RA, Kimmel PL. Course of depression and anxiety diagnosis in patients treated with hemodialysis: a 16-month follow-up. Clin J Am Soc Nephrol 2008;3(6):1752–8.
7. Copyright. In: The American Psychiatric Association Practice Guidelines for the Psychiatric Evaluation of Adults. edn.
8. Clark LA, Watson D. Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. J Abnorm Psychol 1991;100(3):316–36.
9. Kroenke K, Wu J, Yu Z, Bair MJ, Kean J, Stump T, et al. Patient health questionnaire anxiety and depression scale: initial validation in three clinical trials. Psychosom Med 2016;78(6):716–27.
10. Chilcot J, Hudson JL, Moss-Morris R, Carroll A, Game D, Simpson A, et al. Screening for psychological distress using the patient health questionnaire anxiety and depression scale (PHQ-ADS): initial validation of structural validity in dialysis patients. Gen Hosp Psychiatry 2018;50:15–9.
11. Schouten RW, Harmse VJ, Dekker FW, van Ballegooijen W, Siegert CEH, Honig A. Dimensions of depressive symptoms and their association with mortality, hospitalization, and quality of life in dialysis patients: a cohort study. Psychosom Med 2019;81(7):649–58.
12. Steer RA, Clark DA, Beck AT, Ranieri WF. Common and specific dimensions of selfreported anxiety and depression: a replication. J Abnorm Psychol 1995;104(3):542–5.
13. Steer RA, Clark DA, Beck AT, Ranieri WF. Common and specific dimensions of selfreported anxiety and depression: the BDI-II versus the BDI-IA. Behav Res Ther 1999;37(2):183–90.
14. 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.
15. 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.
16. 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.

17. Beck AT. SR: Beck Anxiety Inventory manual. San Antonio, TX: Psychological Corporation; 1993.
18. Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory-II. San Antonio. TX: Psychological Corporation; 1996.
19. Osman A, Kopper BA, Barrios FX, Osman JR, Wade T. The Beck Anxiety Inventory: reexamination of factor structure and psychometric properties. J Clin Psychol 1997;53(1):7–14.
20. 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.
21. Rutten S, Ghielen I, Vriend C, Hoogendoorn AW, Berendse HW, Leentjens AF, et al. Anxiety in Parkinson's disease: symptom dimensions and overlap with depression and autonomic failure. Parkinsonism Relat Disord 2015;21(3):189–93.
22. Wetherell JL, Areán PA. Psychometric evaluation of the Beck Anxiety Inventory with older medical patients. Psychol Assess 1997;9(2):136–44.
23. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67(6):361–70.
24. Untas A, Aguirrezabal M, Chauveau P, Leguen E, Combe C, Rascle N. Anxiety and depression in hemodialysis: validation of the Hospital Anxiety and Depression Scale (HADS). Nephrologie & therapeutique 2009;5(3):193–200.
25. Enders CK. The impact of nonnormality on full information maximum-likelihood estimation for structural equation models with missing data. Psychol Methods 2001;6(4):352–70.
26. Hu L, Bentler PM: Cuttoff criteria for fit indexes in covariances structure analysis: conventional criteria versus new alternatives. In., vol. 6; 1999: 1–55.
27. Rosseel Y. Lavaan: an R package for structural equation modeling. 48(2). 2012. p. 36. 2012.
28. Prenoveau JM, Zinbarg RE, Craske MG, Mineka S, Griffith JW, Epstein AM. Testing a hierarchical model of anxiety and depression in adolescents: a tri-level model. J Anxiety Disord 2010;24(3):334–44.

Supplementary files

Supplementary file S1: R code used for the confirmatory factor analysis

```
# R Code by authors Schouten and van Ballegooijen.
# Libraries.
library(lavaan)

#### Table 2: CFA on general distress

### DIVERS cohort:
## 2 factor BAI-BDI
twofactorBAIBDI <-
 'Depression=~ M0_BDI_1 + M0_BDI_2 + M0_BDI_3 + M0_BDI_4 + M0_BDI_5 + M0_BDI_6 +
M0_BDI_7 + M0_BDI_8 +  M0_BDI_9 + M0_BDI_10 + M0_BDI_11 + M0_BDI_12 + M0_BDI_13 +
M0_BDI_14 + M0_BDI_15 + M0_BDI_16 +  M0_BDI_17 + M0_BDI_18 + M0_BDI_19 + M0_BDI_20 +
M0_BDI_21
Anxiety =~ M0_BAI_1 + M0_BAI_2 + M0_BAI_3 + M0_BAI_4 + M0_BAI_5 + M0_BAI_6 + M0_BAI_7 +
M0_BAI_8 +  M0_BAI_9 + M0_BAI_10 + M0_BAI_11 + M0_BAI_12 + M0_BAI_13 + M0_BAI_14 +
M0_BAI_15 + M0_BAI_16 +  M0_BAI_17 + M0_BAI_18 + M0_BAI_19 + M0_BAI_20 + M0_BAI_21'

## Bi-factor BAI-BDI including a general factor.
bifactorBAIBDI <-
 'Depression=~ M0_BDI_1 + M0_BDI_2 + M0_BDI_3 + M0_BDI_4 + M0_BDI_5 + M0_BDI_6 +
M0_BDI_7 + M0_BDI_8 +  M0_BDI_9 + M0_BDI_10 + M0_BDI_11 + M0_BDI_12 + M0_BDI_13 +
M0_BDI_14 + M0_BDI_15 + M0_BDI_16 +  M0_BDI_17 + M0_BDI_18 + M0_BDI_19 + M0_BDI_20 +
M0_BDI_21
Anxiety =~ M0_BAI_1 + M0_BAI_2 + M0_BAI_3 + M0_BAI_4 + M0_BAI_5 + M0_BAI_6 + M0_BAI_7 +
M0_BAI_8 +  M0_BAI_9 + M0_BAI_10 + M0_BAI_11 + M0_BAI_12 + M0_BAI_13 + M0_BAI_14 +
M0_BAI_15 + M0_BAI_16 +  M0_BAI_17 + M0_BAI_18 + M0_BAI_19 + M0_BAI_20 + M0_BAI_21
General =~ M0_BDI_1 + M0_BDI_2 + M0_BDI_3 + M0_BDI_4 + M0_BDI_5 + M0_BDI_6 + M0_BDI_7 +
M0_BDI_8 +  M0_BDI_9 + M0_BDI_10 + M0_BDI_11 + M0_BDI_12 + M0_BDI_13 + M0_BDI_14 +
M0_BDI_15 + M0_BDI_16 +  M0_BDI_17 + M0_BDI_18 + M0_BDI_19 + M0_BDI_20 + M0_BDI_21 +
M0_BAI_1 + M0_BAI_2 + M0_BAI_3 + M0_BAI_4 + M0_BAI_5 + M0_BAI_6 + M0_BAI_7 + M0_BAI_8
+
 M0_BAI_9 + M0_BAI_10 + M0_BAI_11 + M0_BAI_12 + M0_BAI_13 + M0_BAI_14 + M0_BAI_15 +
M0_BAI_16 +  M0_BAI_17 + M0_BAI_18 + M0_BAI_19 + M0_BAI_20 + M0_BAI_21
General ~~ 0*Depression
General ~~ 0*Anxiety'

## Unidimensional 1 factor model general distress.
GeneraldistressBAIBDI <-
 'General =~ M0_BDI_1 + M0_BDI_2 + M0_BDI_3 + M0_BDI_4 + M0_BDI_5 + M0_BDI_6 + M0_BDI_7
+ M0_BDI_8 +  M0_BDI_9 + M0_BDI_10 + M0_BDI_11 + M0_BDI_12 + M0_BDI_13 + M0_BDI_14 +
M0_BDI_15 + M0_BDI_16 +  M0_BDI_17 + M0_BDI_18 + M0_BDI_19 + M0_BDI_20 + M0_BDI_21 +
M0_BAI_1 + M0_BAI_2 + M0_BAI_3 + M0_BAI_4 + M0_BAI_5 + M0_BAI_6 + M0_BAI_7 + M0_BAI_8
+ M0_BAI_9 + M0_BAI_10 + M0_BAI_11 + M0_BAI_12 + M0_BAI_13 + M0_BAI_14 + M0_BAI_15 +
M0_BAI_16 + M0_BAI_17 + M0_BAI_18 + M0_BAI_19 + M0_BAI_20 + M0_BAI_21'
```

```
fit1 <- cfa(twofactorBAIBDI, estimator = "MLR", data =
SF12_BDI_BAI_for_factor_analysis_v1_5_2019, missing="fiml") summary(fit1, fit.measures = TRUE,
standardized = TRUE)
modindices(fit1, sort=TRUE)

fit2 <- cfa(bifactorBAIBDI, estimator = "MLR", data = SF12_BDI_BAI_for_factor_analysis_v1_5_2019,
missing="fiml") summary(fit2, fit.measures = TRUE, standardized = TRUE)
modindices(fit2, sort=TRUE)

fit3 <- cfa(GeneraldistressBAIBDI, estimator = "MLR", data =
SF12_BDI_BAI_for_factor_analysis_v1_5_2019, missing="fiml") summary(fit3, fit.measures = TRUE,
standardized = TRUE)
modindices(fit3, sort=TRUE)

# Based on previous literature the following changes were made and applied if the model performed
better. M0_BDI_5 ~~ M0_BDI_8
M0_BDI_15 ~~ M0_BDI_20
M0_BAI_12 ~~ M0_BAI_13

### Loosman cohort
## 2 factor HADS
HADS2factor <-
'anxiety=~ HADS1_2Y + HADS3_2Y + HADS5_2Y + HADS7_2Y + HADS9_2Y + HADS11_2Y + HADS13_2Y
depression =~ HADS2_2Y + HADS4_2Y + HADS6_2Y + HADS8_2Y + HADS10_2Y + HADS12_2Y +
HADS14_2Y'

## bifactor HADS
HADSbifactor <-
'anxiety=~ HADS1_2Y + HADS3_2Y + HADS5_2Y + HADS7_2Y + HADS9_2Y + HADS11_2Y + HADS13_2Y
depression =~ HADS2_2Y + HADS4_2Y + HADS6_2Y + HADS8_2Y + HADS10_2Y + HADS12_2Y +
HADS14_2Y
general =~ HADS1_2Y + HADS3_2Y + HADS5_2Y + HADS7_2Y + HADS9_2Y + HADS11_2Y + HADS13_2Y
+ HADS2_2Y + HADS4_2Y + HADS6_2Y + HADS8_2Y + HADS10_2Y + HADS12_2Y + HADS14_2Y
general ~~ 0*anxiety
general ~~ 0*depression'

## 1 factor HADS
HADS1factor <-
'general =~ HADS1_2Y + HADS3_2Y + HADS5_2Y + HADS7_2Y + HADS9_2Y + HADS11_2Y +
HADS13_2Y + HADS2_2Y + HADS4_2Y + HADS6_2Y + HADS8_2Y + HADS10_2Y + HADS12_2Y +
HADS14_2Y'

fit4 <- cfa(HADS2factor, estimator = "MLR", data = D, missing="fiml") summary(fit4, fit.measures =
TRUE, standardized = TRUE)
modindices(fit4, sort=TRUE)

fit5 <- cfa(HADSbifactor, estimator = "MLR", data = D, missing="fiml") summary(fit5, fit.measures =
TRUE, standardized = TRUE)
modindices(fit5, sort=TRUE)

fit6 <- cfa(HADS1factor, estimator = "MLR", data = D, missing="fiml") summary(fit6, fit.measures =
TRUE, standardized = TRUE)
```

```
modindices(fit6, sort=TRUE)

#### Table 3: CFA on Somatic-Cognitive/Affective general distress

## Somatic-Cognitive/Affective general distress
twofactorSomCog <-
'Somatic=~ M0_BAI_1 + M0_BAI_2 + M0_BAI_3 + M0_BAI_6 + M0_BAI_7 + M0_BAI_8 + M0_BAI_12
+ M0_BAI_13 + M0_BAI_15 + M0_BAI_18 + M0_BAI_20 + M0_BAI_21
+ M0_BDI_15 + M0_BDI_16 + M0_BDI_18 + M0_BDI_19 + M0_BDI_20 + M0_BDI_21 Cognitive =~
M0_BAI_4 + M0_BAI_5 + M0_BAI_9 + M0_BAI_10 + M0_BAI_11 + M0_BAI_14 + M0_BAI_16 +
M0_BAI_17 + M0_BAI_19 + M0_BDI_1 + M0_BDI_2 + M0_BDI_3 + M0_BDI_4 + M0_BDI_5 +
M0_BDI_6 + M0_BDI_7 + M0_BDI_8 + M0_BDI_9 + M0_BDI_10 + M0_BDI_11 + M0_BDI_12 +
M0_BDI_13 + M0_BDI_14 + M0_BDI_17
M0_BDI_5 ~~ M0_BDI_8
M0_BDI_15 ~~ M0_BDI_20
M0_BAI_12 ~~ M0_BAI_13'

## General-Somatic-Cognitive/Affective general distress
bifactorSomCog <-
'Somatic=~ M0_BAI_1 + M0_BAI_2 + M0_BAI_3 + M0_BAI_6 + M0_BAI_7 + M0_BAI_8 + M0_BAI_12
+ M0_BAI_13 + M0_BAI_15 + M0_BAI_18 + M0_BAI_20 + M0_BAI_21 + M0_BDI_15 + M0_BDI_16 +
M0_BDI_18 + M0_BDI_19 + M0_BDI_20 + M0_BDI_21 Cognitive =~ M0_BAI_4 + M0_BAI_5 +
M0_BAI_9 + M0_BAI_10 + M0_BAI_11 + M0_BAI_14 + M0_BAI_16 + M0_BAI_17 + M0_BAI_19 +
M0_BDI_1 + M0_BDI_2 + M0_BDI_3 + M0_BDI_4 + M0_BDI_5 + M0_BDI_6 + M0_BDI_7 + M0_BDI_8
+ M0_BDI_9 + M0_BDI_10 + M0_BDI_11 + M0_BDI_12 + M0_BDI_13 + M0_BDI_14 + M0_BDI_17
General =~ M0_BDI_1 + M0_BDI_2 + M0_BDI_3 + M0_BDI_4 + M0_BDI_5 + M0_BDI_6 + M0_BDI_7 +
M0_BDI_8 + M0_BDI_9 + M0_BDI_10 + M0_BDI_11 + M0_BDI_12 + M0_BDI_13 + M0_BDI_14 +
M0_BDI_15 + M0_BDI_16 + M0_BDI_17 + M0_BDI_18 + M0_BDI_19 + M0_BDI_20 + M0_BDI_21 +
M0_BAI_1 + M0_BAI_2 + M0_BAI_3 + M0_BAI_4 + M0_BAI_5 + M0_BAI_6 + M0_BAI_7 + M0_BAI_8
+ M0_BAI_9 + M0_BAI_10 + M0_BAI_11 + M0_BAI_12 + M0_BAI_13 + M0_BAI_14 + M0_BAI_15 +
M0_BAI_16 + M0_BAI_17 + M0_BAI_18 + M0_BAI_19 + M0_BAI_20 + M0_BAI_21
M0_BDI_5 ~~ M0_BDI_8
M0_BDI_15 ~~ M0_BDI_20
M0_BAI_12 ~~ M0_BAI_13
General ~~ 0*Somatic
General ~~ 0*Cognitive'

## The 3-factor model by Clark et al. (2007).
Clark3Factor <-
'Depression=~ M0_BDI_1 + M0_BDI_2 + M0_BDI_3 + M0_BDI_4 + M0_BDI_5 + M0_BDI_6 +
M0_BDI_7 + M0_BDI_8 + M0_BDI_9 + M0_BDI_10 + M0_BDI_11 + M0_BDI_12 + M0_BDI_13 +
M0_BDI_14 + M0_BDI_15 + M0_BDI_16 + M0_BDI_17 + M0_BDI_18 + M0_BDI_19 + M0_BDI_20 +
M0_BDI_21 Somaticanxiety=~ M0_BAI_1 + M0_BAI_2 + M0_BAI_3 + M0_BAI_4 + M0_BAI_6 +
M0_BAI_7 + M0_BAI_8 + M0_BAI_11 + M0_BAI_12 + M0_BAI_13 + M0_BAI_15 + M0_BAI_18 +
M0_BAI_19 + M0_BAI_20 + M0_BAI_21
Subjectiveanxiety=~ M0_BAI_5 + M0_BAI_9 + M0_BAI_10 + M0_BAI_14 + M0_BAI_16 + M0_BAI_17'

fit7 <- cfa(twofactorSomCog, estimator = "MLR", data =
SF12_BDI_BAI_for_factor_analysis_v1_5_2019, missing="fiml") summary(fit7, fit.measures = TRUE,
standardized = TRUE)
modindices(fit7, sort=TRUE)
```

```
fit8 <- cfa(bifactorSomCog, estimator = "MLR", data = SF12_BDI_BAI_for_factor_analysis_v1_5_2019,
missing="fiml") summary(fit8, fit.measures = TRUE, standardized = TRUE)
modindices(fit8, sort=TRUE)

fit9 <- cfa(Clark3Factor, estimator = "MLR", data = SF12_BDI_BAI_for_factor_analysis_v1_5_2019,
missing="fiml") summary(fit9, fit.measures = TRUE, standardized = TRUE)
modindices(fit9, sort=TRUE)

#### Sensitivity analysis using WLS method (ordinal data).

Sensitivity.
fitOrdered <- cfa(twofactorBAIBDI, estimator = "WLSMV", data =
SF12_BDI_BAI_for_factor_analysis_v1_5_2019,
        ordered = c(paste("M0_BDI_", 1:21, sep = ""), paste("M0_BAI_", 1:21, sep = "")))
summary(fitOrdered, fit.measures = TRUE, standardized = TRUE)

fitOrdered <- cfa(bifactorBAIBDI, estimator = "WLSMV", data =
SF12_BDI_BAI_for_factor_analysis_v1_5_2019,
        ordered = c(paste("M0_BDI_", 1:21, sep = ""), paste("M0_BAI_", 1:21, sep = "")))
summary(fitOrdered, fit.measures = TRUE, standardized = TRUE)

fitOrdered <- cfa(GeneraldistressBAIBDI, estimator = "WLSMV", data =
SF12_BDI_BAI_for_factor_analysis_v1_5_2019,
        ordered = c(paste("M0_BDI_", 1:21, sep = ""), paste("M0_BAI_", 1:21, sep = "")))
summary(fitOrdered, fit.measures = TRUE, standardized = TRUE)

fitOrdered <- cfa(HADS2factor, estimator = "WLSMV", data = E,
        ordered = c(paste("HADSA_", 1:7, sep = ""), paste ("HADSD_", 1:7, sep = "")))
summary(fitOrdered, fit.measures = TRUE, standardized = TRUE)

fitOrdered <- cfa(HADSbifactor, estimator = "WLSMV", data = E,
        ordered = c(paste("HADSA_", 1:7, sep = ""), paste ("HADSD_", 1:7, sep = "")))
summary(fitOrdered, fit.measures = TRUE, standardized = TRUE)

fitOrdered <- cfa(HADS1factor, estimator = "WLSMV", data = E,
        ordered = c(paste("HADSA_", 1:7, sep = ""), paste ("HADSD_", 1:7, sep = "")))
summary(fitOrdered, fit.measures = TRUE, standardized = TRUE)
```

Supplementary table S2: Sensitivity analysis: Confirmatory Factor Analysis using Weighted Least Square Mean and Variance adjusted (WLSMV)

Dimension model and cohort	CFI	RMSEA
DIVERS-cohort:		
. 1-factor: General distress	.880	0.067
. 2-factor: BDI + BAI	0.945	0.046
. Tripartite bi-factor: BDI + BAI + general distress	0.988	0.022
Loosman-cohort:		
. 1-factor: General distress	0.903	0.114
. 2-factor: HADS-A + HADS-D	0.991	0.035
. Tripartite bi-factor: HADS-A + HADS-D + general distress	0.997	0.021

CFI>0.900 indicates adequate (or okay) fit and CFI >0.950 indicates good fit. Root Mean Square Error of Approximation (RMSEA)

Chapter 3

Validation of two screening tools for anxiety in hemodialysis patients.

Nadort E, van Geenen NJK, Schouten RW, Boeschoten RE, Chandie Shaw P, Vleming LJ, Schouten M, Farhat K, Dekker FW, van Oppen P, Siegert CEH, Broekman BFP.

Submitted

Abstract

Objective: To identify hemodialysis patients who are in need for treatment of anxiety, brief and valid anxiety screening instruments are needed. We investigated the diagnostic accuracy of two widely used screening tools for anxiety in hemodialysis patients.

Method: For this cross-sectional validation study, chronic hemodialysis patients from 8 dialysis centers in the Netherlands were included. The Beck Anxiety Inventory (BAI) and Hospital Anxiety and Depression Scale – Anxiety subscale (HADS-A) were validated by the MINI-international neuropsychiatric inventory (MINI) diagnostic interview. Receiver Operating Characteristic curves were used to determine optimal cut-off values.

Results: Of 65 participants, 13 (20%) were diagnosed with one or more anxiety disorders on the MINI. ROC curves showed good diagnostic accuracy of the BAI and HADS-A. The optimal cut-off value for the BAI was ≥ 13 (sensitivity 100%, specificity 80%) and for the HADS-A ≥ 10 (sensitivity 80%, specificity 100%).

Conclusions: Both the BAI and the HADS-A are valid screening instruments for anxiety in hemodialysis patients that can be easily administered in routine dialysis care. The HADS-A consists of less items and showed less false positive results than the BAI, which makes it especially useful in clinical practice.

Introduction

Anxiety is characterized by excessive fear that can cause clinically significant distress or impairment of functioning. Excessive anxiety can start without a clear reason (panic disorder), can be triggered by a traumatic event or situation (posttraumatic stress disorder (PTSD)), can be due to a fear of social or performance situations (social anxiety disorder), can be triggered by the presence or anticipation of a specific object or situation (specific phobia) or can be due to a number of events or activities (general anxiety disorder (GAD)).(1)

Recently, the nephrology field has become aware that elevated anxiety symptoms are a common problem in dialysis patients with a prevalence of 42% and with a large impact on quality of life and adverse clinical outcomes such as impaired treatment adherence, hospitalization and mortality.(2-6) Due to the overlap of symptoms of anxiety with symptoms of other medical conditions, like depression and uremia, symptoms of anxiety are often unrecognized and untreated in dialysis patients.(2, 6) Furthermore, international nephrology guidelines inadequately address screening for anxiety and no recommendations on frequency and preferred screening tools have been proposed.(7) Studies in chronic kidney disease and cardiovascular disease patients investigating treatments for anxiety have demonstrated that the results of psychotherapeutic interventions are promising on both lowering symptoms of anxiety as well as reducing clinical outcomes such as mortality.(8-10) To identify dialysis patients who might be in need for treatment of anxiety, validated anxiety screening instruments that can easily be applied in routine dialysis care are needed.(2)

Although there are various screening tools for anxiety available, only few of those have been validated in hemodialysis patients.(11, 12) A well-established screening instrument for anxiety is the Beck Anxiety Inventory (BAI).(13, 14) The BAI was developed to assess severity of anxiety while minimizing the overlap with depression.(13) The BAI has been used extensively and is validated in medical settings as well as in older adults.(15-20) To our knowledge, the BAI has not yet been validated in dialysis patients. The Hospital Anxiety and Depression Scale (HADS) is shorter than the BAI and was developed as a self-assessment screening tool for the detection of the presence of anxiety and depressive disorders specifically for adults attending medical outpatient clinics.(21) The HADS excludes somatic symptoms of anxiety and depression that are common in medical patients related to physical illness. The HADS has been used extensively and was found to perform well in other somatic patients, although evidence in dialysis patients has been inconclusive.(11, 12, 17, 22, 23) Two studies found acceptable performance and recommended the use of the HADS in dialysis patients, however, another study found poor predictive power of the HADS.(11, 12, 23) As diagnostic accuracy of screening tools vary between settings and patient groups, further validation is needed in hemodialysis patients.

This study aims to investigate the diagnostic accuracy of two widely used screening tools for anxiety, the BAI and HADS-A, and validate these screening tools against a structured

psychiatric diagnostic interview for detecting clinically relevant anxiety in hemodialysis patients.

Materials and methods

Study design and population

To validate the BAI and HADS-A in dialysis patients, baseline data were used from the ongoing multicenter Depression Related Factors and Outcomes in Dialysis Patients With Various Ethnicities and Races Study – Internet Intervention (DIVERS-II) which consists of a randomized controlled trial (RCT) and a parallel observational cohort. The extensive study protocol has been published previously.(24) In short, the RCT of DIVERS-II investigates the effectiveness of an online self-help intervention for depressive symptoms in hemodialysis patients. Patients who could not be randomized due to low depression scores were offered to participate in the parallel observational cohort study. Consecutive patients who gave informed consent for participation in both the RCT and observational cohort of the DIVERS-II study between November 28, 2019 and March 10, 2020, were asked to participate in this validation study. Adult patients from 8 dialysis centers affiliated with 5 hospitals in the Netherlands receiving maintenance hemodialysis (>90 days), who were able to read or understand Dutch and were willing to undergo a psychiatric diagnostic interview were included in this validation study. The study protocol, information brochure and informed consent were approved by the Medical Ethics Committee of MEC-U, Nieuwegein, the Netherlands (registration number: NL58520.100.17) and written informed consent was obtained from all participants before participation. The study was prospectively registered in the Dutch Trial Register (Trial NL6648). This study is carried out in accordance with the STARD 2015 reporting guideline for diagnostic accuracy studies.(25)

Anxiety screening tools

Symptoms of anxiety were measured with the BAI and the HADS-A, the most frequently used screening tools for assessing anxiety symptoms in chronic kidney disease patients.(5) The BAI consists of 21 items related to common somatic and cognitive symptoms of anxiety in which respondents are asked how much these symptoms have bothered them in the past week, on a scale ranging from 0 (not at all) to 3 (severely). The total score is between 0 and 63, where higher scores indicate more severe anxiety.(14) The HADS-A is a subscale of the HADS and consists of 7 items on anxiety , on which patients are asked about the frequency or severity of this item in the past week on a scale ranging from 0 (never) to 3 (almost always). The HADS-A total score ranges between 0 and 21, with higher scores indicating more severe anxiety.(21) The BAI takes approximately five minutes to complete and the HADS-A approximately two minutes.

Reference standard

The scores of the BAI and the HADS-A were compared to a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of an anxiety disorder, determined by using the latest version of the MINI-international neuropsychiatric inventory (MINI) 5.0.0 Dutch version.(1, 26) The MINI is a widely used structured psychiatric diagnostic interview instrument and is considered a reference standard diagnostic tool. We used sections for anxiety disorders (panic disorder, agoraphobia, social phobia, specific phobia, PTSD and GAD) and sections for mood disorders (depressive episode and dysthymia). The sections on depression were used to aid in the diagnosis of GAD, as this can only be diagnosed if depression is ruled out. If patients with a specific phobia did not have an encounter with the object or situation of their phobia in the past two weeks, they were excluded from the analysis as these patients were unlikely to have experienced anxiety that could be measured by the BAI or the HADS-A, which measure symptoms experienced in the past week.

The MINI interviews were administered by a medical resident with clinical experience in psychiatric care within one week after the self-reported scales were filled out, during a dialysis session or over the telephone during the first COVID-19 lockdown in the Netherlands (March 2020). Administration time of the MINI was 15 to 45 minutes. The medical resident was trained by a supervising psychiatrist with extensive experience with MINI interviews. All MINI interviews were reviewed by the supervising psychiatrist and 10 random MINI interviews were performed by both the medical resident and the psychiatrist to assess interrater reliability. To minimize rating biased by knowledge of the self-reported scales, the interviewer was blinded for the scores of the self-reported scales.

Data collection

At baseline, sociodemographic and clinical data were collected through self-reported questionnaires 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 and divided into four groups (renal vascular disease, diabetic nephropathy, glomerulonephritis and other).(27) The Davies comorbidity index was used to define the level of comorbidity.(28)

Power calculation

A total sample size of 60 participants was required when selecting a sensitivity of 98% and specificity of 85%, with a clinically acceptable width of no larger than 10% for sensitivity and specificity of the 95% confidence level when accounting for estimated dropout rate of 5% and estimated prevalence of 22% in this cohort.

Statistical analysis

Standard descriptive statistics were used to present the baseline characteristics of the study population, depending on the variable and underlying distribution. Interrater reliability was calculated with the kappa statistic and interpreted using the guidelines for strength of agreement from Landis and Koch.(29) The unidimensionality of the BAI and HADS-A was analyzed in a 1 factor model using Confirmatory factor analysis (CFA) with robust full-information maximum likelihood estimation. Model fit was interpreted by inspecting the comparative fit index (CFI) with acceptable fit if greater than 0.900 and the root mean squared error of approximation (RMSEA) with good fit if less than 0.060. CFA was performed in R (R Core Team), using the package lavaan.(29, 30) Chronbach's alpha was calculated to provide a measure of internal consistency. To determine the diagnostic accuracy of the BAI and HADS-A, receiver operating characteristics (ROC) curves were plotted and the area under the curve (AUC) was determined. The optimal cut-off score was assessed using the highest Youden Index.(31) In addition, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-) were calculated for the optimal cut-off scores. Statistical analysis were performed using SPSS for Windows, version 21 (IBM Corp).

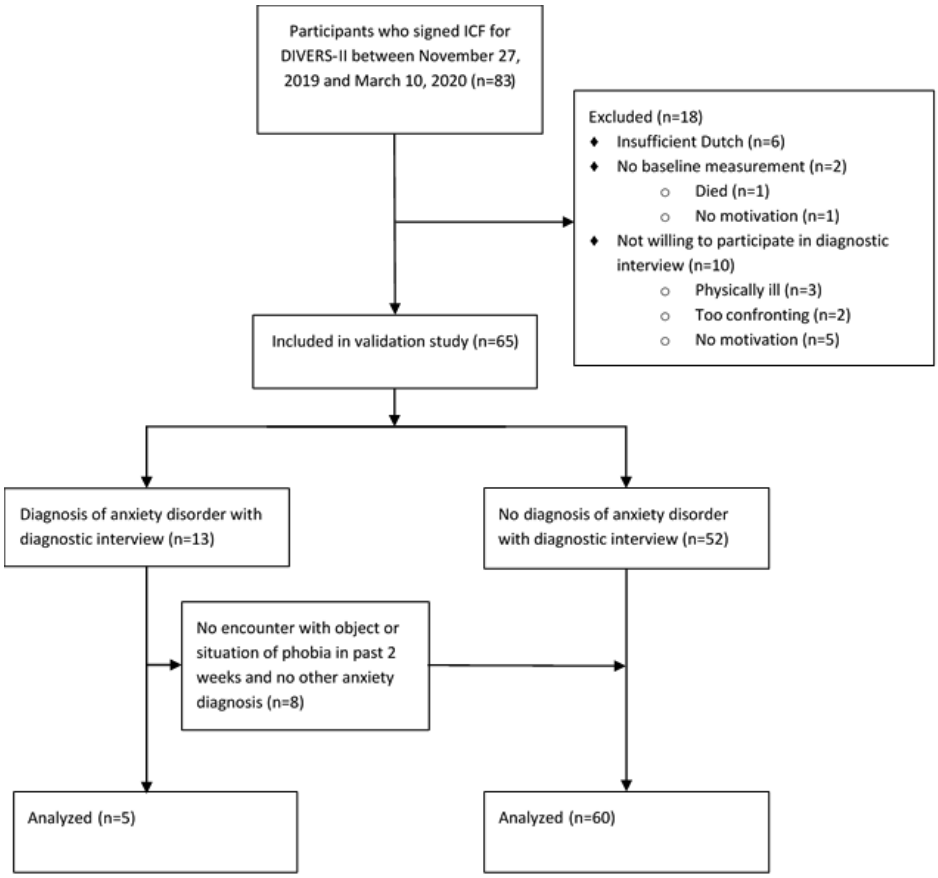
Results

Participants and baseline characteristics

Participant flow is shown in **Figure 1**. Baseline characteristics are presented in **Table 1**. We included a total of 65 patients, of which 69% were male with a mean age of 66 (standard deviation (SD) 13) years. Mean dialysis vintage was 23 months (interquartile range (IQR) 8-38). The majority of patients (62%) had a moderate Davies comorbidity score and almost half of the patients (45%) had diabetes mellitus as a comorbid condition.

In the medical history, 6% had a diagnosis of major depressive disorder and none of the patients had an anxiety disorder. At baseline, one patient was currently treated with psychotherapy and 10 patients (16%) were using antidepressants. Mean baseline BAI score was 8.4 (SD 7.5) and median HADS-A score was 2.0 (inter quartile range (IQR) 0.3-5.0).

Figure 1: Patient flow diagram



Abbreviations: ICF, Informed Consent Form; DIVERS-II, Depression Related Factors and Outcomes in Dialysis Patients With Various Ethnicities and Races Study – Internet Intervention.

Table 1: Baseline characteristics of 65 hemodialysis patients.

Characteristic	All patients (n=65)
Demographic	
Age (year)	66 ± 13
Male sex	45 (69%)
Immigrant*	18 (28%)
Country of birth	
The Netherlands	51 (79%)
Social	
Married/in a relationship	26 (40%)
Has Children	44 (68%)
Education**	
Low	16 (25%)
Middle	31 (48%)
High	17 (27%)
Employed	8 (12%)
Renal and dialysis	
Dialysis vintage (months)	23 [8-39]
Primary kidney disease	
Renal vascular disease	14 (22%)
Diabetic nephropathy	16 (25%)
Glomerulonephritis	11 (17%)
Other	21 (32%)
Kt/V_{urea} at baseline	3.7 ± 1.1
On waiting list for kidney transplant	17 (36%)
Residual diuresis of ≥100ml/24h	47 (72%)
Clinical	
Davies comorbidity score	
Low comorbidity	15 (23)
Moderate comorbidity	40 (62%)
High comorbidity	10 (15%)
Comorbid conditions	
Diabetes mellitus	29 (45%)
Cardiovascular disease***	50 (77%)
Laboratory	
Hemoglobin (g/dL)	10.8 ± 1.3
Phosphate (mg/dL)	5.0 ± 1.6
Albumin (g/L)	3.8 ± 0.5
Parathyroid hormone (pg/mL)	48 ± 37
Psychiatric	
Psychiatric diagnosis in medical history	
None	55 (85%)
Major depressive disorder	4 (6%)
Anxiety disorder	0 (0%)
Other	7 (11%)
Anxiety and Depressive symptoms	
HADS total score	8.7 ± 6.0
Anxiety symptoms	
HADS-A score	2.0 [0.3-5.0]
BAI score	8.4 ± 7.5

Table 1 (continued)

Characteristic	All patients (n=65)
Depressive symptoms	
HADS-D score	5.4 ± 3.2
BDI-II score	13.2 ± 7.7
Current psychotherapy	1 (2%)
Antidepressant use	10 (16%)
SSRI	3 (5%)
SNRI	0 (0%)
Tricyclic	7 (11%)

Note: Values are presented as mean ± standard deviation, median [interquartile range], or frequency (percentage).
Abbreviations: BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory; HADS, Hospital Anxiety and Depression Scale; HADS-A, Hospital Anxiety and Depression Scale – Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale – Depression subscale; SNRI, Serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitor.
*Immigrant status is based on the country of birth of the patient or on country of birth of one or both biological parents.
**Education: Low = primary education, middle = secondary education, high = higher professional education and university.
***Cardiovascular disease = acute coronary syndrome, angina pectoris, percutaneous coronary angioplasty, coronary artery bypass surgery, heart failure, peripheral arterial vascular disease, stroke, hypertension.

Prevalence of anxiety disorders

Of 65 the patients, 13 (20%) had one or more diagnoses of an anxiety disorder and 10 (15%) had a diagnosis of a current depressive episode identified by the reference standard MINI interview. Of the patients with an anxiety disorder, 2 (3%) were diagnosed with a panic disorder, 2 (3%) with social phobia and 2 (3%) with PTSD. In 10 patients (15%), a diagnosis of specific phobia was found, but only one of these patients had an encounter with the object or situation of their phobia in the past two weeks and was therefore included in the analysis.

Interrater reliability and performance

Of 10 random MINI interviews performed both by the medical resident and the psychiatrist, three cases were discussed because of a discrepancy in the diagnosis. Consensus was reached after discussion in two cases. In the third case, a depressive episode was diagnosed by both the medical resident and the psychiatrist, but no consensus on the timing of the episode was reached because different information was given by the participant in the interviews. Interrater reliability was found to be Kappa 0.82 ($p<0.001$). Confirmatory factor analysis showed a CFI of 0.581 and RMSEA of 0.131 for the BAI, and a CFI of 0.938 and RMSAE of 0.107 for the HADS-A, indicating that both the BAI and HADS-A are not unidimensional. Crohnbach's alpha was 0.86 for the BAI and 0.82 for the HADS-A.

Diagnostic accuracy of the BAI and HADS-A

Cross tabulation of the BAI and HADS-A by the MINI are presented in **Table 2a** and **Table 2b**. The ROC curve for the BAI showed good diagnostic accuracy with an AUC of 0.95 (95% confidence interval (CI) 0.89; 1.00) (**Supplemental Figure 1a**). The optimal cut-off value was ≥

13 with a sensitivity of 80% and a specificity of 100% (**Table 3**). Due to 9 false positive cases, the PPV was 36%. These 9 cases scored high on somatic symptoms of anxiety measured by the BAI like difficulty breathing, unsteadiness, wobbliness of legs, sweating and dizziness. With no false negative cases the NPV was 100%. The LR+ is 80 and the LR- is 0.2.

The ROC curve for the HADS-A also showed good diagnostic accuracy with an AUC of 0.95 (95%CI 0.85; 1.00) (**Supplemental Figure 1b**). The optimal cut-off value was ≥ 10, with a sensitivity of 80% and a specificity of 100%. There were no false positive cases making the PPV 100% and with one false negative case the NPV was 98%. The LR+ is 80 and the LR- is 0.2 (**Table 3**).

Table 2a: Cross tabulation of the BAI by the results of the MINI.

	No anxiety diagnosis (MINI)	**Anxiety diagnosis (MINI)**	**Total**
BAI < 13	51	0	51
BAI ≥ 13	9	5	14
Total	60	5	65

Table 2b: Cross tabulation of the HADS-A by the results of the MINI.

	No anxiety diagnosis (MINI)	**Anxiety diagnosis (MINI)**	**Total**
HADS-A < 10	60	1	61
HADS-A ≥ 10	0	4	4
Total	60	5	65

Abbreviations: BAI, Beck Anxiety Inventory; HADS-A, Hospital Anxiety and Depression Scale – Anxiety subscale; MINI, MINI-international neuropsychiatric inventory.

Table 3. Characteristics of the BAI and HADS-A.

Screening tool	**AUC**	**Optimal cut-off**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**LR+**	**LR-**
BAI	95%	10	0.80	1.00	1.00	0.98	80	0.2
HADS-A	95%	13	1.00	0.85	0.36	1.00	80	0.2

Abbreviations: AUC, Area Under the Curve; BAI, Beck Anxiety Inventory; HADS-A, Hospital Anxiety and Depression Scale – Anxiety subscale; LR+, Positive Likelihood Ratio; LR-, Negative Likelihood Ratio; NPV, Negative Predictive Value; PPV, Positive predictive Value.

Discussion

The aim of our study was to validate the diagnostic accuracy of the BAI and HADS-A in detecting clinically relevant anxiety in hemodialysis patients. To the best of our knowledge, there are only few studies that have validated the HADS-A and no studies to validate the BAI in this population. Our results show that the BAI and HADS-A had similar discriminative power to detect clinically relevant anxiety in hemodialysis patients with an optimal cut-off value for the BAI of ≥ 13 and for the HADS-A of ≥ 10.

We found a prevalence of anxiety disorders with the MINI of 20%, including all specific phobias. This is comparable to a recent systematic review and meta-analysis who found a prevalence of 19% of anxiety disorders among chronic kidney disease patients, but less than a comparable validation study in hemodialysis patients who found a prevalence of 46%.(5, 23) In the validation study by Cukor and colleagues, a poor predictive power of the HADS-A was found in contrast to our findings.(23) Similar to our results, specific phobias were the most common diagnosis in this study with a prevalence of 27%. It is possible that we found better performance of the HADS-A in our study because we excluded patients with specific phobias who did not have an encounter with the topic of their phobia in the past two weeks. Validation of screening tools for specific phobias is complicated as these patients may not experience anxiety related to their phobia in the same timeframe in which the screening tool was administered.

Optimal cut-off values for the BAI vary in the literature and range from ≥ 10 in the general population and ≥ 12 to ≥ 16 in other chronically ill patient populations or older adults.(16, 17, 33) This variety in cut-off values for the BAI could be attributable to differences in patient characteristics, but could also be due to an overlap between anxiety symptoms and the symptoms of chronic disease and depression.(6, 15, 19) This overlap with the symptoms of other conditions can be a reason for our finding of the relatively poor PPV (36%) of the BAI in our cohort. On the other hand, the NPV of 100% of the BAI using a cutoff value of ≥ 13 in our cohort suggest that it might be a good instrument to rule out anxiety disorders in hemodialysis patients. Suggested cutoff scores for the HADS-A vary from ≥ 6 in a dialysis cohort, ≥ 7 in Parkinson's disease and ≥ 8 in a review of patients from both the general population as well as in medical settings.(11, 17, 22) We found a higher cut of score of ≥ 10 with a high positive predictive value of 100% and a high negative predictive value of 98%. This suggests that the HADS-A was both good at detecting anxiety disorders and also at ruling them out. The relatively high cutoff score we found might be due to the presence of symptoms related to general distress common in chronically ill patients, instead of symptoms related to an actual anxiety disorder.(34)

As the main goal of our study was to validate instruments in order to screen for clinically relevant anxiety in dialysis patients, it was more important to choose cutoff scores based on their ability to capture all the respondents with anxiety disorders (high sensitivity and high NPV) in exchange for an increased chance of getting a false positive score (lower PPV). The burden of a dialysis patient getting one psychiatric consultation in which no anxiety disorders are identified, is likely to be less harmful than missing a patient who is in actual need of psychiatric treatment and who is at risk of poorer health outcomes associated with the presence of anxiety disorders.(3, 4, 6) Where PPV and NPV depend on the prevalence of a disease in a certain population, likelihood ratios do not. The likelihood ratio is a powerful measure of the diagnostic accuracy of a test and indicates how much that result will raise or lower the probability of disease.(35) For the optimal cut-off values of both the BAI and the HADS-A we found in our study, the LR+ is 80 and the LR- is 0.2. This means that scoring ≥ 13

on the BAI or ≥ 10 on the HADS-A has a large effect on the post-test probability of having a diagnosis of anxiety disorder and that scoring below the cut-off values has a moderate effect on the posttest probability of not having a diagnosis of anxiety disorder. Therefore, screening with the BAI or the HADS-A is useful to detect hemodialysis patients in need for further psychiatric assessment and possible treatment of their anxiety symptoms, although the HADS-A would be the preferred screening tool over the BAI because of a high NPV without compromising on the PPV.

Multiple strengths of this study can be identified. This is the first study to validate two widely used screening tools for anxiety disorders in hemodialysis patients. We included patients from 8 urban dialysis centers with a multi-ethnic population which increases the generalizability of the results. Also, the exclusion of patients with specific phobias who had no exposure to the specific situation or object related to the phobia in the past two weeks in the analysis is a strength, as these patients were likely to not have experienced symptoms of anxiety related to their diagnosis that could be measured by the screening tool. Furthermore, there was an interrater reliability of almost perfect agreement.

Limitations of this study include the limited sample size and relatively low number of diagnoses of anxiety disorders that are included in the analysis which could decrease generalizability. Cukor and colleagues found 46% of patients meeting the criteria of a DSM-IV diagnosis of anxiety disorder in a single urban hemodialysis center compared to 20% in our study.(23) It is possible that anxiety disorders were not that prevalent in the study population of DIVERS-II or that there was a selection bias in patients who were willing to participate in the DIVERS-II study or in a diagnostic interview on anxiety due to avoidant coping style. Second, as we did not have a diagnosis of GAD with the MINI in our study population, we cannot draw conclusions about diagnosing GAD with the BAI or HADS-A in hemodialysis patients. Third, some of the MINI interviews were conducted by telephone instead of face-to-face due to COVID-19 measures. Although this might affect accuracy of diagnosis, we do not expect a large impact on the results because of the structured nature of the MINI. Fourth, there was no Dutch translation of the MINI available compatible with the DSM-5 at the time of data acquisition. The differences between DSM-IV and DSM-5 relevant to this paper are that PTSD is excluded from the anxiety disorders and agoraphobia is separated from panic disorder in DSM-5 in comparison to DSM-IV.(36) The use of DSM-IV could limit clinical utility of our results and comparability with future validation studies.

In conclusion, both the BAI and the HADS-A are valid and quick screening instruments for detecting clinically relevant anxiety in hemodialysis patients that can be easily administered in routine dialysis care. The suggested cut-off value for the BAI is ≥ 13 and for the HADS-A is ≥ 10 in this population. The exclusion of somatic symptoms of anxiety in the HADS-A, the lower number of items and the high predictive value might make it more useful in clinical practice than the BAI. As diagnostic accuracy of screening tools varies between settings and patient groups, further validation of anxiety screening tools in hemodialysis populations from

different health systems is needed to strengthen the current evidence on this topic and to further improve the identification of hemodialysis patients who are in need for treatment of anxiety disorders.

References

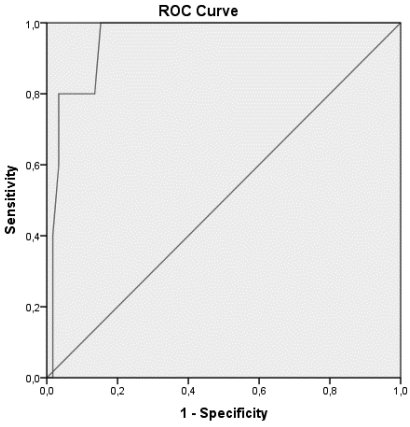
1. Diagnostic and statistical manual of mental disorders : DSM-IV: Fourth edition. Washington, DC : American Psychiatric Association, [1994] ©1994; 1994.
2. Cohen SD, Cukor D, Kimmel PL. Anxiety in Patients Treated with Hemodialysis. Clin J Am Soc Nephrol 11(12): 2250-5, 2016 doi:10.2215/CJN.02590316
3. Preljevic VT, Osthus TB, Os I, Sandvik L, Opjordsmoen S, Nordhus IH, et al. Anxiety and depressive disorders in dialysis patients: association to health-related quality of life and mortality. Gen Hosp Psychiatry 35(6): 619-24, 2013 doi:10.1016/j.genhosppsych.2013.05.006
4. 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 doi:10.1053/j.ajkd.2019.02.017
5. Huang CW, Wee PH, Low LL, Koong YLA, Htay H, Fan Q, et al. Prevalence and risk factors for elevated anxiety symptoms and anxiety disorders in chronic kidney disease: A systematic review and meta-analysis. Gen Hosp Psychiatry 69: 27-40, 2021 doi:10.1016/j.genhosppsych.2020.12.003
6. Kimmel PL, Cukor D. Anxiety Symptoms in Patients Treated With Hemodialysis: Measurement and Meaning. Am J Kidney Dis 74(2): 145-7, 2019 doi:10.1053/j.ajkd.2019.04.012
7. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis 63(5): 713-35, 2014 doi:10.1053/j.ajkd.2014.01.416
8. Pascoe MC, Thompson DR, Castle DJ, McEvedy SM, Ski CF. Psychosocial Interventions for Depressive and Anxiety Symptoms in Individuals with Chronic Kidney Disease: Systematic Review and Meta-Analysis. Front Psychol 8: 992, 2017 doi:10.3389/fpsyg.2017.00992
9. Reavell J, Hopkinson M, Clarkesmith D, Lane DA. Effectiveness of Cognitive Behavioral Therapy for Depression and Anxiety in Patients With Cardiovascular Disease: A Systematic Review and Meta-Analysis. Psychosom Med 80(8): 742-53, 2018 doi:10.1097/PSY.0000000000000626
10. Richards SH, Anderson L, Jenkinson CE, Whalley B, Rees K, Davies P, et al. Psychological interventions for coronary heart disease. Cochrane Database Syst Rev 4: CD002902, 2017 doi:10.1002/14651858.CD002902.pub4
11. Preljevic VT, Osthus TB, Sandvik L, Opjordsmoen S, Nordhus IH, Os I, et al. Screening for anxiety and depression in dialysis patients: comparison of the Hospital Anxiety and Depression Scale and the Beck Depression Inventory. J Psychosom Res 73(2): 139-44, 2012 doi:10.1016/j.jpsychores.2012.04.015
12. Martin CR, Thompson DR. The hospital anxiety and depression scale in patients undergoing peritoneal dialysis: internal and test–retest reliability. Clin Eff Nurs 6(2): 78-80, 2002 doi:https://doi.org/10.1016/S1361-9004(02)00029-8
13. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 56(6): 893-7, 1988
14. Beck AT SR. Beck Anxiety Inventory Manual: San Antonia, TX: Psychological Corp; 1993.
15. Balsamo M, Cataldi F, Carlucci L, Fairfield B. Assessment of anxiety in older adults: a review of self-report measures. Clin Interv Aging 13: 573-93, 2018 doi:10.2147/CIA.S114100

16. Dennis RE, Boddington SJ, Funnell NJ. Self-report measures of anxiety: are they suitable for older adults? Aging Ment Health 11(6): 668-77, 2007 doi:10.1080/13607860701529916
17. Leentjens AF, Dujardin K, Marsh L, Richard IH, Starkstein SE, Martinez-Martin P. Anxiety rating scales in Parkinson's disease: a validation study of the Hamilton anxiety rating scale, the Beck anxiety inventory, and the hospital anxiety and depression scale. Mov Disord 26(3): 407-15, 2011 doi:10.1002/mds.23184
18. Leyfer OT, Ruberg JL, Woodruff-Borden J. Examination of the utility of the Beck Anxiety Inventory and its factors as a screener for anxiety disorders. J Anxiety Disord 20(4): 444-58, 2006 doi:10.1016/j.janxdis.2005.05.004
19. Muntingh 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 12: 66, 2011 doi:10.1186/1471-2296-12-66
20. Kabacoff RI, Segal DL, Hersen M, Van Hasselt VB. Psychometric properties and diagnostic utility of the Beck Anxiety Inventory and the State-Trait Anxiety Inventory with older adult psychiatric outpatients. J Anxiety Disord 11(1): 33-47, 1997 doi:10.1016/s0887-6185(96)00033-3
21. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 67(6): 361-70, 1983 doi:10.1111/j.1600-0447.1983.tb09716.x
22. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 52(2): 69-77, 2002 doi:10.1016/s0022-3999(01)00296-3
23. Cukor D, Coplan J, Brown C, Friedman S, Newville H, Safier M, et al. Anxiety disorders in adults treated by hemodialysis: a single-center study. Am J Kidney Dis 52(1): 128-36, 2008 doi:10.1053/j.ajkd.2008.02.300
24. 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 19(1): 372, 2019 doi:10.1186/s12888-019-2363-5
25. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. BMJ Open 6(11): e012799, 2016 doi:10.1136/bmjopen-2016-012799
26. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59 Suppl 20: 22-33;quiz 4-57, 1998
27. 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 16(6): 1120-9, 2001 doi:10.1093/ndt/16.6.1120
28. 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 17(6): 1085-92, 2002 doi:10.1093/ndt/17.6.1085
29. Landis JR, Koch GG. An application of hierarchical kappa-type statistics in the assessment of majority agreement among multiple observers. Biometrics 33(2): 363-74, 1977

30. Rosseel Y. lavaan: An R Package for Structural Equation Modeling. 2012 48(2): 36, 2012 doi:10.18637/jss.v048.i02
31. Krzanowski WJ, Hand DJ. ROC Curves for Continuous Data: Chapman & Hall/CRC; 2009.
32. Wolitzky-Taylor KB, Horowitz JD, Powers MB, Telch MJ. Psychological approaches in the treatment of specific phobias: a meta-analysis. Clin Psychol Rev 28(6): 1021-37, 2008 doi:10.1016/j.cpr.2008.02.007
33. de Lima Osório F, Crippa JAS, Loureiro SR. Further psychometric study of the Beck Anxiety Inventory including factorial analysis and social anxiety disorder screening. Int J Psychiatry Clin Pract 15(4): 255-62, 2011 doi:10.3109/13651501.2011.605955
34. Hudson J, Chilcot J. Psychological Distress in Physical Long-Term Conditions. In: Goldsmith D, Covic A, Spaak J, editors. Cardio-Renal Clinical Challenges. PART III: Springer International Publishing; 2015. p. 227-34.
35. Hayden SR, Brown MD. Likelihood ratio: A powerful tool for incorporating the results of a diagnostic test into clinical decisionmaking. Ann Emerg Med 33(5): 575-80, 1999 doi:10.1016/s0196-0644(99)70346-x
36. Kupfer DJ. Anxiety and DSM-5. Dialogues Clin Neurosci 17(3): 245-6, 2015

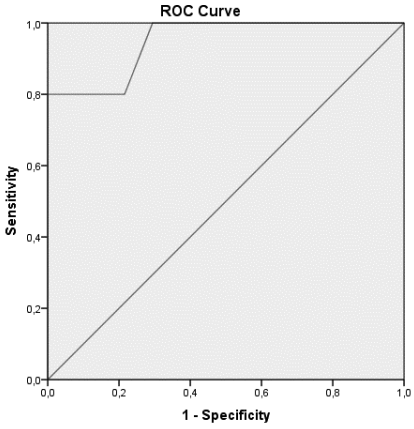
Supplementary files

Supplemental Figure 1a: ROC curve of the BAI



Note: AUC BAI = 95%

Supplemental Figure 1b: ROC curve of the HADS-A



Note: AUC HADS-A = 95%

Abbreviations: AUC, area under the curve; HADS-A, Hospital Anxiety and Depression Scale – Anxiety subscale; ROC, receiver operating characteristic.

Chapter 4

Symptom dimensions of anxiety and their association with mortality, hospitalization and quality of life in dialysis patients.

Schouten RW, Nadort E, Harmse V, Honig A,
van Ballegooijen W, Broekman BFP, Siegert CEH.

Journal of Psychosomatic Research; Volume 133, June 2020, 109995

Abstract

Objective: Symptoms of anxiety are highly prevalent in dialysis patients and are associated with adverse clinical outcomes. Identifying symptom dimensions may help to understand the pathophysiology, improve screening and guide treatment. Currently, there are no data on symptom dimensions of anxiety in dialysis patients. This study aimed to identify the best fitting dimensional model for anxiety in dialysis patients and assess the association between symptom dimensions of anxiety and adverse clinical outcomes.

Methods: This study is a prospective observational cohort study including patients from 10 urban dialysis centers between 2012 and 2017. Anxiety symptoms were measured using the self-reported questionnaire Beck Anxiety Inventory. Confirmatory factor analysis was used to identify symptom dimensions. The association between dimensions and mortality, hospitalization and quality of life was investigated using stepwise cox, poisson and lineair regression models. Multivariable models included demographic, social, laboratory and clinical variables to adjust for possible confounding.

Results: In total 687 chronic dialysis patients were included. A Somatic and Subjective anxiety dimension were identified. Only Somatic anxiety symptoms showed an association with increased risk of hospitalization and mortality (Rate Ratio 1.73 (1.45–2.06) p = .007 and Hazard Ratio 1.65 (1.15–2.37) p = .007 respectively). These associations were independent from somatic comorbidity. All symptom dimensions of anxiety showed an association with Quality of Life.

Conclusion: This study shows that anxiety is common in chronic dialysis patients and comprises of a somatic, subjective, and a total score. The discrimination between anxiety dimensions can be useful for clinical practice, as they are related to different clinical outcomes.

Highlights

- Anxiety symptoms are very common in patients with kidney disease
- Better insight in these symptoms is needed to aid in screening and treatment
- This study identified several key symptom dimensions
- The somatic symptom dimension was related to a decreased survival
- All dimensions of anxiety showed a marked effect on Quality of Life

Introduction

Mental health disorders, like anxiety and depression, are common in patients with end stage renal disease receiving dialysis therapy. Although recently a few studies reported on the role of depressive symptom dimensions on clinical outcomes in dialysis patients, to the best of our knowledge dimensions of anxiety have not yet been described (1,2). This is important as the prevalence of anxiety symptoms ranges from 22 to 53%, and a body of literature recognized the clinical relevance of anxiety symptoms. (3–9)

Several studies in dialysis patients described an association between anxiety symptoms and adverse clinical outcomes, such as an increased hospitalization rate and higher risk for all-cause mortality (4,6,10). Despite the burden of anxiety symptoms, these symptoms are often underdiagnosed and undertreated in dialysis patients (8). The poor detection of anxiety might be explained by the overlap of anxiety symptoms with symptoms of CKD (i.e., faint/lightheaded due to blood pressure variability, high blood pressure, difficulty breathing, indigestion), as is the case with depressive symptoms in CKD. To aid in the implementation of screening and ultimately improve outcomes, it is important to gain further insight in anxiety symptoms and their relation to clinical outcomes. Identifying clusters or dimensions of anxiety symptoms with factor analysis is one of the first steps that may aid the understanding of the clinical presentation and pathophysiology of anxiety and outcomes in dialysis patients.

Data on symptom dimensions of anxiety in dialysis patients is scarce. Besides studies investigating the distinction between depression and anxiety in dialysis patients, no studies have thoroughly investigated symptom dimensions of anxiety (2). Furthermore, it is not known whether there is a differential association between the dimensions of anxiety and adverse clinical outcomes, such as hospitalization, quality of life and mortality.

To identify possible symptom dimensions of anxiety in dialysis patients, this study will test three hypotheses or constructs described in literature in other patient populations. First, Beck et al. described a model with a Somatic and Cognitive anxiety dimension in psychiatric outpatients (11,12). Second, Steer et al. adjusted this model to a Somatic and Subjective anxiety dimension and found a good performance in a variety of clinical cohorts (13–15). Third, a 4-factor model was described by Osman included a) Neurophysiologic, b) Autonomic c) Panic and d) Subjective anxiety dimension, which provided a good fit in other somatically ill patient groups (15–21).

There are two primary aims of this study: 1) to identify dimensions of anxiety symptoms by investigating existing models with confirmatory factor analysis and 2) to investigate the association between these anxiety symptom dimensions and adverse clinical outcomes, including all-cause mortality, hospitalization and quality of life. The present study is the first study to investigate symptom dimensions of anxiety in dialysis patients using the Beck Anxiety Inventory. These data may provide new insights in the understanding of both the clinical

presentation of anxiety and possible pathophysiological mechanisms to adverse clinical outcomes in dialysis patients.

Methods

Study cohort

Data were obtained from the 'DIVERS' study. This is an observational, prospective cohort study among dialysis patients from 10 urban dialysis centers in the Netherlands. The cohort consists of both prevalent and incident dialysis patients, included between June 2012 and October 2016, as described elsewhere (4). Inclusion criteria included: a) age ≥ 18 years, b) chronic dialysis patients (≥90 days on dialysis therapy). Exclusion criteria included: a) patients who were unable to understand the questionnaires, despite bedside assistance. To promote the generalizability of these results, all patients were considered eligible and no exclusion criteria were applied regarding the medical history or current medical condition of patients. This study was approved by the medical ethics committees of all participating hospitals and was carried out in accordance with the Declaration of Helsinki.

Demographic, social and clinical data

At baseline, the following socio-demographic and clinical data were collected from electronic medical records: age, gender, dialysis modality and vintage, comorbidities (summarized in the Davies comorbidity score), primary cause of kidney disease, routine laboratory measures, transplantation waiting list and medication use. Incident dialysis patients were defined as new patients on renal replacement therapy> 90 days and < 180 days. The primary cause of kidney disease was classified according to the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) coding system and causes were divided into 4 groups: diabetes mellitus, glomerulonephritis, renal vascular disease, and other (22). The level of comorbidity was defined according to the Davies comorbidity index, indicating no, intermediate or severe comorbidity and a 7-point severity scale (used in the multivariable analyses) (23).

We collected the following characteristics through self-reported questionnaires: ethnicity (defined as immigrant status based on the country of birth), marital status, children, educational level, working status, current smoking and alcohol use. Patients were assisted if they were not able to fill in the questionnaires themselves, however when patients could not understand the questions or scoring, they were marked as 'missing'. To improve generalizability, all questionnaires and variables were available in Dutch, English, Turkish, and Moroccan Arabic translations.

Assessment of anxiety symptoms

Anxiety symptoms were measured using the self-questionnaire Beck Anxiety Inventory (BAI) (12). Respondents were asked to rate how much each of these symptoms had bothered them

in the past week, on 21 items on a scale ranging from 0 (not at all) to 3 (severely). The total score ranges from a minimum of 0 to a maximum of 63. The BAI was analyzed primarily using cut-off values (BAI ≥ 16) to aid in the interpretation of the hazard ratio's and relative risks. Sensitivity analysis included the use of the continuous scores. Although the BAI has not been validated in dialysis patients, it has been validated in a large variety of cohorts, including cohorts with somatically ill patients (11,15,18,19,21). These studies show that the BAI has a high internal consistency (Crohnbachs α = 0.92) and a test-retest reliability over one week of 0.75 in cardiology patients. The Crohnbach α in the present study was 0.914. For the BAI the cut-off of 16 was based on the manual provided by Beck et al. indicating 'clinically significant' anxiety symptoms (12). In this study the term 'anxiety' refers to patients who scored above this predefined cut-off score for clinically relevant anxiety symptoms, not to a clinical diagnosis based on the DSM. This study used validated BAI translations in Dutch, English, Turkish and Moroccan Arabic.

Assessment of clinical outcomes: mortality, hospitalization rate and QoL

The primary clinical endpoint of this study was all-cause mortality. Cause and time of death were collected with a maximum follow-up of 4 years. Cause of death was classified using the ERA-EDTA coding system. Data from baseline to 1 year after inclusion was used to calculate the hospitalization rate in number of hospitalizations per year. When a patient had been discharged from hospital and was admitted again on the same day, the hospital admittance was considered 1 event. Quality of life was measured using the 12-item Short Form health survey (SF-12), consisting of both a mental component score and physical component score.

Statistical analysis

Standard descriptive statistics were used to present baseline characteristics for the total population and stratified by the presence of Anxiety symptoms (BAI ≥ 16).

Factor analysis

The factor structure of the BAI was analyzed using confirmatory factor analysis (CFA) with robust full information maximum likelihood (FIML) estimation. FIML estimation is robust for missing data and non-normally distributed data (24). The models were identified using the marker-item approach, which means that the loading of the first item of every subscale is fixed to 1 and its intercept is set to 0. Model fit was interpreted by inspecting fit indices, employing the following rules of thumb: the comparative fit index (CFI) indicates acceptable fit above,900 and good fit above,950; the root mean squared error of approximation (RMSEA) indicates good fit below,060; and the standardized root mean squared residual (SRMR) indicates good fit below,080 (25). These fit indices should be considered in combination, so a good fit meets all these criteria (25). The best fitting model was obtained by means of an iterative process, starting with factor models found in the literature (11,13,15) and, if necessary, adapting the model until adequate model fit was obtained. These analyses were performed in R (R Core Team), using the package lavaan (26).

Association with adverse clinical outcomes

Univariable and multivariable regression models were used to investigate the association between the different dimensions of anxiety symptoms and adverse clinical outcomes, including QoL, hospitalization rate and all-cause mortality. General, somatic and subjective symptom dimensions were investigated in all regression models. Variables were included in a predefined stepwise manner to show the effect of the extra included variables on the effect estimates. Several variables are deliberately within the causal pathway to investigate the effect/change on the association between anxiety and outcome. The change in HR, RR or beta can give an indication of the effect of these variables on the causal pathway itself. The pre-defined steps included in the multivariable models include the following variables:

- Model 1: Crude effect measure
- Model 2: Adding: Gender, Age, Ethnicity Incident/prevalent to model
- Model 3: Adding: Children yes/no, Married yes/no, Paid job yes/no, Education level
- Model 4: Adding: Dialysis vintage, Dialysis modality (hemodialysis versus peritoneal dialysis), Incident/prevalent and the 7-point DAVIES comorbidity score (including DM, congestive heart failure, ischemic heart disease, peripheral vascular disease, COPD, liver disease, cancer, collagen vascular disease), laboratory measures (Hemoglobin, Albumin, Kt/V, and Calcium)
- Model 5: Adding: Physical component score of the Quality of Life (SF-12).

All models used the dichotomous scores for the symptom dimensions as the predictor variable to improve clinical interpretation. Sensitivity analyses will use the continuous scores of the symptom dimensions. Since no cut-off value for the Subjective and Somatic symptom dimension were described or validated, the median value was used for dichotomization. For the general BAI score, a validated cut-off of 16 was used.

Quality of life

QoL was investigated using the SF-12 total scores as a continuous variable in linear regression models, where a beta was calculated to show the decrease in Quality of Life scores associated with a higher symptom burden of anxiety.

Hospitalization

Hospitalization numbers were presented as count data, displaying the number of hospitalizations during the first year after inclusion (number / year). The association between anxiety symptoms dimensions and hospitalization was studied using Poisson regression models.

Mortality

Median survival time was calculated using the life table method (Kaplan Meier). Time to event was calculated using the moment of inclusion as starting point. Patients who at the end of

their follow-up, were lost to follow-up, were transplanted or had recovery of renal function were censored. The hazard ratio (HR) for survival for the different dimensions was estimated using Cox proportional hazards analysis. To allow for direct comparison between groups of patients, we divided the population into binary (lowest-highest) subjective, somatic, and general anxiety dimensions.

Missing values

To maximize the generalizability of the results, participating patients had the option to participate in a non-questionnaire part of the study. These patients only gave consent to gather information from their electronic patient file, without filling in self-reported questionnaires. This provided us data on characteristics of patients who were otherwise excluded. To assess the impact of missed items on the results, missing values of BAI were imputed by using multiple imputation techniques (10 repetitions) as a sensitivity analysis. All statistical analyses were performed using SPSS for Windows version 24, 'R' and R-studio v.3.5.3.

Results

Baseline characteristics

A total of 687 dialysis patients were included in this cohort study. **Table 1** described the baseline characteristics for all patients, and stratified by the presence of anxiety symptoms above the cut-off value (BAI≥16). The cohort consisted of 433 (64%) prevalent and 240 (36%) incident dialysis patients. Prevalent patients had a median dialysis vintage of 13 months (IQR, 4–47 months). The mean age was 65 +/ 15 (SD) years, 62% of patients were men and 48% of patients were immigrants. The cohort had a follow-up for a maximum of 4 years, with a median follow-up of 3.1 years (IQR, 3.0–3.5). A total of 173 patients (25%) died during follow-up. Total comorbidity scores were divided into low (27%), intermediate (55%) and severe (18%). The most prevalent comorbidities were diabetes and hypertension, with prevalence rates of 42% and 64% respectively. Most of the patients had children (78%), 52% were married, 38% had a low education level and 89% of this cohort did not have paid work. A third (34%) of the patients described a self-perceived need of a psychologist now or in the future.

Baseline demographic and clinical variables had<5% missing values, the overall percentage of missing items on returned questionnaires was 7.8%. Missing data on self-reported questionnaires consisted of (1) patients who participated in the non-questionnaire part of this study (8% of the total cohort), (2) patients with missing items on the BAI (14%) and (3) patients with a completely missing BAI score (4%). Sensitivity analyses, using multiple imputation of missing items and questionnaires, showed no major differences compared to the complete case analyses.

Table 1: Baseline characteristics

Characteristic	All patients (n = 687)[a]	Anxiety[e]	
		No (n = 395)	Yes (n = 113)
Demographic			
Age, years	65 +/− 15	65 +/− 15	62 +/− 14
Male Sex	424 (62%)	238 (62%)	71 (63%)
Immigrant	300 (48%)	163 (43%)	67 (61%)
Country of Birth			
European	366 (58%)	244 (64%)	45 (41%)
Sub-Saharan Africa/ Northern Africa	22 (4%)	13 (3%)	2 (2%)
Western Asia / Southern Asia/South Eastern Asia	54 (9%)	19 (5%)	17 (16%)
South-America/	57 (9%)	33 (9%)	14 (13%)
Caribbean	131 (21%)	75 (20%)	32 (29%)
Social			
Married	316 (52%)	207 (52%)	55 (49%)
Has Children	474 (78%)	306 (78%)	87 (78%)
Low education[b]	127 (22%	90 (24%)	19 (17%)
Not employed	534 (89%)	336 (86%)	107 (95%)
Renal and dialysis			
Incident dialysis patient[c]	240 (36%)	142 (37%)	33 (30%)
Vintage of prevalent group, mo	13 [4–47]	11 [4–45]	28 [5–57]
Treatment modality:			
Hemodialysis	592 (88%)	336 (88%)	100 (89%)
Peritoneal dialysis	80 (12%)	47 (12%)	12 (11%)
Primary kidney disease:			
Diabetic Nephropathy	155 (24%)	82 (23%)	38 (36%)
Renal vascular disease	163 (26%)	100 (28%)	18 (17%)
Glomerulonephritis	70 (11%)	40 (11%)	11 (10%)
Other	247 (39%)	140 (39%)	40 (37%)
AVG or AVF[d]	435 (65%)	246 (64%)	73 (65%)
Kt/V urea at baseline	2.0 [1.5–3.6]	2.0 [1.5–3.4]	1.7 [1.4–3.6]
Residual diuresis > 100 ml/24 h	475 (71%)	277 (72%)	68 (61%)
On waiting list for Tx			
Yes	201 (30%)	124 (32%)	30 (27%)
No, for medical reasons	425 (63%)	235 (61%)	71 (63%)
No, for patient preference	46 (7%)	24 (6%)	11 (10%)
Clinical			
Current smoking	108 (18%)	68 (18%)	23 (21%)
Current alcohol use	161 (27%)	110 (28%)	27 (24%)
Davies co-morbidity score:			
Low comorbidity	183 (27%)	109 (29%)	24 (21%)
Moderate comorbidity	370 (55%)	212 (55%)	58 (52%)
Severe comorbidity	119 (18%)	62 (16%)	30 (27%)
Comorbidities:			
Diabetes mellitus	284 (42%)	154 (40%)	58 (52%)
Chronic heart disease	111 (17%)	59 (15%)	24 (21%)
Peripheral vascular disease	84 (13%)	53 (14%)	12 (11%)
Psychiatric and quality of life			
BAI score	10.3 +/−10.1	6.0 +/− 4.5	25.4 +/− 9.5
Anxiety symptoms (BAI ≥ 16)	113 (22%)	-	-

Table 1 (continued)

Characteristic	All patients (n = 687)[a]	Anxiety[e]	
		No (n = 395)	Yes (n = 113)
HRQoL (SF-12)			
PCS score	38.1 (11.1)	38.2 (10.5)	40.0 (11.2)
MCS score	48.9 (10.8)	50.9 (9.5)	33.0 (10.1)

Values are presented as mean +/− SD, median [IQR] or frequency (percentage). HRQoL, Health related quality of life; PCS, physical component summary; MCS, mental component summary.

[a] 56 of 687 participating patients gave only permission to collect data from electronic medical records and did not provide consent for self-report measurement of anxiety, depression and more. Details on missing values can be found in **Table S6**.

[b] low education: highest level of education is high school or less.

[c] < 180 days on dialysis. d versus central venous catheter, for HD patients only.

[e] Defined as BAI < 16 vs ≥16.

Anxiety symptoms

Anxiety symptoms were common in 22% of the cohort. Patients with high anxiety symptoms differed from patients with low anxiety symptoms in a number of baseline characteristics: the proportion of immigrants was higher in the anxiety group (61% vs 43%), the prevalence of diabetes was higher in the anxiety group (52% vs 40%), and the mental component score of the health-related quality of life was lower in the anxiety group (33 (±10) vs 51 (±10)). No major differences were found in social characteristics, vascular access, treatment modality, residual diuresis, and the SF-12 physical component score, as described in **Table 1**.

Table 2 describes the prevalence and severity for each anxiety symptom in this cohort. The most prevalent somatic anxiety symptoms were a) Faint, b) Dizzy/lightheaded, c) Unsteady, d) Numbness/tingling. The most severe and prevalent Subjective or Cognitive anxiety symptoms were a) Unable to relax, b) Fear of the worst happening and c) Nervousness.

Identifying symptom dimensions using factor analysis

Several pre-defined factor models were tested in the confirmatory factor analyses. **Table 3** describes the fit of the dimensional models in this cohort. The Somatic-Cognitive model by Beck et al. did not yield an adequate fit in this sample, with a low CFI and RMSEA and negative or low factor loadings, especially for the somatic items. The models by Steer (Somatic-Subjective) and Osman (Subjective-Autonomic- Neuromotor-Panic) provided a better fit compared to the Beck model, with adequate factor loadings on all dimensions, however the fit indices did not yield an adequate fit in this sample. In an iterative process, we tried to add a general factor to the models, as suggested by several other studies on anxiety and depression (1,2,27). Furthermore, we allowed for correlation between item 12 (Hands trembling) and item 13 (Shaky) (19). These changes improved both the 2 and 4 factor model, as shown in **Table 3**. **Fig. 1** described the found dimensions in this cohort of dialysis patients, including their factor loadings on the dimensions.

Table 2: Prevalence and mean scores of BAI items in this cohort.[b]

Symptoms scored in the Beck Anxiety Inventory, listed by decreasing prevalence	% of patients with this symptom (marker for prevalence)	Mean (SD) (marker for severity)
Somatic dimension[a]		
Faint	55%	0.78 (0.86)
Dizzy or lightheaded	54%	0.78 (0.90)
Unsteady	53%	0.79 (0.92)
Numbness or tingling	49%	0.78 (0.96)
Wobbliness in legs	40%	0.63 (0.89)
Heart pounding or racing	40%	0.59 (0.81)
Feeling hot	37%	0.53 (0.81)
Indigestion or discomfort abdomen	35%	0.52 (0.83)
Hands trembling	34%	0.48 (0.77)
Difficulty breathing	31%	0.40 (0.67)
Shaky	30%	0.40 (0.70)
Face flushed	25%	0.34 (0.67)
Sweating (not due to heat)	25%	0.40 (0.78)
Feelings of choking	17%	0.25 (0.64)
Subjective dimension[a]		
Nervous	43%	0.59 (0.81)
Unable to relax	41%	0.61 (0.88)
Fear of the worst happening	40%	0.64 (0.92)
Fear of losing control	29%	0.42 (0.76)
Scared	27%	0.40 (0.77)
Fear of dying	25%	0.41 (0.82)
Terrified	20%	0.31 (0.72)

Presence of symptoms are scored as yes when the score ≥ 1 (including mild, moderate, and severe).
[a] According to the Steer model of Somatic-Subjective symptoms for the BAI (13).
[b] Items that are part of the cognitive dimension in the Beck model (11).

The General-Somatic-Subjective model showed a good model fit (CFI = 0.962, RMSEA = 0.043**, Table 3**). The factor loadings on the Somatic items however, were low, especially compared to the General and Subjective items on the BAI, as shown in **Supplementary table S1**. This indicates that the somatic dimension did not show a good correlation between the items. The 4-factor model (Subjective-Autonomic-Neurophysical-Panic) also showed a good model fit after the iterative process (CFI = 0.965, RMSEA = 0.042, **Table 3**). Furthermore, this model did show adequate to good factor loadings on the Somatic dimensions (Autonomic, Neurophysical, Panic), indicating that this model performs better compared to the Somatic-Subjective model. The process for obtaining these models can be found in the R code provided in **Supplementary file S2**. In conclusion, we consider that the best fitting factor model for this cohort of chronic dialysis patients included a General dimension (with all BAI items), a Subjective anxiety dimension and a Somatic anxiety dimensions which can be further divided into an Autonomic, Neurophysiologic and Panic symptom dimension. The symptom dimensions did not show major differences between incident and prevalent dialysis patients.

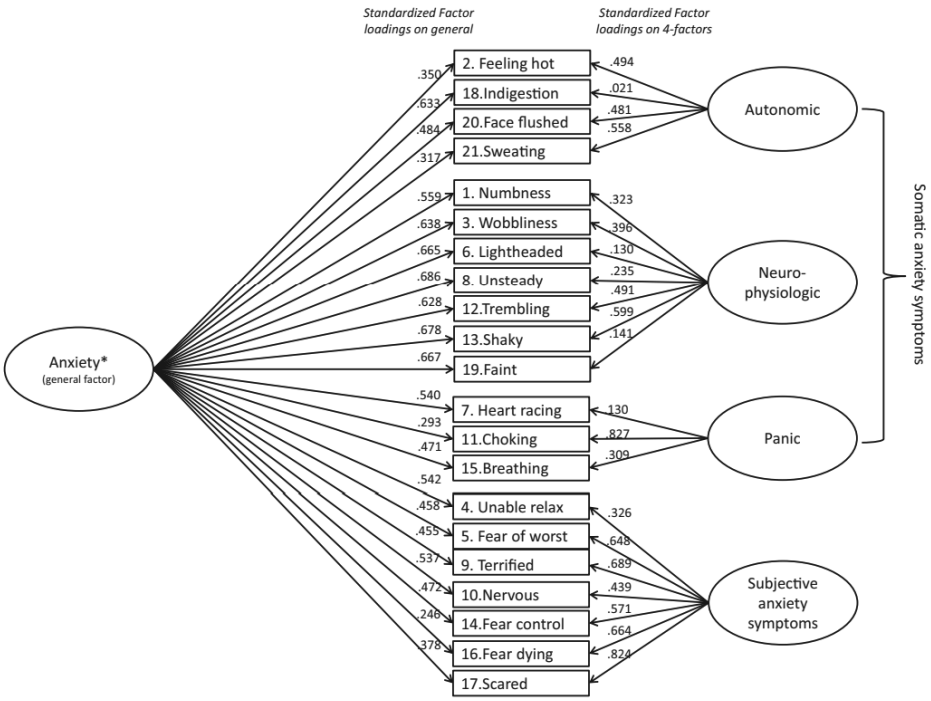
Table 3: Performance of dimension models of the BAI in the DIVERS cohort.

Dimension models:	CFI (robust)	RMSEA (robust)
Somatic-Cognitive (Beck 1988)	0.762	0.102
Somatic-Subjective (Steer 1993)	0.859	0.078
Subjective-Autonomic-Neuromotor-Panic (Osman 1993)	0.900	0.067
Adjustments after the iterative process		
General-Somatic-Subjective[a] (Steer 1993 + general factor)	0.962	0.043
Subjective-Autonomic-Neuromotor-Panic (Osman 1993 + general factor)	0.965	0.042

CFI ≥ 0.90 indicates adequate (or okay) fit and CFI ≥ 0.95 indicates good fit (37). Root Mean Square Error of Approximation (RMSEA) < 0.06 is considered to demonstrate good fit (38). The R-code for the factor analyses and the iterative process can be found in the **Supplementary file S2**.

[a] The somatic items on this model showed relatively low factor loadings, indicating that the somatic factor does not fit good. The factor loadings on the 4-factor model did show good factor loadings, as shown in **Fig. 1**.

Figure 1: Dimensional structure of the BAI in this cohort of dialysis patients.



Factor loadings < 0.30 are low. ≥0.30 are acceptable. Factor loadings ≥0.50 are moderate/good. The factor loadings are from the confirmatory factor analysis on a 4-factor Autonomic-Neurophysiologic-Panic-Subjective model. Item 12 and 13 are allowed to correlate. All items were allowed to correlate with the General factor (including all 21 items), of which the factor loadings are shown on the left of the items of the BAI.

Relation between symptom dimensions of anxiety and adverse clinical outcomes

After the identification of the symptom dimensions of anxiety, we assessed which dimensions were the most important risk factors for adverse clinical outcomes. **Table** 4 describes the association between symptom dimensions of anxiety, all-cause mortality, hospitalization rate and health related quality of life. During follow-up, 172 deaths occurred with the following causes: cardiovascular n = 52, infectious n = 32, Cancer n = 13, dialysis withdrawal n = 15, and other n = 57 (missing cause of death n = 3).

Survival analyses showed that the Somatic anxiety symptoms, and not the Subjective anxiety symptoms, were associated with all-cause mortality, with a HR of 1.65 (1.15–2.37) p = .007, **Table 4**). **Fig. 2** visualizes this increased mortality risk separately for the Somatic anxiety dimension and the Subjective anxiety dimension, using the Kaplan Meier Survival method. Analyses on the hospitalization rate showed the same trend, where only Somatic anxiety symptoms were associated with an increased risk of hospitalization (RR of 1.56 (1.32–1.85), p < .001, **Table 4**)). **Supplementary table S3** describes the association between the Autonomic, Neurophysiologic and Panic dimensions and clinical outcome, which indicate that especially Neurophysiologic and Panic symptoms were associated with both mortality and hospitalization, while Autonomic symptoms were not. The Subjective symptom dimension did not show an association with both all-cause mortality and hospitalization rate, with Hazard and Rate Ratio's close to 1. Sensitivity analyses using continuous predictor variables showed similar results on mortality and Quality of Life, as shown in **supplementary table S4**. However, in contrast to the results in **Table 4**, the association between the continuous variable of the subjective score did show an association with hospitalization, suggesting there is no differential association between Somatic and Subjective dimensions with hospitalization.

Figure 2: Kaplan Meier survival plots for the somatic and subjective symptom dimension of the BAI.

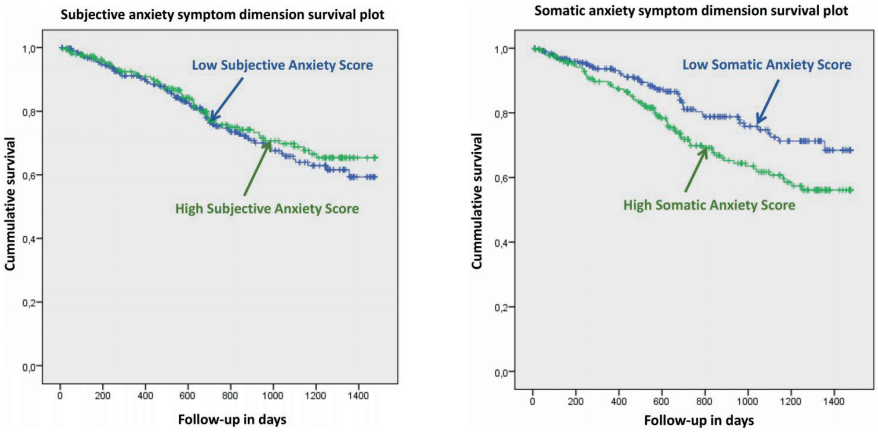


Table 4: Association between symptom dimensions of the BAI and Mortality, Hospitalization rate & Quality of Life.

Sequential modeling	General BAI score (BAI ≥ 16)	Somatic anxiety dimension (≥5)	Subjective anxiety dimension (≥2)
Mortality (HR + 95%CI)			
1. Univariable / Crude	1.38 (0.93–2.05) p = .11	1.65 (1.15–2.37) p = .007	0.89 (0.63–1.25) p = .50
2. + Age, Sex, Ethnicity	1.71 (1.14–2.56) p = .010	1.87 (1.29–2.71) p = .001	1.08 (0.76–1.53) p = .68
3. + Social characteristics	1.74 (1.16–2.62) p = .008	1.94 (1.33–2.82) p = .001	1.12 (0.79–1.60) p = .52
4. + Dialysis, comorbidity, laboratory	1.72 (1.08–2.74) p = .02	1.73 (1.13–2.66) p = .013	1.00 (0.67–1.50) p > .99
5. + Physical component score SF-12	1.55 (0.97–2.49) p = .07	1.57 (1.00–2.46) p = .049	0.92 (0.61–1.38) p = .68
Hospitalization (RR + 95%CI)			
1. Univariable/Crude	1.42 (1.18–1.72) p < .001	1.73 (1.45–2.06) p < .001	1.07 (0.91–1.26) p = .39
2. + Age, Sex, Ethnicity	1.36 (1.12–1.66) p = .002	1.71 (1.43–2.05) p < .001	1.04 (0.88–1.23) p = .65
3. + Social characteristics	1.37 (1.12–1.68) p = .002	1.76 (1.46–2.11) p < .001	1.05 (0.88–1.25) p = .59
4. + Dialysis, comorbidity, laboratory	1.45 (1.16–1.81) p = .001	1.53 (1.25–1.88) p < .001	1.06 (0.88–1.29) p = .55
5. + Physical component score SF-12	1.32 (1.05–1.66) p = .017	1.40 (1.13–1.72) p = .002	1.00 (0.82–1.22) p > .99
Quality of life (beta + 95%CI)			
1. Univariable/Crude	−16.16 (−19.36–12.97) p < .001	−15.67 (−18.20–13.14) p < .001	−13.60 (−16.12–11.08) p < .001
2. + Age, Sex, Ethnicity	−16.80 (−20.07–13.52) p < .001	−16.16 (−18.77–13.55) p < .001	−14.46 (−17.06–11.85) p < .001
3. + Social characteristics	−16.65 (−20.00–13.00) p < .001	−15.86 (−18.52–13.19) p < .001	−14.61 (−17.26–11.95) p < .001
4. + Dialysis, comorbidity, laboratory	−15.85 (−19.49–12.20) p < .001	−14.84 (−17.81–11.87) p < .001	−14.25 (−17.13–11.37) p < .00

Stepwise sequential modeling approach to investigate the associations of depressive symptoms with adverse clinical outcomes using cut-off values.
The median value is used for the cognitive and somatic scores and BAI ≥ 16 for the general score.
Social characteristics include: Children, Paid Job, Education, Married.
Dialysis characteristics include: Dialysis vintage, dialysis modality (HD vs PD), Incident or Prevalent, DAVIES comorbidity (0–7).
Laboratory measures include: Hemoglobin, Albumin, Kt/V, Calcium.

Demographic and social characteristics did not influence the association between somatic anxiety symptoms, mortality and hospitalization. Further, the association did not show major differences when a large variety of somatic and clinical variables are added to the model, including dialysis vintage, dialysis modality (HD vs PD), incident or prevalent, DAVIES comorbidity (0–7), Hemoglobin, Albumin, Kt/V, and Calcium. This indicates that the association between Somatic anxiety symptoms and mortality seems to be independent of sociodemographic variables and the severity of somatic disease and comorbidity. In the final model, the physical component score from the SF-12 Quality of Life questionnaire is added. This shows a slight decrease in HR from 1.65 to 1.57 with a large overlap in confidence intervals (**Table 4**), which indicates that the associations remain largely unchanged after including a subjective variable for somatic comorbidity.

The total BAI score showed associations with both mortality and hospitalization, with similar effect sizes compared to the Somatic symptom dimension, indicating that this association is probably due to the Somatic items with no additive effect of high Subjective items. **Supplementary table S5** shows the same results were there is no additive effect on clinical outcome when both Somatic and Subjective symptoms are elevated.

All symptom dimensions, including the subjective anxiety dimension, were associated with a substantial decrease in Quality of Life scores, both in the crude models as in the multivariable models, indicating that all anxiety symptom dimensions seem to be relevant to Quality of Life.

Discussion

The first aim of this study was to identify symptom dimensions or clusters of anxiety in dialysis patients using the BAI. In this sample we found evidence for a Subjective, and Somatic anxiety dimension, besides the total score (General dimension). The Somatic anxiety dimension included an Autonomic, Neurophysiologic and Panic dimension. The second aim was to determine the association between these symptom dimensions and adverse clinical outcomes. We found that Somatic anxiety symptoms showed a clear association with hospitalization rate and all-cause mortality, in contrast to Subjective anxiety symptoms. These associations were independent from a large set of sociodemographic, laboratory and comorbidity variables. All dimensions of anxiety showed a clear association with Quality of Life in this cohort.

Identifying symptom dimensions

Comparing our results with the available evidence is difficult due to the scarcity of studies on anxiety symptoms in dialysis patients. Most studies available on mental health symptoms or distress focused on depression, and not on anxiety. One of the few studies available on anxiety dimensions by Chilcot et al. did a factor analysis on the combined scales of both depressive and anxiety symptoms (measured with the PHQ and GAD-7). They found evidence for a general distress factor and to a lesser extent a ‘general’ anxiety factor (the total GAD-7 score).

(2) Despite the relevant data from this study, they did not investigate specific dimensions of anxiety itself, probably limited due to the 7-item GAD questionnaire, compared to the 21-item BAI questionnaire used in the present study. Due to the paucity of data on factor analysis in dialysis patients we compared our results to studies on other somatic, psychiatric or general population cohorts. Studies on other (older) somatically ill patient groups are likely to resemble the dialysis cohort and give us an indication for the performance of the models. Studies in cardiology patients or elderly medical patients showed a comparable performance of the 4-factor model, thus supporting our results. Future studies in dialysis patients are needed to confirm these results in the appropriate patient cohorts.

Association with adverse clinical outcomes

To the best of our knowledge there are no studies that investigated the association between symptom dimensions of anxiety and adverse outcomes in dialysis patients, therefore limiting our ability to verify that our results are generalizable. There is however, some data on dimensions of depression and their association with adverse outcomes which supports the results on the differential association between Somatic and Cognitive depressive symptoms and adverse outcomes (1). A study in the same cohort as the present study showed that only the Somatic symptom dimension of depression was associated with allcause mortality, in contrast to the Cognitive symptom dimension of depression (1). Similar results were found in a comparable study in patients with heart disease by de Jonge et al. (27)

In the present study, we could not find a somatic marker that could explain or mediate the association between somatic anxiety symptoms and adverse clinical outcomes (hospitalization and mortality), suggesting that there is an independent association between anxiety symptoms and mortality. However, the association between anxiety symptoms and adverse outcomes, such as mortality, is multifactorial and complex. Therefore, it is difficult to fully capture possible confounding or common causes to isolate the stand-alone effect of anxiety on outcome. Studies have shown there is an overlap between somatic symptoms from end-stage renal disease and psychiatric symptoms, such as those of depression and anxiety, which suggest an underlying common pathway (5,28). Furthermore, the possible pathophysiological pathways between psychiatric symptoms and clinical outcomes might provide better insight and give suggestions for future treatments. Studies on depressive symptoms for example have suggested possible parallel inflammatory or hypothalamic-pituitary-adrenal axis pathways.

Regardless of the complex interplay, the results of this and other studies emphasize the impact of anxiety symptoms on dialysis patients, suggesting a holistic approach with adequate screening and treatment of these symptoms (3,18). In the development of clinical guidelines, it is important to gain insight in the type of symptoms that are reported and possible clusters of symptoms. The associations with adverse clinical outcomes, independent of somatic variables, highlights the clinical relevance of anxiety symptoms for patients, caregivers and policy makers. Future research should focus on both 1) the possible pathophysiological mechanisms involved in the pathway between anxiety and clinical outcome and 2) on the

investigation of effective treatments for these type of symptoms in relation to clinical outcomes. Moreover, data from this study can help Value Based Health Care (VBHC) initiatives with the development of Patient Reported Outcomes Measures (PROM).

Strengths and limitations

The results of this study need to be interpreted with possible limitations in mind. First, the complex interplay between anxiety, somatic disease and clinical outcome cannot be fully captured in variables, thus allowing for unmeasured confounding. To minimize this, we used a relatively large amount of variables on somatic markers compared to existing literature, including laboratory markers, dialysis efficiency and vintage, and comorbidity-scores. Second, this study uses self-reported questionnaires on anxiety and not a definitive diagnosis by a psychiatrist. At the same time this underscores the need to explore anxiety symptoms instead regardless of a clinical diagnoses of anxiety disorders. Third, there is a paucity in the data on validation of anxiety measures in dialysis patients, and although the BAI lacks validation in this patient group, it is one of the most accepted tools internationally to measure anxiety in clinical populations. (19,21,29,30) Fourth, this study uses a cohort with a high percentage of immigrant patients, which can both promote and limit the generalizability of our results. Fifth, the BAI has been criticized because of its predominant focus on physical symptoms of anxiety which are most akin to a panic disorders / response (11,29,31). The BAI however, showed a good ability to indicate the severity of anxiety symptoms in a variety of different cohorts (32). Furthermore, the Somatic symptoms are also the most prevalent in dialysis patients and seem to be clinically relevant in relation to subjective and objective clinical outcomes, independent of somatic comorbidity.

Conclusion

Anxiety symptoms are highly prevalent in dialysis patients and show associations with decreased quality of life and an increased hospitalization and mortality rate. Results from this study suggest that both Subjective and Somatic dimensions can be used to provide insight in these symptoms in relation to outcomes. The Somatic anxiety dimension includes Autonomic, Neurophysiologic and Panic dimensions. Data shows that only the Somatic symptom dimensions are associated with hospitalization and mortality, independent of somatic comorbidity. Our results underscore the need for common screening practices for mental health, including anxiety, in dialysis patients. Moreover, these dimensions could aid in understanding the pathways between mental health and hospitalization and mortality in dialysis patients.

References

1. R.W. Schouten, V.J. Harmse, F.W. Dekker, W. van Ballegooijen, C.E.H. Siegert, A. Honig, Dimensions of depressive symptoms and their association with mortality, hospitalization, and quality of life in Dialysis patients: a cohort study, Psychosom. Med. 81 (2019) 649–658.
2. J. Chilcot, J.L. Hudson, R. Moss-Morris, A. Carroll, D. Game, A. Simpson, M. Hotopf, Screening for psychological distress using the patient health questionnaire anxiety and depression scale (PHQ-ADS): initial validation of structural validity in dialysis patients, Gen. Hosp. Psychiatry 50 (2018) 15–19.
3. P.L. Kimmel, D. Cukor, Anxiety symptoms in patients treated with Hemodialysis: measurement and meaning, Am. J. Kidney Dis. 74 (2) (2019) 145–147.
4. R.W. Schouten, G.L. Haverkamp, W.L. Loosman, P.K. Chandie Shaw, F.J. van Ittersum, Y.F.C. Smets, L.J. Vleming, F.W. Dekker, A. Honig, C.E.H. Siegert, Anxiety symptoms, mortality, and hospitalization in patients receiving maintenance Dialysis: a cohort study, Am. J. Kidney Dis. 74 (2) (2019) 158–166.
5. D. Cukor, J. Coplan, C. Brown, S. Friedman, A. Cromwell-Smith, R.A. Peterson, P.L. Kimmel, Depression and anxiety in urban hemodialysis patients, Clin. J. Am. Soc. Nephrol. 2 (2007) 484–490.
6. V.T. Preljevic, T.B. Osthus, I. Os, L. Sandvik, S. Opjordsmoen, I.H. Nordhus, T. Dammen, Anxiety and depressive disorders in dialysis patients: association to health-related quality of life and mortality, Gen. Hosp. Psychiatry 35 (2013) 619–624.
7. F.E. Murtagh, J. Addington-Hall, I.J. Higginson, The prevalence of symptoms in end-stage renal disease: a systematic review, Adv. Chronic Kidney Dis. 14 (2007) 82–99.
8. S.D. Cohen, D. Cukor, P.L. Kimmel, Anxiety in patients treated with Hemodialysis, Clin. J. Am. Soc. Nephrol. 11 (2016) 2250–2255.
9. D. Cukor, J. Coplan, C. Brown, R.A. Peterson, P.L. Kimmel, Course of depression and anxiety diagnosis in patients treated with hemodialysis: a 16-month follow-up, Clin. J. Am. Soc. Nephrol. 3 (2008) 1752–1758.
10. A. Mykletun, O. Bjerkeset, M. Dewey, M. Prince, S. Overland, R. Stewart, Anxiety, depression, and cause-specific mortality: the HUNT study, Psychosom. Med. 69 (2007) 323–331.
11. A.T. Beck, N. Epstein, G. Brown, R.A. Steer, An inventory for measuring clinical anxiety: psychometric properties, J. Consult. Clin. Psychol. 56 (1988) 893–897.
12. A.T. Beck, SR: Beck Anxiety Inventory Manual, Psychological Corporation, San Antonio, TX, 1993.
13. R.A. Steer, D.J. Rissmiller, W.F. Ranieri, A.T. Beck, Structure of the computer-assisted Beck anxiety inventory with psychiatric inpatients, J. Pers. Assess. 60 (1993) 532–542.
14. R.A. Steer, G. Kumar, W.F. Ranieri, A.T. Beck, Use of the Beck anxiety inventory with adolescent psychiatric outpatients, Psychol. Rep. 76 (1995) 459–465.
15. A. Osman, B.A. Kopper, F.X. Barrios, J.R. Osman, T. Wade, The Beck anxiety inventory: reexamination of factor structure and psychometric properties, J. Clin. Psychol. 53 (1997) 7–14.
16. A. Osman, F.X. Barrios, D. Aukes, J.R. Osman, K. Markway, The Beck anxiety inventory: psychometric properties in a community population, J. Psychopathol. Behav. Assess. 15 (1993) 287–297.

17. A. Osman, J. Hoffman, F.X. Barrios, B.A. Kopper, J.L. Breitenstein, S.K. Hahn, Factor structure, reliability, and validity of the Beck anxiety inventory in adolescent psychiatric inpatients, J. Clin. Psychol. 58 (2002) 443–456.
18. S. Rutten, I. Ghielen, C. Vriend, A.W. Hoogendoorn, H.W. Berendse, A.F. Leentjens, Y.D. van der Werf, J.H. Smit, O.A. van den Heuvel, Anxiety in Parkinson's disease: symptom dimensions and overlap with depression and autonomic failure, Parkinsonism Relat. Disord. 21 (2015) 189–193.
19. J.L. Wetherell, P.A. Areán, Psychometric evaluation of the Beck anxiety inventory with older medical patients, Psychol. Assess. 9 (1997) 136–144.
20. S.D. Sanford, A.J. Bush, K.C. Stone, K.L. Lichstein, N. Aguillard, Psychometric evaluation of the Beck anxiety inventory: a sample with sleep-disordered breathing, Behav. Sleep Med. 6 (2008) 193–205.
21. J.M. Clark, J.M. Marszalek, K.K. Bennett, K.M. Harry, A.D. Howarter, K.R. Eways, K.S. Reed, Comparison of factor structure models for the Beck anxiety inventory among cardiac rehabilitation patients, J. Psychosom. Res. 89 (2016) 91–97.
22. P.C. van Dijk, K.J. Jager, F. de Charro, F. Collart, R. Cornet, F.W. Dekker, C. Gronhagen-Riska, R. Kramar, T. Leivestad, K. Simpson, Briggs JD, registry E-E: 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. 16 (2001) 1120–1129.
23. S.J. Davies, L. Phillips, P.F. Naish, G.I. Russell, Quantifying comorbidity in peritoneal dialysis patients and its relationship to other predictors of survival, Nephrol. Dial. Transplant. 17 (2002) 1085–1092.
24. C.K. Enders, The impact of nonnormality on full information maximum-likelihood estimation for structural equation models with missing data, Psychol. Methods 6 (2001) 352–370.
25. L. Hu, P.M. Bentler, Cuttoff Criteria for fit Indexes in Covariances Structure Analysis: Conventional Criteria Versus new Alternatives, (1999), pp. 1–55.
26. Y. Rosseel, lavaan: An R Package for Structural Equation Modeling, 48 (2012), p. 36.
27. Peter de Jonge, Johan Ormel, Rob H.S. van den Brink, Joost P. van Melle, Titia A. Spijkerman, Astrid Kuijper, Dirk J. van Veldhuisen, Maarten P. van den Berg, Adriaan Honig, Harry J.G.M. Crijns, H. Aart, Schene.: symptom dimensions of depression following myocardial infarction and their relationship with somatic health status and cardiovascular prognosis, Am. J. Psychiatr. 163 (2006) 138–144.
28. A.T. Olagunju, E.A. Campbell, J.D. Adeyemi, Interplay of anxiety and depression with quality of life in endstage renal disease, Psychosomatics 56 (2015) 67–77.
29. O.T. Leyfer, J.L. Ruberg, J. Woodruff-Borden, Examination of the utility of the Beck anxiety inventory and its factors as a screener for anxiety disorders, J. Anxiety Disord. 20 (2006) 444–458.
30. J.D. Kopple, B.B. Shapiro, U. Feroze, J.C. Kim, M. Zhang, Y. Li, D.J. Martin, Hemodialysis treatment engenders anxiety and emotional distress, Clin. Nephrol. 88 (2017) 205–217.
31. A.T. Beck, R.A. Steer, Relationship between the beck anxiety inventory and the Hamilton anxiety rating scale with anxious outpatients, J. Anxiety Disord. 5 (1991) 213–223.
32. A.D. Muntingh, C.M. van der Feltz-Cornelis, H.W. van Marwijk, P. Spinhoven, B.W. Penninx, A.J. van Balkom, 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. 12 (2011) 66.

Supplementary tables and files

Supplementary table S1. Standardized factor loadings from the CFA of General-Somatic-Subjective model of the BAI

Depressive symptoms from BAI	Factor 1 (general)	Factor 2 (somatic)	Factor 3 (subjective)
Numbness or tingling	0.499	0.227	
Feeling hot	0.608	-0.268	
Wobbliness in legs	0.538	0.329	
Unable to relax	0.556		0.228
Fear of the worst happening	0.499		0.576
Dizzy or lightheaded	0.577	0.240	
Heart pounding or racing	0.580	-0.040	
Unsteady	0.554	0.468	
Terrified	0.518		0.599
Nervous	0.567		0.338
Feelings of choking	0.551		0.154
Hands trembling	0.549	0.235	
Shaky	0.593	0.260	
Fear of losing control	0.529		0.470
Difficulty breathing	0.530	0.111	
Fear of dying	0.325		0.604
Scared	0.451		0.761
Indigestion or discomfort abdomen	0.569	0.189	
Faint	0.562	0.320	
Face flushed	0.700	-0.229	
Sweating (not due to heat)	0.614	-0.321	

Factor loadings <.30 are low. ≥0.30 are acceptable. Factor loadings ≥0.50 are moderate/good.

Supplementary file S2: R code for the factor analysis and iterative process

```
# R code by Wouter van Ballegooijen and Robbert Schouten
# CFA of BAI on sample of dialysis patients

#install packages.
install.packages("lavaan")
install.packages("qgraph")

#libraries.
library(lavaan)
library(qgraph)

# Import SPSS
library(haven)
library(lavaan)

# Set working directory.
setwd()

# Load data
library(haven)
D <- read_sav("C:/Users/robbe/Google Drive/Promotie/Manuscripten/Dimensions anxiety/Anxiety
dimensions/SF12 BDI BAI for factor analysis v1-5-2019.sav")

#### Performing the confirmatory factor analyses

# The 2-factor model by Beck et al. (1988).
Beck2Factor <-
'Somatic=~ M0_BAI_1 + M0_BAI_2 + M0_BAI_3 + M0_BAI_6 + M0_BAI_7 + M0_BAI_8 + M0_BAI_12
+
M0_BAI_13 + M0_BAI_17 + M0_BAI_19 + M0_BAI_20 + M0_BAI_21
Cognitive =~ M0_BAI_4 + M0_BAI_5 + M0_BAI_9 + M0_BAI_10 + M0_BAI_11 + M0_BAI_14 +
M0_BAI_15 + M0_BAI_16 + M0_BAI_18'

# The 2-factor model by Steer et al. (1993).
Steer2Factor <-
'Somatic=~ M0_BAI_1 + M0_BAI_2 + M0_BAI_3 + M0_BAI_6 + M0_BAI_7 + M0_BAI_8 + M0_BAI_11
+ M0_BAI_12 +
M0_BAI_13 + M0_BAI_15 + M0_BAI_18 + M0_BAI_19 + M0_BAI_20 + M0_BAI_21
Subjective =~ M0_BAI_4 + M0_BAI_5 + M0_BAI_9 + M0_BAI_10 + M0_BAI_14 + M0_BAI_16 +
M0_BAI_17'

# The 4-factor model by Osman et al. (1993).
Osman4Factor<-
'Subjective=~ M0_BAI_4 + M0_BAI_5 + M0_BAI_9 + M0_BAI_10 + M0_BAI_14 + M0_BAI_16 +
M0_BAI_17
Autonomic=~ M0_BAI_2 + M0_BAI_18 + M0_BAI_20 + M0_BAI_21
Neuromotor=~ M0_BAI_1 + M0_BAI_3 + M0_BAI_6 + M0_BAI_8 + M0_BAI_12 + M0_BAI_13 +
M0_BAI_19
Panic=~ M0_BAI_7 + M0_BAI_11 + M0_BAI_15'
```

Starting iterative process using the Steer2Factor model (best factor loadings and only 2 factors).

```
# Taking Steer2Factor model, changing item 11 to subjective due to the translation to Dutch, this
item is more subjective than somatic.
Steer2FactorAdjust <-
'Somatic=~ M0_BAI_1 + M0_BAI_2 + M0_BAI_3 + M0_BAI_6 + M0_BAI_7 + M0_BAI_8 + M0_BAI_12
+
M0_BAI_13 + M0_BAI_15 + M0_BAI_18 + M0_BAI_19 + M0_BAI_20 + M0_BAI_21
Subjective =~ M0_BAI_4 + M0_BAI_5 + M0_BAI_9 + M0_BAI_10 + M0_BAI_11 + M0_BAI_14 +
M0_BAI_16 + M0_BAI_17'

# Allowing 12 and 13 to correlate (Trembling and Shaking).
Steer2FactorAdjust2 <-
'Somatic=~ M0_BAI_1 + M0_BAI_2 + M0_BAI_3 + M0_BAI_6 + M0_BAI_7 + M0_BAI_8 + M0_BAI_12
+
M0_BAI_13 + M0_BAI_15 + M0_BAI_18 + M0_BAI_19 + M0_BAI_20 + M0_BAI_21

Subjective =~ M0_BAI_4 + M0_BAI_5 + M0_BAI_9 + M0_BAI_10 + M0_BAI_11 + M0_BAI_14 +
M0_BAI_16 + M0_BAI_17
M0_BAI_12 ~~ M0_BAI_13'

# Adding a general factor to Steer2FactorAdjust2.
Steer2FactorAdjust3 <-
'Somatic=~ M0_BAI_1 + M0_BAI_2 + M0_BAI_3 + M0_BAI_6 + M0_BAI_7 + M0_BAI_8 + M0_BAI_12
+
M0_BAI_13 + M0_BAI_15 + M0_BAI_18 + M0_BAI_19 + M0_BAI_20 + M0_BAI_21
Subjective =~ M0_BAI_4 + M0_BAI_5 + M0_BAI_9 + M0_BAI_10 + M0_BAI_11 + M0_BAI_14 +
M0_BAI_16 + M0_BAI_17
Overall =~ M0_BAI_1 + M0_BAI_2 + M0_BAI_3 + M0_BAI_4 + M0_BAI_5 + M0_BAI_6 + M0_BAI_7 +
M0_BAI_8 +
M0_BAI_9 + M0_BAI_10 + M0_BAI_11 + M0_BAI_12 + M0_BAI_13 + M0_BAI_14 + M0_BAI_15 +
M0_BAI_16 +
M0_BAI_17 + M0_BAI_18 + M0_BAI_19 + M0_BAI_20 + M0_BAI_21
Overall ~~ 0*Somatic
Overall ~~ 0*Subjective
M0_BAI_12 ~~ M0_BAI_13'

# Items 2,20 and 21 are highly correlated, measure the same thing? Thus adding a 'hot' factor
Steer2FactorAdjust3.
Steer2FactorAdjust4 <-
'Somatic=~ M0_BAI_1 + M0_BAI_2 + M0_BAI_3 + M0_BAI_6 + M0_BAI_7 + M0_BAI_8 + M0_BAI_12
+
M0_BAI_13 + M0_BAI_15 + M0_BAI_18 + M0_BAI_19 + M0_BAI_20 + M0_BAI_21
Subjective =~ M0_BAI_4 + M0_BAI_5 + M0_BAI_9 + M0_BAI_10 + M0_BAI_11 + M0_BAI_14 +
M0_BAI_16 + M0_BAI_17
Overall =~ M0_BAI_1 + M0_BAI_2 + M0_BAI_3 + M0_BAI_4 + M0_BAI_5 + M0_BAI_6 + M0_BAI_7 +
M0_BAI_8 +
M0_BAI_9 + M0_BAI_10 + M0_BAI_11 + M0_BAI_12 + M0_BAI_13 + M0_BAI_14 + M0_BAI_15 +
M0_BAI_16 +
M0_BAI_17 + M0_BAI_18 + M0_BAI_19 + M0_BAI_20 + M0_BAI_21
Hot =~ M0_BAI_2 + M0_BAI_20 + M0_BAI_21
Overall ~~ 0*Subjective
```

```
Overall ~~ 0*Hot
Overall ~~ 0*Somatic
M0_BAI_12 ~~ M0_BAI_13'

# Removing the Somatic factor due to relatively low factor loadings using Steer2FactorAdjust4.
Steer2FactorAdjust5 <-
'Subjective =~ M0_BAI_4 + M0_BAI_5 + M0_BAI_9 + M0_BAI_10 + M0_BAI_11 + M0_BAI_14 +
M0_BAI_16 + M0_BAI_17
Overall =~ M0_BAI_1 + M0_BAI_2 + M0_BAI_3 + M0_BAI_4 + M0_BAI_5 + M0_BAI_6 + M0_BAI_7 +
M0_BAI_8 +
M0_BAI_9 + M0_BAI_10 + M0_BAI_11 + M0_BAI_12 + M0_BAI_13 + M0_BAI_14 + M0_BAI_15 +
M0_BAI_16 +
M0_BAI_17 + M0_BAI_18 + M0_BAI_19 + M0_BAI_20 + M0_BAI_21
Hot =~ M0_BAI_2 + M0_BAI_20 + M0_BAI_21
Overall ~~ 0*Subjective
Overall ~~ 0*Hot
M0_BAI_12 ~~ M0_BAI_13'

# 12 and 13 correlating (Wetherell?)
Osman4FactorAdjust<-
'Subjective=~ M0_BAI_4 + M0_BAI_5 + M0_BAI_9 + M0_BAI_10 + M0_BAI_14 + M0_BAI_17
Autonomic=~ M0_BAI_2 + M0_BAI_18 + M0_BAI_20 + M0_BAI_21
Neuromotor=~ M0_BAI_1 + M0_BAI_3 + M0_BAI_6 + M0_BAI_8 + M0_BAI_12 + M0_BAI_13 +
M0_BAI_19
Panic=~ M0_BAI_7 + M0_BAI_11 + M0_BAI_15 + M0_BAI_16
M0_BAI_12 ~~ M0_BAI_13'

# Correlation 16 and 17 and 16 with subjective (According to steer)
Osman4FactorAdjust2<-
'Subjective=~ M0_BAI_4 + M0_BAI_5 + M0_BAI_9 + M0_BAI_10 + M0_BAI_14 + M0_BAI_16 +
M0_BAI_17
Autonomic=~ M0_BAI_2 + M0_BAI_18 + M0_BAI_20 + M0_BAI_21
Neuromotor=~ M0_BAI_1 + M0_BAI_3 + M0_BAI_6 + M0_BAI_8 + M0_BAI_12 + M0_BAI_13 +
M0_BAI_19
Panic=~ M0_BAI_7 + M0_BAI_11 + M0_BAI_15
M0_BAI_12 ~~ M0_BAI_13'

# adding general
Osman4FactorAdjust3<-
'Subjective=~ M0_BAI_4 + M0_BAI_5 + M0_BAI_9 + M0_BAI_10 + M0_BAI_14 + M0_BAI_16 +
M0_BAI_17 Autonomic=~ M0_BAI_2 + M0_BAI_18 + M0_BAI_20 + M0_BAI_21 Neuromotor=~
M0_BAI_1 + M0_BAI_3 + M0_BAI_6 + M0_BAI_8 + M0_BAI_12 + M0_BAI_13 + M0_BAI_19
Panic=~ M0_BAI_7 + M0_BAI_11 + M0_BAI_15
Overall =~ M0_BAI_1 + M0_BAI_2 + M0_BAI_3 + M0_BAI_4 + M0_BAI_5 + M0_BAI_6 + M0_BAI_7 +
M0_BAI_8 +
M0_BAI_9 + M0_BAI_10 + M0_BAI_11 + M0_BAI_12 + M0_BAI_13 + M0_BAI_14 + M0_BAI_15 +
M0_BAI_16 +
M0_BAI_17 + M0_BAI_18 + M0_BAI_19 + M0_BAI_20 + M0_BAI_21
Overall ~~ 0*Subjective
Overall ~~ 0*Autonomic
Overall ~~ 0*Neuromotor
Overall ~~ 0*Panic
```

```
M0_BAI_12 ~~ M0_BAI_13'

#### Fitting the models using robust maximum likelihood estimation, because of missing responses in the dataset.

fit1 <- cfa(Beck2Factor, estimator = "MLR", data = D, missing="fiml")
summary(fit1, fit.measures = TRUE, standardized = TRUE)
modindices(fit1, sort=TRUE)

fit2 <- cfa(Osman4Factor, estimator = "MLR", data = D, missing="fiml")
summary(fit2, fit.measures = TRUE, standardized = TRUE)
modindices(fit2, sort=TRUE)

fit3 <- cfa(Steer2Factor, estimator = "MLR", data = D, missing="fiml")
summary(fit3, fit.measures = TRUE, standardized = TRUE)
modindices(fit3, sort=TRUE)

fit4 <- cfa(Steer2FactorAdjust, estimator = "MLR", data = D, missing="fiml")
summary(fit4, fit.measures = TRUE, standardized = TRUE)
modindices(fit4, sort=TRUE)

fit4 <- cfa(Steer2FactorAdjust2, estimator = "MLR", data = D, missing="fiml")
summary(fit4, fit.measures = TRUE, standardized = TRUE)
modindices(fit4, sort=TRUE)

fit5 <- cfa(Steer2FactorAdjust3, estimator = "MLR", data = D, missing="fiml")
summary(fit5, fit.measures = TRUE, standardized = TRUE)
modindices(fit5, sort=TRUE)

fit6 <- cfa(Steer2FactorAdjust4, estimator = "MLR", data = D, missing="fiml")
summary(fit6, fit.measures = TRUE, standardized = TRUE)
modindices(fit6, sort=TRUE)

fit7 <- cfa(Steer2FactorAdjust5, estimator = "MLR", data = D, missing="fiml")
summary(fit7, fit.measures = TRUE, standardized = TRUE)
modindices(fit7, sort=TRUE)

fit8 <- cfa(Osman4FactorAdjust, estimator = "MLR", data = D, missing="fiml")
summary(fit8, fit.measures = TRUE, standardized = TRUE)
modindices(fit8, sort=TRUE)

fit9 <- cfa(Osman4FactorAdjust2, estimator = "MLR", data = D, missing="fiml")
summary(fit9, fit.measures = TRUE, standardized = TRUE)
modindices(fit9, sort=TRUE)

fit10 <- cfa(Osman4FactorAdjust3, estimator = "MLR", data = D, missing="fiml")
summary(fit10, fit.measures = TRUE, standardized = TRUE)
modindices(fit10, sort=TRUE)
```

Supplementary table S3. Associations between symptom dimensions of the BAI and Mortality, Hospitalization rate & Quality of Life

Sequential modelling	Autonomic	Neurophysiologic	Panic	Subjective
Mortality (HR + 95%CI)				
1. Univariable / Crude	1.05 (0.75-1.47) p=0.786	1.48 (1.05-2.08) p=0.024	1.45 (1.04-2.04) p=0.031	0.89 (0.63-1.25) p=0.500
4. + Dialysis, comorbidity, laboratory	1.20 (0.80-1.81) p=0.377	1.43 (0.97-2.12) p=0.075	1.75 (1.18-2.60) p=0.006	1.00 (0.67-1.50) p=0.998
Hospitalization (RR + 95%CI)				
1. Univariable / Crude	1.24 (1.05-1.45) p=0.009	1.71 (1.45-2.02) p<0.001	1.37 (1.17-1.62) p<0.001	1.07 (0.91-1.26) p=0.386
4. + Dialysis, comorbidity, laboratory	1.18 (0.97-1.42) p=0.093	1.52 (1.25-1.84) p<0.001	1.36 (1.12-1.64) p=0.002	1.06 (0.88-1.29) p=0.545

Stepwise sequential modeling approach to investigate the associations of depressive symptoms with adverse clinical outcomes using cut-off values.
The median value is used for the cognitive and somatic scores and BAI≥16 for the general score.
Social characteristics include: Children, Paid Job, Education, Married
Dialysis characteristics include: Dialysis vintage, dialysis modality (HD vs PD), Incident or Prevalent, DAVIES comorbidity (0-7)
Laboratory measures include: Hemoglobin, Albumin, Kt/V, Calcium

Supplementary table S4. Association between symptom dimensions of the BAI and adverse clinical outcomes using continuous BAI scores

Sequential modelling	General BAI score	Somatic anxiety dimension	Subjective anxiety dimension
Mortality (HR + 95%CI)	1.018 (1.001-1.034) p=0.034	1.032 (1.009-1.056) p=0.006	0.993 (0.954-1.035) p=0.751
Hospitalization (RR + 95%CI)	1.021 (1.013-1.028) p<0.001	1.032 (1.021-1.043) p<0.001	1.030 (1.012-1.047) p<0.001
Quality of Life (beta + 95%CI)	-.864 (-.987--.740) p<0.001	-1.211 (-1.390--1.032) p<0.001	-1.532 (-1.827--1.238) p<0.001

Supplementary table S5. Interactions between symptom dimensions and their association with Mortality & Hospitalization

Sequential modelling	**↓ Somatic ↓ Subjective**	**↓ Somatic ↑ Subjective**	**↑ Somatic ↓ Subjective**	**↑ Somatic ↑ Subjective**
Mortality (HR + 95%CI)				
1. Univariable / Crude	1.0 (reference)	0.59 (0.25-1.39) p=0.229	1.64 (1.01-2.65) p=0.046	1.39 (0.91-2.14) p=0.132
4. + Dialysis, comorbidity, laboratory	1.0 (reference)	0.54 (0.16-1.79) p=0.312	1.71 (0.99-3.0) p=0.053	1.49 (0.90-2.47) p=0.122
Hospitalization (RR + 95%CI)				
1. Univariable / Crude	1.0 (reference)	0.87 (0.59-1.26) p=0.866	1.77 (1.40-2.23) p<0.001	1.63 (1.33-2.01) p<0.001
4. + Dialysis, comorbidity, laboratory	1.0 (reference)	0.90 (0.59-1.39) p=0.640	1.52 (1.17-1.99) p=0.002	1.47 (1.16-1.87) p=0.001

Stepwise sequential modeling approach to investigate the associations of depressive symptoms with adverse clinical outcomes using cut-off values.
The median value is used for the cognitive and somatic scores and BAI≥16 for the general score.
Social characteristics include: Children, Paid Job, Education, Married
Dialysis characteristics include: Dialysis vintage, dialysis modality (HD vs PD), Incident or Prevalent, DAVIES comorbidity (0-7)
Laboratory measures include: Hemoglobin, Albumin, Kt/V, Calcium

Chapter 5

Symptom dimensions of anxiety and depression in patients on Peritoneal dialysis compared to Hemodialysis.

Nadort E, Schouten RW, Luijkx X, Chandie Shaw P, van Ittersum FJ, Smets YFC, Vleming LJ, Dekker FW, Broekman BFP, Siegert CEH.

Submitted

Abstract

Objective: Differences in symptom burden, treatment satisfaction and autonomy between peritoneal dialysis (PD) and hemodialysis (HD) patients could be reflected by a difference in symptom dimensions of anxiety and depression. The aim of this study is to assess differences in prevalence and symptom dimensions of anxiety and depression between PD and HD patients.

Methods: Baseline data from the Depression Related Factors and Outcomes in Dialysis Patients With Various Ethnicities and Races Study (DIVERS) were used. Symptoms of anxiety and depression were measured with the Beck Anxiety Inventory (BAI) and Beck Depression Inventory – second edition (BDI-II). Linear and logistic regression models were used to compare BAI and BDI-II total scores and somatic and subjective/cognitive symptom dimension scores between PD and HD patients, adjusted for potential confounders.

Results: In total, 84 PD and 601 HD patients were included. Clinically significant symptoms of anxiety and depression were present in respectively 22% and 43% of the patients, with no differences between dialysis modality. Both modalities scored high on the somatic symptom dimensions and on individual somatic items of the BAI and BDI-II. Almost all patients reported symptoms related to loss of energy and sleep.

Conclusions: No differences in symptom dimensions of anxiety and depression were found between PD and HD patients. The high prevalence of somatic symptom dimensions in both groups underscores the possible interaction between somatic and psychiatric symptoms in dialysis patients, and the need for early recognition and treatment of symptoms of anxiety and depression regardless of treatment modalities.

Introduction

In the dialysis population, symptoms of anxiety and depression are highly common with a prevalence range of 27% to 53% for anxiety and 29% to 42% for depression.(1-3) These symptoms are associated with impaired quality of life, treatment non-adherence and adverse clinical outcomes such as hospitalization and mortality.(3-7) Despite the high burden and negative consequences, symptoms of anxiety and depression in dialysis patients are often not recognized and treated.(8, 9) Several factors have been associated with anxiety and depression, including physiological, psychological and dialysis-related factors.(10) However, the impact of dialysis modality on symptoms of anxiety and depression remains unclear.(10, 11)

In general, peritoneal dialysis (PD) patients report lower burden of kidney disease, are more satisfied with treatment, have greater opportunities for control and autonomy and report that dialysis has less impact on daily life than hemodialysis (HD) patients.(7, 12) On the other hand, PD patients experience a greater burden of daily commitment compared to the intermittent nature of HD.(11, 13) The choice for either treatment modality is influenced by comorbidities, such as the ability to tolerate volume shifts related to cardiac condition, socioeconomic factors, such as the home situation of the patient, and patient's preferences.(14) Despite these differences, quality of life is found to be comparable between PD and HD patients.(7, 11, 13) Studies comparing PD and HD patients on symptoms of anxiety are scarce, with one study finding higher anxiety scores in HD patients,(13) and one study finding comparable rates of anxiety in HD and PD patients.(11) A recent meta-analysis found that there was limited and deficient quality evidence on the association between dialysis modalities and depression for any conclusions to be made.(15) However, depressive symptoms in PD patients are associated with an increased risk of peritonitis and technique failure.(16, 17)

Symptoms of anxiety and depression can overlap with each other and with symptoms of chronic renal failure and dialysis therapy itself.(3) The complex interplay between biological, psychological and social factors makes it difficult to isolate psychiatric symptoms from symptoms of the somatic disease and dialysis.(18) The difference in symptom burden, treatment satisfaction and autonomy between PD and HD patients could be reflected by a difference in symptom dimensions and symptom profile of anxiety and depression between these modalities. Constructs of symptom dimensions that are described in the literature are a somatic and subjective symptom dimension for anxiety and a somatic and cognitive symptom dimension for depression.(19-22). More insight in the differences of anxiety and depression between dialysis modalities on a symptom dimension and individual symptom level may lead to better understanding of various clinical presentations of these common psychiatric symptoms in specific subgroups and may enhance personalized care in dialysis patients.

The aim of this study is to assess the differences in prevalence, somatic and subjective/cognitive symptom dimensions and individual symptoms of anxiety and depression between PD and HD patients.

Methods

Study design

Baseline data was used from the Depression-In-Various-Ethnicities-and-Races-Study (DIVERS). This multicenter observational prospective cohort study included prevalent and incident patients receiving maintenance HD or PD in 10 Dutch dialysis centers from June 2012 till September 2016. Patients were included if they were above 18 years old and received dialysis treatment for at least 90 days. Patients were excluded if they were unable to fill in the questionnaire due to impaired cognitive skills or language restrictions. The questionnaires were available in Dutch, English, Turkish and Arabic to improve generalizability. Written informed consent was obtained from all participants before inclusion. The study complies with the rules of the Declaration of Helsinki and was approved by the medical ethics committee of the VU University Medical Center (approval number: 2010/064).

Demographic and clinical characteristics

Demographic and clinical characteristics were collected from electronic patient files and through self-reported questionnaires. Immigrant status was defined by using the country of birth of both the patient and biological parents. Davies comorbidity index was used to define the level of comorbidities, which is based on the presence or absence of seven comorbid conditions, divided in three groups; low, moderate or high comorbidity.(23) The primary cause of kidney disease was classified according to the ERA-EDTA coding system (European Renal Association European Dialysis and Transplant Association) and divided into four groups; renal vascular disease, diabetes nephropathy, glomerulonephritis and other.

Anxiety and depression

Symptoms of anxiety were measured with the Beck Anxiety Inventory (BAI) and symptoms of depression were measured with the Beck Depression Inventory – second edition (BDI-II).(24, 25) Both questionnaires consist of 21 items which rate the severity of common somatic and cognitive symptoms of anxiety and depression from 0 (not at all) to 3 (severely), with a maximum score of 63 and a higher score indicating more severe anxiety or depression. The BAI has been validated in a large variety of cohorts, including somatically ill patients. A cutoff value of □ 16 for the BAI was used based on the manual by Beck and Steer, indicating clinically relevant anxiety. The BDI-II has been widely used in dialysis patients and a cut-off value of □ 13, as validated in dialysis patients, was used for clinically relevant depression.(26)

Symptom dimensions

There are several constructs of factorial structure or symptom dimensions of the BAI and BDI-II described in the literature in different patient populations.(19-21, 27) However, literature from the dialysis population is scarce.(22) Recently, our study group identified a somatic and subjective dimension for anxiety (measured with the BAI) and a somatic and cognitive dimension for depression (measured with the BDI-II in the DIVERS cohort.(28, 29) These identified constructs were used to determine differences in symptom dimensions between PD and HD patients in the present study.

Statistical Analysis

Standard descriptive statistics were used to present baseline characteristics. Mean differences (MD) in continuous BAI and BDI-II total scores and of symptom dimension scores between PD and HD patients at baseline were analyzed with linear regression models. Multivariable analysis was performed sequentially to adjust for potential confounding. The first step included age, sex and ethnicity, the second step included marital state, having children and current employment and the final step included the Davies comorbidity index. Logistic regression models were used to compare the percentage of patients scoring above the predefined cutoff scores for clinically relevant anxiety and depression and the percentages of patients scoring 1 or higher on the different symptom dimensions between PD and HD patients. The prevalence and mean scores of individual BAI and BDI-II items were calculated for PD and HD patients separately.

Missing data

Participants had the option to take part in a non-questionnaire part of the study. These patients gave consent for extracting information from their electronic patient file only without filling out self-reported questionnaires. By collecting characteristics of patients who otherwise would have been excluded, we aimed to maximize generalizability. To avoid bias, missing BAI and BDI-II items were imputed by using multiple imputation techniques (10 repetitions). Complete case sensitivity analysis was performed on questionnaires with no missing items. All statistical analysis were performed using SPSS for Windows, version 26 (IBM Corp).

Results

Baseline Characteristics

A total of 685 dialysis patients were included of which 84 received PD and 601 received HD therapy. Baseline characteristics for all patients and stratified by dialysis modality are presented in **Table 1**. Mean age in the total cohort was 64 ± 15 years, 62% of patients were men and 48% of patients were immigrants. The cohort consisted of 253 (37%) incident dialysis patients and 433 (63%) prevalent patients who had a median dialysis vintage of 13 months (interquartile range [IQR] = 4-47). Patients receiving HD had a higher prevalence in diabetes (43% versus 35%) and more often a high Davies comorbidity score (19% versus 9%) compared to patients receiving PD. PD patients had a higher percentage of employment (20 vs 10%), had

more often residual diuresis (88 versus 69%) and were more often on the waiting list for transplantation (42 versus 28%) compared to HD patients. No major differences were found in age, gender, social characteristics, primary cause of kidney disease, prevalence of cardiovascular disease or previous psychiatric care for depression.

Anxiety and depression

Mean score of the BAI for all patients was 10.8 (standard deviation (SD) 9.9) with a crude mean difference of 0.2 (95% confidence interval (CI) = -2.4; 2.9) between PD and HD patients (**Table 2**). Overall, 159 patients (23%) had clinically significant anxiety symptoms (BAI score $\geq$ 16). In the PD group, 19% scored above 16 on the BAI and in the HD group 24% (crude odds ratio (OR) = 0.7, 95%CI = 0.4; 1.4).

Mean BDI-II score of all patients was 12.9 (SD 9.6), crude mean difference between PD and HD patients was 0.1 (95%CI = -2.5; 2.6). In the total cohort, 282 patients (41%) had clinically significant depressive symptoms (BDI-II score $\geq$ 13)(**Table 2**). Of PD patients, 44% scored above 13 on the BDI-II, for HD patients this was 41% (crude OR=1.2, 95%CI = 0.7; 2.0).

When confounders were stepwise introduced into the model for the BAI and BDI-II both as continuous scores as well as using the predefined cutoff scores, only minor changes were seen in the regression coefficients and the odds ratios (**Table 2**). No clinically or statistically significant differences were found in the prevalence and severity of anxiety and depression between PD and HD patients.

Table 1. Baseline characteristics

Characteristic	All patients (n=685)	PD (n=84)	HD (n=601)
Demographic			
Age, years	64 ± 15	64 ± 14	65 ± 16
Male sex	424 (62%)	53 (63%)	370 (62%)
Immigrant*	300 (48%)	33 (46%)	267 (48%)
Country of birth			
European	366 (58%)	42 (58%)	324 (58%)
Sub-Saharan Africa	22 (4%)	0 (0%)	22 (4%)
Northern Africa/Western Africa	54 (9%)	4 (6%)	50 (9%)
Southern Asia/Western Asia	57 (9%)	11 (15%)	46 (8%)
South America/Caribbean	131 (21%)	15 (21%)	116 (21%)
Social			
Married	316 (52%)	40 (56%)	276 (52%)
Has Children	474 (78%)	56 (78%)	418 (78%)
Low formal education**	220 (36%)	22 (31%)	198 (37%)
Not employed	534 (89%)	57 (80%)	477 (90%)
Renal and dialysis			
Incident dialysis patients***	253 (37%)	27 (32%)	225 (37%)
Vintage of prevalent group, months	13 [4 - 47]	10 [5-35]	14 [4-47]
Primary kidney disease			
Renal vascular disease	163 (26%)	18 (25%)	145 (26%)
Diabetic nephropathy	155 (24%)	15 (21%)	140 (25%)
Glomerulonephritis	70 (11%)	12 (17%)	58 (10%)
Other	247 (39%)	27 (38%)	220 (39%)
Kt/V_{urea}	4.0 ± 1.1	2.2 ± 0.7	4.2 ± 1.1
Residual diuresis > 100 mL/24h	488 (71%)	74 (88%)	414 (69%)
On waiting list for kidney transplantation	203 (30%)	35 (42%)	168 (28%)
Clinical			
Davies comorbidity score			
Low comorbidity	183 (27%)	22 (28%)	161 (27%)
Moderate comorbidity	370 (55%)	51 (64%)	319 (54%)
High comorbidity	119 (18%)	7 (9%)	112 (19%)
Comorbid conditions			
Diabetes mellitus	288 (42%)	29 (35%)	259 (43%)
Cardiovascular disease	541 (79%)	65 (77%)	476 (79%)
Current alcohol use	161 (27%)	27 (39%)	134 (25%)
Current smoking	108 (18%)	11 (16%)	97 (19%)
Laboratory			
Hemoglobin (mmol/L)	7.1 ± 0.8	7.1 ± 0.8	7.1 ± 0.8
Albumin (g/L)	37.0 ± 5.3	35.5 ± 5.0	37.3 ± 5.3
Phosphate (mmol/L)	1.6 ± 0.5	1.6 ± 0.4	1.6 ± 0.5
Parathyroid hormone (pmol/L)	34.1 ± 26.8	32.9 ± 24.2	34.3 ± 27.2
Psychiatric			
History of major depression	27 (4%)	3 (4%)	24 (4%)
Receiving psychological care	24 (4%)	3 (4%)	21 (4%)
Use of psychofarmaca	65 (10%)	8 (10%)	57 (10%)

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

Abbreviations: Kt/V_{urea}, dialyser clearance of urea * dialysis time / volume of distribution of urea.

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

**Low formal education: highest level of education is high school or less.

***Less than 180 days on dialysis.

Table 2. Differences in BAI and BDI-II scores and prevalence of clinically significant symptoms of anxiety and depression between HD and PD patients at baseline (crude and multivariable model).

	All patients n = 685	**PD n = 84**	**HD n = 601**	**MD (95%CI) / OR (95%CI)***	**p**
Anxiety (BAI)					
Mean ± SD	10.8 ± 9.9	10.4 ± 9.0	10.8 ± 10.0		
1. Univariable/crude				0.2 (-2.4; 2.9)	0.87
2. + Age, sex, ethnicity				0.1 (-2.5; 2.8)	0.91
3. + Social characteristics				-0.2 (-2.8; 2.4)	0.86
4. + Comorbidity				-0.4 (-2.9; 2.2)	0.80
BAI ≥ 16*	159 (23%)	16 (19%)	142 (24%)		
1. Univariable/crude				0.7 (0.4; 1.4)	0.35
2. + Age, sex, ethnicity				0.7 (0.4; 1.4)	0.35
3. + Social characteristics				0.8 (0.4; 1.5)	0.45
4. + Comorbidity				0.8 (0.4; 1.6)	0.58
Depression (BDI-II)					
Mean ± SD	12.9 ± 9.6	12.9 ± 8.7	12.9 ± 9.7		
1. Univariable/crude				0.1 (-2.5; 2.6)	0.97
2. + Age, sex, ethnicity				0.0 (-2.5; 2.5)	0.99
3. + Social characteristics				-0.2 (-2.7; 2.3)	0.86
4. + Comorbidity				-0.3 (-2.8; 2.2)	0.79
BDI-II ≥ 13*	282 (41%)	37 (44%)	244 (41%)		
1. Univariable/crude				1.2 (0.7; 2.0)	0.54
2. + Age, sex, ethnicity				1.2 (0.7; 2.0)	0.51
3. + Social characteristics				1.2 (0.7; 2.1)	0.47
4. + Comorbidity				1.2 (0.7; 2.1)	0.46

Abbreviations: HD, hemodialysis; PD, peritoneal dialysis; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory – second edition; MD, mean difference; OR, odds ratio.
*logistic regression was used for the pre-defined cut-off values and results are presented as OR.

Symptom dimensions

Mean score on the somatic symptom dimension of anxiety in PD patients was 7.3 (SD 6.3) and in HD patients 7.5 (SD 6.8) (adjusted mean difference -0.3 (95%CI =-2.1; 1.5) (**Table 3**). Subjective symptom dimension mean scores were 3.1 (SD 3.1) in PD patients and 3.3 (SD 3.3) in HD patients (adjusted mean difference 0.0 (95%CI = -1.1; 1.1). In both groups, almost all patients (92%) had a score of ≥ 1 on the somatic symptom dimension and 70% of patients scored ≥ 1 on the subjective symptom dimension, with no difference between the groups.

For depression, mean score on the somatic symptom dimensions in PD patients was 6.8 (SD 3.1) and in HD patients 6.5 (SD 3.6) (adjusted mean difference -0.6 (95%CI = -1.5; 0.3) (**Table**

3). Mean score of the cognitive symptom dimensions was 6.1 (SD 6.1) in PD patients and 6.3 (SD 6.3) in HD patients (adjusted mean difference 0.3 (95%CI = -1.6; 2.1). Both the somatic symptom dimension (97%) and the cognitive dimension (83%) were scored ≥ 1 by the majority of the patients.

Table 3. Differences in symptom dimensions scores of the BAI and BDI-II s between HD and PD patients at baseline (crude model and multivariable model).

	All patients n = 685	**PD n = 84**	**HD n = 601**	**MD (95%CI) / OR (95%CI)***	**p**
Anxiety (BAI)					
Somatic dimension					
- Mean ± SD	7.5 ± 6.8	7.3 ± 6.3	7.5 ± 6.8		
1. Univariable/crude				0.4 (-1.8; 1.9)	0.97
2. + Age, sex, ethnicity				0.0 (-1.8; 1.8)	0.98
3. + Social characteristics				-0.3 (-2.1; 1.5)	0.77
4. + Comorbidity				-0.3 (-2.1; 1.5)	0.71
- Prevalence (% ≥ 1)*	631 (92%)	75 (89%)	555 (92%)		
1. Univariable/crude				0.7 (0.3; 1.5)	0.31
2. + Age, sex, ethnicity				0.7 (0.3; 1.5)	0.33
3. + Social characteristics				0.7 (0.3; 1.6)	0.37
4. + Comorbidity				0.6 (0.3; 1.5)	0.30
Subjective dimension					
- Mean ± SD	3.3 ± 3.3	3.1 ± 3.1	3.3 ± 3.3		
1. Univariable/crude				0.2 (-0.9; 1.3)	0.75
2. + Age, sex, ethnicity				0.2 (-0.9; 1.2)	0.76
3. + Social characteristics				0.0 (-1.0; 1.1)	0.95
4. + Comorbidity				0.0 (-1.1; 1.1)	0.97
- Prevalence (% ≥ 1)*	478 (70%)	58 (69%)	421 (70%)		
1. Univariable/crude				1.0 (0.6; 1.8)	0.95
2. + Age, sex, ethnicity				1.0 (0.6; 1.8)	0.91
3. + Social characteristics				1.1 (0.6; 1.9)	0.86
4. + Comorbidity				1.1 (0.6; 1.9)	0.86
Depression (BDI-II)					
Somatic dimension					
- Mean ± SD	6.6 ± 3.5	6.8 ± 3.1	6.5 ± 3.5		
1. Univariable/crude				-0.4 (-1.3; 0.5)	0.37
2. + Age, sex, ethnicity				-0.5 (1.4; 0.4)	0.30
3. + Social characteristics				-0.5 (-1.5; 0.4)	0.24
4. + Comorbidity				-0.6 (-1.5; 0.3)	0.21

Table 3 (continued)

	All patients n = 685	PD n = 84	HD n = 601	MD (95%CI) / OR (95%CI)*	p
- Prevalence (% ≥ 1)*	664 (97%)	83 (99%)	580 (97%)		
1. Univariable/crude				2.7 (0.3; 20.1)	0.35
2. + Age, sex, ethnicity				2.7 (0.4; 20.5)	0.34
3. + Social characteristics				2.9 (0.4; 22.4)	0.31
4. + Comorbidity				2.8 (0.4; 21.8)	0.33
Cognitive dimension					
- Mean ± SD	6.3 ± 6.3	6.1 ± 6.1	6.3 ± 6.3		
1. Univariable/crude				0.5 (-1.4; 2.4)	0.63
2. + Age, sex, ethnicity				0.5 (1.4; 2.3)	0.63
3. + Social characteristics				0.3 (-1.5; 2.2)	0.73
4. + Comorbidity				0.3 (-1.6; 2.1)	0.79
- Prevalence (% ≥ 1)*	574 (83%)	74 (88%)	500 (83%)		
1. Univariable/crude				1.3 (0.6; 2.8)	0.47
2. + Age, sex, ethnicity				1.3 (0.6; 2.8)	0.45
3. + Social characteristics				1.3 (0.6; 2.8)	0.47
4. + Comorbidity				1.3 (0.6; 2.8)	0.45

Abbreviations: HD, hemodialysis; PD, peritoneal dialysis; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory – second edition; SD, standard deviation; MD, mean difference; OR, odds ratio.
Note: BAI somatic symptom dimension maximum score = 42, subjective symptom dimension maximum score = 21. BDI-II somatic symptom dimension maximum score = 18, cognitive symptom dimension maximum score = 45.
*Percentage of patients scoring 1 or higher on symptom dimension.

Individual symptoms

Table 4 describes the prevalence and severity of individual items of the BAI in PD and HD patients. Of the somatic anxiety symptoms, more than half of both PD and HD patients experience faintness (PD 64% and HD 53%), dizziness or lightheadedness (55% and 53%) and unsteadiness (51% and 53%), but PD patients more often experience abdominal discomfort (45% versus 33%) and HD patients experience more numbness or tingling (49% versus 42%). The most severe and prevalent subjective anxiety symptoms in both PD and HD patients were nervousness (44% and 42%), being unable to relax (43% and 40%) and fear of the worst happening (42% and 39%).

Table 4. Prevalence and mean score of BAI items in PD and HD patients in this cohort.

Symptoms scored in the BAI, listed by decreasing prevalence in PD	**% of PD patients with this symptom** (marker for prevalence)	**Mean ± SD** (marker for severity)	**% of HD patients with this symptom** (marker for prevalence)	**Mean ± SD** (marker for severity)
Somatic dimension*				
Faintness	64%	0.85 ± 60.9	53%	0.77 ± 0.88
Dizziness or lightheaded	55%	0.77 ± 0.84	53%	0.78 ± 0.91
Unsteadiness	51%	0.70 ± 0.80	53%	0.81 ± 0.94
Stomach pains or abdominal discomfort	45%	0.64 ± 0.80	33%	0.50 ± 0.83
Wobbly legs	43%	0.63 ± 0.83	40%	0.62 ± 0.90
Numbness or tingling	42%	0.63 ± 0.90	49%	0.79 ± 0.96
Heart pounding or racing	40%	0.63 ± 0.85	40%	0.55 ± 0.79
Feeling hot	36%	0.51 ± 0.78	36%	0.54 ± 0.81
Shaking hands	36%	0.52 ± 0.79	33%	0.47 ± 0.77
Difficulty with breathing	36%	0.47 ± 0.70	30%	0.39 ± 0.67
Trembling	31%	0.39 ± 0.62	30%	0.41 ± 0.72
Sweating (not due to feeling warm)	23%	0.35 ± 0.70	25%	0.40 ± 0.79
Hot or flushed face	23%	0.27 ± 0.51	24%	0.35 ± 0.69
Chocking sensation	12%	0.14 ± 0.39	17%	0.27 ± 0.66
Subjective dimension*				
Nervous	44%	0.62 ± 0.80	42%	0.59 ± 0.82
Unable to relax	43%	0.54 ± 0.70	40%	0.62 ± 0.90
Fear of the worst happening	42%	0.63 ± 0.88	39%	0.64 ± 0.94
Fear of losing control	37%	0.46 ± 0.65	27%	0.42 ± 0.78
Scared	27%	0.36 ± 0.64	27%	0.41 ± 0.79
Fear of dying	23%	0.38 ± 0.80	25%	0.42 ± 0.82
Terrified	15%	0.19 ± 0.43	19%	0.33 ± 0.75

Note: Presence of symptoms are scored as yes when the score is ≥ 1 (including mild, moderate and severe)
*According to the Schouten model of somatic-subjective symptoms for the BAI.(29)

Almost all patients reported to experience the somatic depressive symptoms loss of energy (PD 94% and HD 89%), fatigue (94% and 84%) and changes in sleeping (83% and 73%)(**Table 5**). Concerning cognitive depressive symptoms, more than half of the patients experience loss of pleasure (61% and 53%) and almost one third of patients experience loss of interest (32% and 35%) and feelings of sadness or a depressed mood (26% and 27%).

Table 5. Prevalence and mean score of BDI-II items in PD and HD patients in this cohort.

Symptoms scored in the BDI-II, listed by decreasing prevalence in PD	**% of PD patients with this symptom** (marker for prevalence)	**Mean ± SD** (marker for severity)	**% of HD patients with this symptom** (marker for prevalence)	**Mean ± SD** (marker for severity)
Somatic dimension*				
Loss of energy	94%	1.47 ± 0.79	89%	1.37 ± 0.82
Fatigue	94%	1.38 ± 0.76	84%	1.27 ± 0.87
Changes in sleeping	83%	1.25 ± 0.84	73%	1.10 ± 0.90
Loss of libido	77%	1.36 ± 1.03	70%	1.36 ± 1.16
Change in appetite	65%	0.88 ± 0.79	60%	0.83 ± 0.82
Concentration	44%	0.57 ± 0.69	47%	0.620 ± 0.76
Cognitive dimension*				
Loss of pleasure	61%	0.79 ± 0.75	53%	0.73 ± 0.82
Pessimism	40%	0.62 ± 0.92	47%	0.76 ± 0.97
Irritability	40%	0.45 ± 0.56	34%	0.47 ± 0.74
Agitation	39%	0.51 ± 0.73	32%	0.42 ± 0.70
Crying	38%	0.60 ± 0.90	30%	0.47 ± 0.84
Self-dislike	36%	0.46 ± 0.65	28%	0.39 ± 0.70
Loss of interest	32%	0.43 ± 0.71	35%	0.49 ± 0.78
Indecisiveness	32%	0.51 ± 0.87	33%	0.50 ± 0.82
Self-criticalness	31%	0.43 ± 0.73	31%	0.44 ± 0.76
Sadness	26%	0.31 ± 0.58	27%	0.40 ± 0.75
Guilt	20%	0.27 ± 0.59	16%	0.23 ± 0.59
Worthlessness	19%	0.26 ± 0.61	28%	0.39 ± 0.70
Sense of failure	15%	0.30 ± 0.74	19%	0.34 ± 0.76
Punishment	14%	0.35 ± 0.93	14%	0.29 ± 0.82
Suicidal ideas	5%	0.07 ± 0.31	11%	0.15 ± 0.48

Note: Presence of symptoms are scored as yes when the score is ≥ 1 (including mild, moderate and severe).
*According to the Schouten model of somatic-cognitive symptoms for the BDI-II.(28)

Missing data

Baseline demographic and clinical variables had <5% missing values. The overall percentage of missing items on the BAI was 7.8% and on the BDI was 4.6%. Of the total cohort, 8% of patients participated in the non-questionnaire part of the study. Complete BAI was available of 508 patients and complete BDI-II of 533 patients. Complete case sensitivity analysis showed no major differences compared to the main analysis using multiple imputation.

Discussion

This study assessed the differences in prevalence, somatic and subjective/cognitive symptom dimensions and individual symptoms of anxiety and depression between PD and HD patients. Despite the known difference in symptom burden, treatment satisfaction and autonomy between the two dialysis modalities, clinically relevant symptoms of anxiety and depression were highly prevalent in both PD and HD patients and no differences in prevalence or severity were found between these groups. In both groups, the somatic symptom dimensions of both anxiety and depression were more prevalent and more severe than the subjective anxiety symptom dimension or cognitive depression symptom dimension. The most prevalent somatic symptoms of anxiety and depression in both PD and HD patients were related to faintness, fatigue and loss of energy, which may underscore the interplay between mental and physical health.

Prevalence of anxiety and depression

In our cohort, symptoms of anxiety and depression were highly prevalent in both PD and HD patients. Anxiety in dialysis patients can be triggered by the activities of attending dialysis or the dialysis treatment itself, for instance by the dialysis machine alarming in HD treatment.(30, 31) Depression in dialysis patients can be triggered by grief over the loss of a normal life, an uncertain future with dreading complications and mortality and guilt of burdening family members.(30) A recent study found different perspectives on anxiety and depression between PD and HD patients. Whereas HD patients had major concerns about the lack of control over management, feeling enslaved to a machine, feeling confined to the dialysis schedule and the healthcare system and being concerned about the risk of symptomatic hypotension on dialysis, PD patients, on the other hand, felt vulnerable in being solely responsible for dialysis and protecting independence, felt guilt and self-blame over complications and were particularly concerned about the risk of peritonitis.(30)

Although the dialysis modality related triggers of anxiety and depression seem to differ according to the literature, we did not find a difference in prevalence or symptom dimensions of anxiety and depression between PD and HD patients. A possible explanation for this finding might be that both our groups are very similar in demographic, social and clinical characteristics, making their other risk factors for anxiety and depression, besides dialysis modality, comparable. Previous studies show that HD patients are more likely to be older and to have a history of vascular disease, cardiac disease and cancer compared to PD patients. Indeed, these diseases are barriers to start PD.(32) It is possible that we did not find these differences in patient characteristics between PD and HD patients in our sample because living kidney donation has increased in the Netherlands before and during our study period. Younger patients with less comorbidities who would have been more likely to start PD, might have received a living kidney transplant before initiating dialysis therapy. It would be interesting to further investigate the effect of dialysis modality on symptom dimensions in samples from

other countries with different health systems, with possibly more differences in sociodemographic and clinical characteristics between PD and HD patients.

Symptom dimensions

Somatic symptoms of anxiety and depression measured by the BAI and BDI-II overlap with symptoms of kidney failure and dialysis therapy, which might be an explanation of the high number of patients scoring on the somatic symptom dimensions of anxiety and depression in our cohort. However, studies have shown that exclusion of somatic symptoms in the BDI-II does not lead to a better screening performance.(33) Also, the associations between the somatic symptom dimensions of anxiety and depression and increased mortality risk in dialysis patients are independent of somatic comorbidities and other clinical variables.(28, 29) This underscores that interpretation of these somatic symptoms as being only related to chronic kidney disease and dialysis therapy is short-sighted, as physical and mental health are in complex interaction with each other. Furthermore, the core features of depression from the cognitive symptom dimension, depressed mood and loss of pleasure and interest, and the subjective dimension of anxiety are also present in the majority of patients. Is it possible that the high prevalence of somatic symptoms of anxiety and depression might be a cause of the underrecognition of these mental health problems in dialysis patients.

Individual symptoms

Interestingly, almost all patients in our study cohort reported somatic depressive symptoms related to energy, fatigue and sleep (73-94%). A recent systematic review on dialysis patients experiences of sleep underlines the magnitude of sleeping problems and lack of energy in this population.(34) Overwhelming exhaustion can lead to the depletion of the sense of control and capacity to do daily activities due to lack of energy, which might lead to feelings of sadness, guilt and frustration. Sleep disorders are also highly associated with mental health problems, and regarded as one of the most important trans-diagnostic processes influencing mental health.(35) Moreover, sleep disorders influence quality of life due to effects on cognitive, emotional and interpersonal functioning,(36, 37) and can also have effects on general health.(38) There is an important bidirectional association between sleep quality and health: insomnia can be an important symptom, cause or consequence of depression and anxiety.(39) For example, previous studies over the last decades show that insomnia often precedes and exacerbates depression, results in reduced treatment responses and increases relapse rates of depression.(40, 41) As such, it is an important symptom and it is possible that strategies to improve sleep quality might lead to subsequent improvement of anxiety and depression in both PD and HD patients.

Strengths and limitations

The strengths of this study are the relatively large sample size of PD and HD patients, the multicenter nature of the cohort, the use of questionnaires in four languages and the inclusion of a large proportion of ethnic minorities and immigrants, which improves the generalizability

of our results. Also, this is the first study to assess differences in symptom dimensions of anxiety and depression in dialysis patients and to compare individual symptoms between dialysis modalities.

Our study has several limitations that should also be taken in mind when interpreting the results. First, we have assessed anxiety and depression by using self-reported screening questionnaires and with the use of cut off scores for indication of a possible diagnosis of anxiety and depression instead of a clinical diagnosis according to Diagnostic and Statistical Manual of Mental Disorders (DSM) 5. This might lead to overestimation of the prevalence we found. Second, the imbalance in sample size between the HD and PD group may lower our effective sample size. However, this ratio is equal to the percentage of HD and PD in the general dialysis population in the Netherlands. Third, although we used multiple imputation techniques to handle missing data, remaining effect on the validity of the results cannot be excluded. Fourth, although we adjusted for confounding factors in our analysis, it is possible that there is residual confounding between PD and HD patients which might lead to bias in our results. Finally, we used a cutoff score for clinical relevant anxiety of ≥ 16 on the BAI based on the manual by Beck and Steer as there is no published data yet on a validated cutoff score for the BAI in dialysis patients.

Conclusion

In conclusion, symptoms of anxiety and depression are highly prevalent in both PD and HD patients. Although dialysis modalities are known to be different in autonomy and therapy burden, we did not find differences in prevalence or symptom dimensions of anxiety and depression between these groups. This may be related to the fact that in this sample PD and HD patients were comparable with regards to comorbidities and other clinical parameters. The somatic symptom dimensions of both anxiety and depression were more prevalent than the subjective or cognitive symptom dimensions in both PD and HD patients, which is possibly related to the high comorbidity level and the impact on general health status in both the PD and HD sample. Almost all patients experienced symptoms related to loss of energy, fatigue and sleep. Some of these symptoms are not only symptoms of anxiety and depression but can also be a risk factor to develop symptoms of anxiety and depression. Our findings underscore the need for early recognition of somatic symptoms that relate to anxiety and depression in dialysis patients, with the purpose to get proper treatment regardless of treatment modality. Future research should focus on effective treatment for symptoms of anxiety and depression as well as preventative interventions in both HD and PD patients.

References

1. Palmer S, Vecchio M, Craig JC, Tonelli M, Johnson DW, Nicolucci A, Pellegrini F, Saglimbene V, Logroscino G, Fishbane S, Strippoli GF. Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. Kidney Int. 2013;84(1):179-91.
2. Cukor D, Coplan J, Brown C, Friedman S, Cromwell-Smith A, Peterson RA, Kimmel PL. Depression and Anxiety in Urban Hemodialysis Patients. Clin J Am Soc Nephrol. 2007;2(3):484-90.
3. Murtagh FE, Addington-Hall J, Higginson IJ. The prevalence of symptoms in end-stage renal disease: a systematic review. Adv Chronic Kidney Dis. 2007;14(1):82-99.
4. Cukor D, Rosenthal DS, Jindal RM, Brown CD, Kimmel PL. Depression is an important contributor to low medication adherence in hemodialyzed patients and transplant recipients. Kidney Int. 2009;75(11):1223-9.
5. Farrokhi 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.
6. Mok MMY, Liu CKM, Lam MF, Kwan LPY, Chan GCW, Ma MKM, Yap DYH, Chiu F, Choy CBY, Tang SCW, Chan TM. A Longitudinal Study on the Prevalence and Risk Factors for Depression and Anxiety, Quality of Life, and Clinical Outcomes in Incident Peritoneal Dialysis Patients. Perit Dial Int. 2019;39(1):74-82.
7. Brown EA, Zhao J, McCullough K, Fuller DS, Figueiredo AE, Bieber B, Finkelstein FO, Shen J, Kanjanabuch T, Kawanishi H, Pisoni RL, Perl J, Group PPSW. Burden of Kidney Disease, Health-Related Quality of Life, and Employment Among Patients Receiving Peritoneal Dialysis and In-Center Hemodialysis: Findings From the DOPPS Program. Am J Kidney Dis. 2021.
8. Johnson S, Dwyer A. Patient perceived barriers to treatment of depression and anxiety in hemodialysis patients. Clin Nephrol. 2008;69(3):201-6.
9. 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.
10. Goh ZS, Griva K. Anxiety and depression in patients with end-stage renal disease: impact and management challenges - a narrative review. Int J Nephrol Renovasc Dis. 2018;11:93-102.
11. Griva K, Kang AW, Yu ZL, Mooppil NK, Foo M, Chan CM, Newman SP. Quality of life and emotional distress between patients on peritoneal dialysis versus community-based hemodialysis. Qual Life Res. 2014;23(1):57-66.
12. Wuerth DB, Finkelstein SH, Schwetz O, Carey H, Kliger AS, Finkelstein FO. Patients' descriptions of specific factors leading to modality selection of chronic peritoneal dialysis or hemodialysis. Perit Dial Int. 2002;22(2):184-90.
13. Ginieri-Coccossis M, Theofilou P, Synodinou C, Tomaras V, Soldatos C. Quality of life, mental health and health beliefs in haemodialysis and peritoneal dialysis patients: investigating differences in early and later years of current treatment. BMC Nephrol. 2008;9:14.

14. Devoe DJ, Wong B, James MT, Ravani P, Oliver MJ, Barnieh L, Roberts DJ, Pauly R, Manns BJ, Kappel J, Quinn RR. Patient Education and Peritoneal Dialysis Modality Selection: A Systematic Review and Meta-analysis. Am J Kidney Dis. 2016;68(3):422-33.
15. He R, Tung TH, Liu T, Chien CW. A meta-analysis on the relationship between different dialysis modalities and depression in end-stage renal disease patients. Curr Pharm Des. 2021.
16. Lin J, Ye H, Yi C, Li J, Yu X, Zhu L, Zhang X, Wu X, Mao H, Yu X, Yang X. The negative impact of depressive symptoms on patient and technique survival in peritoneal dialysis: a prospective cohort study. Int Urol Nephrol. 2020;52(12):2393-401.
17. Troidle L, Watnick S, Wuerth DB, Gorban-Brennan N, Kliger AS, Finkelstein FO. Depression and its association with peritonitis in long-term peritoneal dialysis patients. Am J Kidney Dis. 2003;42(2):350-4.
18. Kimmel PL. Depression in patients with chronic renal disease: what we know and what we need to know. J Psychosom Res. 2002;53(4):951-6.
19. 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.
20. Osman A, Kopper BA, Barrios FX, Osman JR, Wade T. The Beck Anxiety Inventory: reexamination of factor structure and psychometric properties. J Clin Psychol. 1997;53(1):7-14.
21. Steer RA, Rissmiller DJ, Ranieri WF, Beck AT. Structure of the computer-assisted Beck Anxiety Inventory with psychiatric inpatients. J Pers Assess. 1993;60(3):532-42.
22. Chilcot J, Norton S, Wellsted D, Almond M, Davenport A, Farrington K. A confirmatory factor analysis of the Beck Depression Inventory-II in end-stage renal disease patients. J Psychosom Res. 2011;71(3):148-53.
23. 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.
24. 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.
25. Beck AT SR. Beck Anxiety Inventory Manual: San Antonia, TX: Psychological Corp; 1993.
26. 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.
27. Thombs BD, Ziegelstein RC, Beck CA, Pilote L. A general factor model for the Beck Depression Inventory-II: validation in a sample of patients hospitalized with acute myocardial infarction. J Psychosom Res. 2008;65(2):115-21.
28. Schouten RW, Harmse VJ, Dekker FW, van Ballegooijen W, Siegert CEH, Honig A. Dimensions of Depressive Symptoms and Their Association With Mortality, Hospitalization, and Quality of Life in Dialysis Patients: A Cohort Study. Psychosom Med. 2019;81(7):649-58.
29. Schouten RW, Nadort E, Harmse V, Honig A, van Ballegooijen W, Broekman BFP, Siegert CEH. Symptom dimensions of anxiety and their association with mortality, hospitalization and quality of life in dialysis patients. J Psychosom Res. 2020;133:109995.

30. Nataatmadja M, Evangelidis N, Manera KE, Cho Y, Johnson DW, Craig JC, Baumgart A, Hanson CS, Shen J, Guha C, Scholes-Robertson N, Tong A. Perspectives on mental health among patients receiving dialysis. Nephrol Dial Transplant. 2020.
31. Kopple JD, Shapiro BB, Feroze U, Kim JC, Zhang M, Li Y, Martin DJ. Hemodialysis treatment engenders anxiety and emotional distress. Clin Nephrol. 2017;88(10):205-17.
32. Oliver MJ, Garg AX, Blake PG, Johnson JF, Verrelli M, Zacharias JM, Pandeya S, Quinn RR. Impact of contraindications, barriers to self-care and support on incident peritoneal dialysis utilization. Nephrol Dial Transplant. 2010;25(8):2737-44.
33. Kondo K, Antick JR, Ayers CK, Kansagara D, Chopra P. Depression Screening Tools for Patients with Kidney Failure: A Systematic Review. Clin J Am Soc Nephrol. 2020;15(12):1785-95.
34. Cheng E, Evangelidis N, Guha C, Hanson CS, Unruh M, Wilkie M, Schell J, Hecking M, Gonzalez AM, Ju A, Eckert DJ, Craig JC, Tong A. Patient experiences of sleep in dialysis: systematic review of qualitative studies. Sleep Med. 2021;80:66-76.
35. Harvey AG, Murray G, Chandler RA, Soehner A. Sleep disturbance as transdiagnostic: consideration of neurobiological mechanisms. Clin Psychol Rev. 2011;31(2):225-35.
36. Kahn M, Sheppes G, Sadeh A. Sleep and emotions: bidirectional links and underlying mechanisms. Int J Psychophysiol. 2013;89(2):218-28.
37. Rasch B, Born J. About sleep's role in memory. Physiol Rev. 2013;93(2):681-766.
38. Sivertsen B, Lallukka T, Salo P, Pallesen S, Hysing M, Krokstad S, Simon O. Insomnia as a risk factor for ill health: results from the large population-based prospective HUNT Study in Norway. J Sleep Res. 2014;23(2):124-32.
39. Neckelmann D, Mykletun A, Dahl AA. Chronic insomnia as a risk factor for developing anxiety and depression. Sleep. 2007;30(7):873-80.
40. Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, Lombardo C, Riemann D. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disord. 2011;135(1-3):10-9.
41. Paunio T, Korhonen T, Hublin C, Partinen M, Koskenvuo K, Koskenvuo M, Kaprio J. Poor sleep predicts symptoms of depression and disability retirement due to depression. J Affect Disord. 2015;172:381-9.

Chapter 6

Depression, anxiety and perceived stress of hemodialysis patients before and during the COVID-19 pandemic.

Nadort E, Rijkers N, Schouten RW, Hoogeveen EK, Bos WJW, Vleming LJ, Westerman M, Schouten M, Dekker MJE, Smets YFC, Chandie Shaw P, Farhat K, Dekker FW, van Oppen P, Siegert CEH, Broekman BFP.

Submitted

Abstract

Objective: To investigate the impact of the coronavirus pandemic on mental health in hemodialysis patients, we assessed depression, anxiety and quality of life with valid mental health measures before and after the start of the pandemic.

Methods: Data were used from 121 hemodialysis patients from the ongoing prospective multicenter DIVERS-II study. COVID-19 related stress was measured with the Perceived Stress Scale – 10, depression with the Beck Depression Inventory – second edition (BDI-II)), anxiety with the Beck Anxiety Inventory (BAI) and quality of life with the Short Form – 12 (SF-12). Scores during the first and second COVID-19 lockdown in the Netherlands were compared to data prior to the pandemic with linear mixed models.

Results: No significant differences were found in BDI-II, BAI and SF-12 scores between before and during the pandemic. During the first lockdown, 33% of participants reported COVID-19 related stress and in the second lockdown 37%. These patients had higher stress levels (mean difference (MD) 4.7 (95%CI 1.5; 8.0), p=0.005) and BDI-II scores (MD 4.9 (95%CI 0.7; 9.0), p=0.021) and lower SF-12 mental component summary scores (MD -5.3 (95%CI -9.0, -1.6), p=0.006) than patients who did not experienced COVID-19 stress. These differences were already present before the pandemic.

Conclusion: The COVID-19 pandemic does not seem to influence mental health in hemodialysis patients. However, a substantial subgroup of patients with pre-existent mental health problems seems to be more susceptible to experience COVID-19 related stress.

Introduction

The impact of the coronavirus disease 2019 (COVID-19) pandemic on mental health among the general population becomes more evident as the pandemic is continuing. Previous studies show that symptoms of depression, anxiety and stress are common reactions to the COVID-19 pandemic.(1-4) Longitudinal studies report an increase of mental health problems compared to the pre-pandemic era.(5-7) Factors that may cause COVID-19 related stress are: fear of the contagious disease itself, loss of employment and financial insecurity, deaths of family members, friends, or colleagues, forced quarantine and social isolation.(8) Risk factors identified in published studies are female sex, younger or older age, previous psychiatric history, pre-existent physical or mental health problems, economic insecurity, and accompanying chronic disease including renal disease.(9-13)

Only a limited number of studies investigating mental health during the COVID-19 pandemic among patients with chronic diseases have been performed. This is important as this group of patients are already vulnerable due to high levels of physical and mental distress. Indeed, in dialysis patients, symptoms of depression and anxiety are highly prevalent and associated with adverse clinical outcomes such as decreased quality of life, increased hospitalization and mortality.(14-19) Perceived stress during the COVID-19 pandemic could increase the burden of these symptoms in these patients.

Research investigating mental health problems in dialysis patients during the COVID-19 pandemic could therefore aid in assessing risk factors for and prevention of increased stress levels in these patients. The association between the COVID-19 pandemic and mental health problems in dialysis patients has been investigated in three studies, however, two studies did not compare results during the pandemic with pre-pandemic data.(20-22) Only the study by Bonenkamp and colleagues compared mental health before and during the COVID-19 pandemic and found no significant difference in mental health related quality of life (HRQoL) and mental health-related symptoms measured with single items from the Dialysis Symptom Index among peritoneal and hemodialysis patients during the COVID-19 pandemic compared to pre-pandemic data.(20) To the best of our knowledge, no studies have investigated the symptom severity of depression, anxiety and perceived stress in hemodialysis patients before and during the COVID-19 pandemic.

The aim of this article is first to investigate symptom levels of depression, anxiety and HRQoL in hemodialysis patients during the first and second wave of the COVID-19 pandemic compared to the pre-pandemic era. And second to explore whether depression, anxiety and HRQoL are associated to COVID-19 related stress.

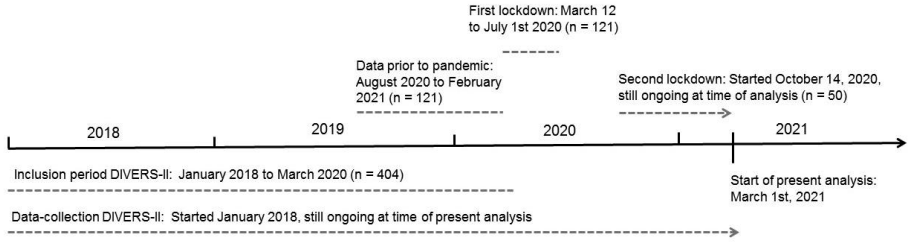
Methods

Study design and participants

To compare depression, anxiety, quality of life and perceived stress in hemodialysis patients before and during the COVID-19 pandemic in both the first and second lockdown in the Netherlands, data were used from the ongoing multicenter prospective DIVERS-II study which consists of a randomized controlled trial (RCT) and a parallel observational cohort. The extensive study protocol has been published earlier.(23) In short, the RCT investigates the effectiveness of guided self-help problem solving therapy for depressive symptoms in hemodialysis patients. Inclusion criteria for the RCT were adult patients receiving maintenance hemodialysis (>90 days), who were able to fill out a questionnaire in Dutch and who had a depressive symptom score of 10 or higher on the Beck Depression Inventory – second edition (BDI-II).(24, 25) Patients who were excluded from the randomization because of a low score on the BDI-II or because of insufficient Dutch language skills, were offered to participate in a parallel observational cohort. In this parallel cohort, questionnaires were also available in Arabic, English and Turkish. The inclusion period of the total DIVERS-II study ran between January 2018 and March 2020. Participants in both the trial and observational cohort were asked to fill out self-reported questionnaires on symptoms of depression, anxiety and HRQoL every three to six months, for a total follow-up period of 21 months. The study protocol, information brochure and informed consent were approved by the Medical Ethics Committee of MEC-U, the Netherlands (registration number: NL58520.100.17) and written informed consent was obtained from all participants before participation. This study is carried out in accordance with de declaration of Helsinki and was prospectively registered in the Dutch Trial Register (Trial NL6648).

For the present analysis, patients from the DIVERS-II RCT and observational cohort were included, if they completed a questionnaire during the first lockdown period in the Netherlands, defined as the period between March 12 and July 1st 2020. The second lockdown period started on October 14, 2020, and data-collection during the second lockdown includes only data from patients who were already included during the first lockdown. Data-collection for the present analysis ended on the first of March, 2021. The second lockdown was still ongoing at the time of data-analysis. Questionnaires collected during the lockdowns were compared with the last pre-lockdown questionnaires which had to have been supplied within 6 months before the first lockdown. Seventeen patients started the intervention of the RCT between September 2019 and March 2021, of which eleven patients were excluded because they were considered to be treatment-completers. A timeline of the data-collection is presented in **Figure 1**.

Figure 1: Timeline of data collection DIVERS-II study and present analysis.



Outcome measurements

The primary outcomes were the severity of symptoms of depression and anxiety, measured with the BDI-II and the Beck Anxiety Inventory (BAI), respectively.(24-26) Both questionnaires consist of 21 items each, in which respondents are asked how much these symptoms have bothered them in the past two weeks, on a scale ranging from 0 (not at all) to 3 (severely), with a total score between 0 and 63 where higher scores indicate more severe depression and anxiety. BDI-II and BAI scores were analyzed as continuous scores. Both the BDI-II and the BAI are validated in various cohorts of patients with chronic somatic diseases.(26-28) The minimum clinically important difference (MCID) in symptom score on the BDI-II and BAI which we used was a difference of at least 5 points.(29)

The secondary outcome of HRQoL was measured with the Short Form-12 (SF-12), a validated questionnaire developed for patients with chronic conditions and frequently used in dialysis patients.(30) The SF-12 consists of a Mental Component Summary (MCS) score and a Physical Component Summary (PCS) score, on a scale of 0 to 100, where higher scores reflect better HRQoL.(31) We used a MCID of at least 5 points difference on PCS and MCS scores.(32)

The secondary outcome of COVID-19 related stress was measured by the Perceived Stress Scale-10 (PSS-10). This is a widely used and validated questionnaire which measures the global levels of stress in the last month by asking to which degree persons find their lives unpredictable, uncontrollable and overloaded.(33, 34) The Dutch version of the PSS-10 translated by the Longitudinal Aging Study Amsterdam (LASA) was used.(35) The 10 questions were answered on a five point Likert scale from 'never' (0) to 'very often' (4), with a total score between 0 and 40. The scale consists of six negatively worded items and four positively worded items, from which a negative subscale and a positive subscale can be calculated. We consider 4 points difference as MCID.(36) To determine if perceived stress was related to COVID-19, the following question was added to the PSS-10: "In the last month, how often have you felt that the tensions or "stress", as answered by you in the above questions, were caused by the corona outbreak?" If patients answered 'never' or 'almost never', their stress was considered COVID-19 unrelated. Patients who answered 'sometimes', 'fairly often' of 'very often' were considered to experience COVID-19 related stress.

Data collection

At baseline, sociodemographic and clinical data were collected through self-reported questionnaires 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 and divided into four groups (renal vascular disease, diabetic nephropathy, glomerulonephritis and other).(37) The Davies comorbidity index was used to define the level of comorbidity.(38) Follow-up data on COVID-19 PCR test results and COVID-19 related hospitalization and mortality was extracted from electronic patient files.

Statistical analysis

Standard descriptive statistics were used to present baseline characteristics. Differences in continuous scores of the BDI-II, BAI and SF-12 before the COVID-19 pandemic and during both lockdowns were analyzed with linear mixed model analysis, adjusted for age, sex, immigrant status, high formal education, dialysis vintage and high comorbidity score. Effects of individual confounders on the outcomes were analyzed in univariate mixed model analysis. Sensitivity analysis was performed excluding all patients from the intervention group of the RCT to assess treatment effect on the outcomes. PSS-10 total score and positive and negative subscales in patients with COVID-19 related stress were compared to the scores of patients without COVID-19 related stress with linear regression analysis, adjusted for age, sex, immigrant status and high comorbidity score. BDI-II, BAI and SF-12 scores of patients with COVID-19 related stress and COVID-19 unrelated stress were compared with linear mixed model analysis, adjusted for age, sex, immigrant status, high formal education, dialysis vintage and high comorbidity score.

Missing values

To assess the impact of missing values on results, missing BDI-II, BAI and SF-12 items of 121 patients before and during the first lockdown and of 50 patients in the second lockdown were imputed by using multiple imputation techniques (10 repetitions) as a sensitivity analysis. All statistical analyses were performed using SPSS for Windows, version 22 (IBM Corp).

Results

The patient flow is presented in **Figure 2**. A total of 121 patients were included in the analysis of the first lockdown and 50 patients in the analysis of the second lockdown. Baseline characteristics are summarized in **Table 1**. The majority of the patients were male (69%), mean age was 67 years, median dialysis vintage was 23 months and ten percent of the patients had a history of depression.

Figure 2: Flow diagram

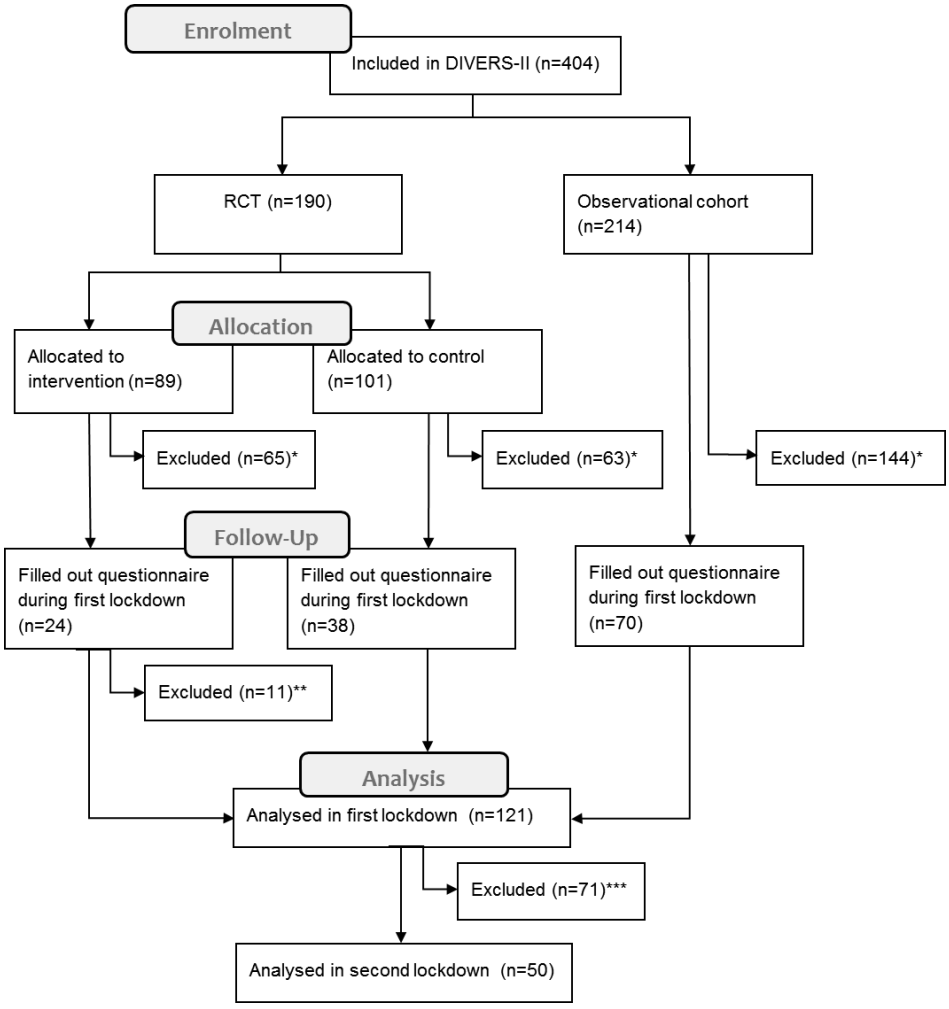


Table 1: Patient characteristics of 121 participating hemodialysis patients at baseline.

Characteristic	All patients (n=121)
Demographic	
Age (year)	67 ± 13
Male sex	84 (69%)
Immigrant*	44 (36%)
Country of birth	
European	86 (71%)
South America/Caribbean	17 (14%)
Southern Asia/South Eastern Asia	10 (8%)
Sub Saharan Africa	5 (4%)
Northern Africa	3 (3%)
Social	
Married	54 (45%)
Has Children	91 (75%)
Education**	
Low	44 (36%)
Middle	48 (40%)
High	29 (24%)
Not employed	106 (88%)
Renal and dialysis	
Dialysis vintage (months)	23 [9 - 42]
Primary kidney disease	
Renal vascular disease	30 (25%)
Diabetic nephropathy	36 (30%)
Glomerulonephritis	9 (7%)
Other	46 (38%)
Kt/V_{urea} at baseline	3.6 ± 1.2
Residual diuresis of ≥100ml/24h	83 (69%)
On waiting list for kidney transplant	
Yes	33 (27%)
No, for medical reasons	74 (61%)
No, by patient preference	14 (12%)
Clinical	
Davies comorbidity index	
Low comorbidity	22 (18%)
Medium comorbidity	82 (68%)
High comorbidity	17 (14%)
Comorbid conditions	
Diabetes mellitus	63 (52%)
Cardiovascular disease	101 (84%)
Psychiatric	
Current psychotherapy	5 (4%)
History of depressive disorder	12 (10%)
History of anxiety disorder	0 (0%)

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

In the first lockdown, a SARS-CoV-2 PCR test was performed in 23 of 121 patients of which none tested positive. Two patients were admitted to the hospital with a suspected COVID-19 infection, but test results were negative. In the second lockdown, a PCR was performed in 13 out of 50 patients of which five (10%) tested positive for SARS-CoV-2. One patient was admitted to the hospital for three days and one patient was admitted to a nursing home for 20 days because care options at home were insufficient. No COVID-19 related mortality was reported in this cohort during the study period.

No significant differences in BDI-II and BAI scores were found with mixed model analysis adjusted for predefined confounders, between the measurements up to six months before COVID-19 and during the first and second lockdown (**Table 2**). Univariate analysis showed a higher BDI score of 4.4 points (95%CI 0.5;8.2, p=0.03) and a BAI score of 5.9 points (95%CI 2.5;9.3, p=0.001) in women compared to men, independent of time effect. The effect of sex on HRQoL was seen only in the MCS score, where women scored 5.3 (95%CI 1.7; 8.8, p=0.004) points lower than men. No significant differences were found in univariate analysis of the other confounders. Sensitivity analysis excluding all patients from the intervention group of the RCT showed no major differences.

Table 2: Depression, anxiety and health related quality of life scores before the COVID-19 pandemic and during the first and second lockdown.

	Pre-pandemic	First lockdown	Mean difference (95% CI)*	p-value	Second lockdown	Mean difference (95% CI)*	p-value
Depression							
BDI-II	10.4 ± 8.5	9.8 ± 8.3	-0.9 (-2.0; 0.1)	0.09	9.1 ± 8.9	0.2 (-1.3; 1.7)	0.79
Anxiety							
BAI	8.7 ± 8.6	8.0 ± 7.9	-1.0 (-2.5; 0.6)	0.21	7.9 ± 7.5	-0.7 (-2.8; 1.4)	0.51
HRQoL							
SF-12 PCS	37.2 ± 9.7	37.3 ± 9.3	0.37 (-2.1; 2.8)	0.76	36.1 ± 10.6	0.8 (-2.5; 4.2)	0.62
SF-12 MCS	54.0 ± 9.0	53.9 ± 8.8	0.1 (-1.7; 2.0)	0.88	53.6 ± 9.2	-0.2 (-2.8; 2.4)	0.86

Note: Values are presented as mean ± standard deviation.
Note: Pre-pandemic and during first lockdown n=121, during second lockdown n=50.
*Analyzed with a linear mixed model, adjusted for age, sex, immigrant status, high formal education, dialysis vintage and high comorbidity score.
Abbreviations: COVID-19, Corona virus disease 2019; 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.

During the first lockdown, 33% of the participants reported that the stress they experienced was caused by the COVID-19 pandemic. During the second lockdown this was 37%. Participants who reported that their perceived stress was caused by the pandemic, scored 4.7 points higher on the PSS-10 during the first lockdown compared to participants who reported their stress was unrelated to COVID-19 (95%CI 1.5; 8.0, p=0.005) (**Table 3, Figure 3**). In the second lockdown this difference was 7.2 points (95%CI 2.7; 11.7, p=0.003). This difference is explained largely by a significant difference on the negative subscale, which consists of

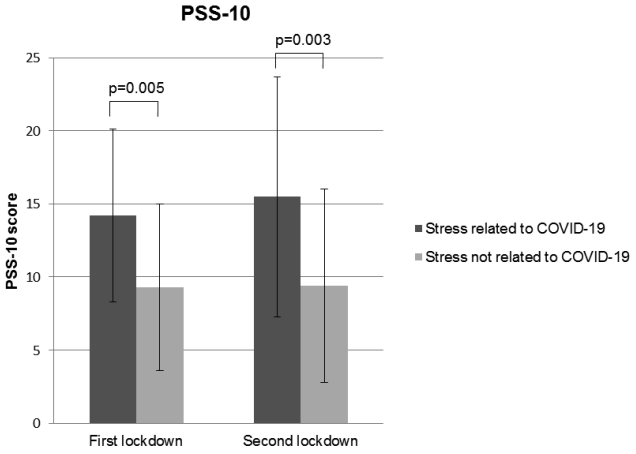
questions on being upset about unexpected things, unable to control important things in life, feeling nervous and stressed, not being able to cope with things you have to do, feeling angry about things outside of your control and not being able to overcome difficulties.

Table 3: Perceived stress scores in hemodialysis patients during the first and the second COVID-19 lockdown.

First lockdown PSS-10	**Perceived stress in total group**	**Stress related to COVID-19**	**Stress not related to COVID-19**	**Mean difference (95% CI)***	**P-value**
Overall score	11.0 ± 6.4	14.2 ± 5.9	9.3 ± 5.7	4.7 (1.5; 8.0)	**0.005**
Positive subscale	6.9 ± 4.3	6.7 ± 6.7	6.4 ± 4.3	0.4 (-1.9; 2.7)	0.76
Negative subscale	4.1 ± 4.1	7.5 ± 4.8	2.9 ± 3.9	4.4 (2.1; 6.7)	**<0.001**
Second lockdown PSS-10					
Overall score	11.7 ± 7.6	15.5 ± 8.2	9.4 ± 6.6	7.2 (2.7; 11.7)	**0.003**
Positive subscale	6.0 ± 3.7	6.2 ± 3.3	5.8 ±4.1	1.2 (-3.0; 5.2)	0.58
Negative subscale	5.6 ± 5.5	9.3 ± 6.9	3.6 ± 3.5	6.1 (2.0; 10.2)	**0.006**

Note: Values are presented as mean ± standard deviation, or frequency (percentage).
Note: Before the pandemic and during the first lockdown COVID-19 related stress n=24 and COVID-19 unrelated stress n=49. During the second lockdown COVID-19 related stress n=15 and COVID-19 unrelated stress n=25.
*Analyzed with a linear regression model, adjusted for age, sex, immigrant status and high comorbidity score.
Abbreviations: PSS-10, perceived stress scale – 10; HD, hemodialysis; COVID-19, Corona virus disease 2019; CI, confidence interval.

Figure 3: Bar chart of difference in perceived stress scores of patients with COVID-19 related stress and COVID-19 unrelated stress during the first and second COVID-19 lockdown.



Participants who reported to experience COVID-19 related stress, scored 4.9 points higher on the BDI-II (95% CI 0.7; 9.0, p=0.02) and 5.3 points lower on the MCS of the SF-12 (-9.0, -1.6, p=0.006) than participants with COVID-19 unrelated stress both before and during the pandemic in a mixed model analysis adjusted for confounders (**Table 4**).

Table 4: Depression, anxiety and health related quality of life scores of patients with COVID-19 related stress and COVID-19 unrelated stress before the COVID-19 pandemic and during the first and the second lockdown.

	Stress related to COVID-19	**Stress not related to COVID-19**	**Mean difference (95% CI)***	**P-value**
BDI-II				
Before COVID-19	13.3 ± 9.2	8.5 ± 7.1		
During first lockdown	12.6 ± 9.0	7.4 ± 7.4	4.9 (0.7; 9.0)	**0.021**
During second lockdown	13.7 ± 7.8	7.8 ± 7.8		
BAI				
Before COVID-19	12.1 ± 9.7	6.9 ± 6.9		
During first lockdown	10.5 ± 7.8	6.0 ± 6.0	2.9 (0.6; 6.3)	0.11
During second lockdown	12.5 ± 9.6	6.4 ± 6.1		
SF-12 - PCS				
Before COVID-19	35.6 ± 8.9	38.6 ± 10.2		
During first lockdown	35.9 ± 9.9	38.9 ±9.0	-2.3 (-6.8; 2.2)	0.31
During second lockdown	34.5 ±10.6	36.5 ± 11.9		
SF-12 - MCS				
Before COVID-19	50.2 ± 9.2	56.4 ± 8.3		
During first lockdown	48.9 ± 8.5	56.8 ± 7.0	-5.3 (-9.0, -1.6)	**0.006**
During second lockdown	46.3 ± 11.0	55.6 ± 7.4		

Note: Values are presented as mean ± standard deviation.
Note: Before the pandemic and during the first lockdown COVID-19 related stress n=24 and COVID-19 unrelated stress n=49. During the second lockdown COVID-19 related stress n=15 and COVID-19 unrelated stress n=25.
*Analyzed with a linear mixed model, adjusted for age, sex, immigrant status, high formal education, dialysis vintage and high comorbidity score.
Abbreviations: COVID-19, Corona virus disease 2019; CI, confidence interval; BDI-II; Beck Depression Inventory – Second edition, BAI; Back Anxiety Inventory, SF-12, 12-Item Short Form Health Survey; PCS, Physical Component Summary; MCS, Mental Component Summary.

Missing values

Baseline demographic and clinical variables were missing in 0.4% of the cases. The overall percentage of missing questions in the first lockdown on the BDI-II, BAI and SF-12 was <5%. Sensitivity analysis, using multiple imputation of missing items, showed no substantial differences compared to the complete case analysis.

Discussion

This study aimed to investigate depression, anxiety and HRQoL in hemodialysis patients during the COVID-19 pandemic compared to the pre-pandemic era and to explore whether depression, anxiety and HRQoL are related to COVID-19 related stress. Overall, no clinically significant differences in severity of symptom levels of depression, anxiety and HRQoL in hemodialysis patients were found between the pre-pandemic era and during the first and second COVID-19 lockdown in the Netherlands. We did find higher levels of depression and anxiety and lower mental health related quality of life scores in women than in men, which is consistent with literature from the general population.(9-11, 13, 39) Importantly, we found that high depression, anxiety and HRQoL scores were already pre-existent in hemodialysis patients before the COVID-19 outbreak.

Cross-sectional studies in dialysis patients during COVID-19 without comparison to pre-pandemic data show a prevalence of depression of 22-27% and a prevalence of anxiety of 12%, but these scores are difficult to interpret as symptoms of depression and anxiety were already highly prevalent in dialysis cohorts before the pandemic.(21, 22) Our findings are in concordance with the only other prospective study in 177 dialysis patients by Bonenkamp and colleagues, which compared mental health related symptoms measured with single items from the Dialysis Symptom Index and HRQoL with the SF-12 before and during the pandemic, who also found no evidence for increase of mental health problems during the pandemic.(20) In addition, we used valid and more detailed mental health measures specifically for measuring depression and anxiety. A possible explanation for the lack of influence of COVID-19 on symptom levels of depression and anxiety in hemodialysis patients could be the fact that their daily lives did not change as much as the lives of the general population during the lockdown since in-center hemodialysis care was continued unchanged. The high prevalence of depression and anxiety before the pandemic may also be responsible for a diminished effect of a pandemic on mental wellbeing.

In our cohort, one third of all hemodialysis patients reported COVID-19 related stress. These patients had more severe symptoms of depression and lower mental health related quality of life both before and during the pandemic compared to participants who reported their stress to be unrelated to COVID-19. There was no difference between participants with COVID-19 related stress and participants with COVID-19 unrelated stress on severity of symptoms of anxiety and physical health related quality of life. These findings suggest that hemodialysis patients with more severe symptoms of depression and lower levels of mental health related quality of life prior to the COVID-19 pandemic, are more susceptible to experience stress caused by the pandemic.

Meta-analyses on self-reported stress among the general population during the COVID-19 pandemic demonstrated similar results (30-40%).(2, 3) In a cross sectional study, 31% of hemodialysis patients experienced high levels of stress during the COVID-19 pandemic using

a cut off of ≥ 6 on the PSS-4.(21) We found an even higher prevalence of high stress levels of 38-39% in our cohort using the same cut off score in these four questions from the PSS-10. Although our study does not provide insight in specific reasons for perceived stress during the COVID-19 pandemic, other studies from dialysis populations report that 85% of hemodialysis patients were worried about the risk of infection during the hemodialysis treatment and the transportation to the hospital, and 38% of peritoneal dialysis patients reported that their life was affected by the COVID-19 pandemic because they experienced restriction of activity, fear and panic, restricted hospital access and social isolation.(21, 22) Mortality rates of COVID-19 are known to be higher among patients with pre-existing kidney diseases compared to individuals without pre-existing kidney diseases.(40),(41) It has been reported that this is one of the reasons that a substantial part of the dialysis patients experiences fear of COVID-19.(20-22) In our cohort, none of the hemodialysis patients were diagnosed with COVID-19 during the first lockdown and 10% during the second lockdown. However, observing COVID-19 related disease and mortality of fellow-patients might increase stress in hemodialysis patients.

Strengths & limitations

This study has several strengths. First, we compared data on depressive and anxiety symptoms measured with validated questionnaires during the pandemic with data of the pre-pandemic era in hemodialysis patients. Second, this is the first prospective study that reports mental health in hemodialysis patients with additional data from the second lockdown. This provides longitudinal information about the development of mental health problems during the COVID-19 pandemic in hemodialysis patients. Lastly, we used data from a large multicenter cohort study in the Netherlands, which increases generalizability.

This study has several limitations. First, we have a relatively small sample size of 121 patients in the first lockdown and an even smaller sample size of 50 patients in the second lockdown. This is comparable to the current literature on COVID-19 related mental health in dialysis patients with sample sizes of 49 to 177 patients. (20-22) Also, as the upper levels of the 95% confidence intervals we found are still lower than the MCID, it is unlikely that with a larger sample size a clinically relevant difference will be found. Second, selection bias might have occurred since this cohort included patients from an RCT which may play a role in which patients were willing to participate. To address this issue, we offered patients the opportunity to participate in a parallel observational cohort if patients were not willing or motivated to participate in an interventional study. To limit the effect of the intervention on the outcomes of this study, we excluded patients who completed the intervention during the period of the present study from the analysis and performed sensitivity analysis excluding all patients from the intervention group. Third, we were not able to compare perceived stress during COVID-19 with pre-pandemic data since the PSS-10 is not part of the original DIVERS-II protocol. Fourth, although the MCID has been used and validated in other chronically ill patient groups, it has not been validated in the dialysis population.(42) Finally, our low infection rate in the first lockdown and low COVID-19 related mortality rate could decrease generalizability as currently

reported COVID-19 infection rates in the hemodialysis population are 3-6% and COVID-19 mortality rates are up to 25%.(40, 41, 43, 44)

Conclusion

In conclusion, the COVID-19 pandemic does not seem to influence severity of symptoms of depression, anxiety and quality of life in hemodialysis patients during the first and second COVID-19 lockdown in the Netherlands, compared to pre-pandemic data. However, a substantial subgroup of patients with pre-existent higher symptom levels of depression and lower mental health related quality of life seems to be more susceptible to experience COVID-19 related stress. This underscores the need for screening and treatment of depression and mental health related quality of life in hemodialysis patients to prevent increase of stress symptoms in this group during pandemics and other major stressful events in the future.

References

1. Bueno-Notivol J, Gracia-Garcia P, Olaya B, Lasheras I, Lopez-Anton R, Santabarbara J. Prevalence of depression during the COVID-19 outbreak: A meta-analysis of community-based studies. Int J Clin Health Psychol. 2021;21(1):100196.
2. Luo M, Guo L, Yu M, Jiang W, Wang H. The psychological and mental impact of coronavirus disease 2019 (COVID-19) on medical staff and general public - A systematic review and meta-analysis. Psychiatry Res. 2020;291:113190.
3. Salari N, Hosseinian-Far A, Jalali R, Vaisi-Raygani A, Rasoulpoor S, Mohammadi M, et al. Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: a systematic review and meta-analysis. Global Health. 2020;16(1):57.
4. Wang Y, Kala MP, Jafar TH. Factors associated with psychological distress during the coronavirus disease 2019 (COVID-19) pandemic on the predominantly general population: A systematic review and meta-analysis. PLoS One. 2020;15(12):e0244630.
5. Kwong ASF, Pearson RM, Adams MJ, Northstone K, Tilling K, Smith D, et al. Mental health before and during the COVID-19 pandemic in two longitudinal UK population cohorts. Br J Psychiatry. 2020:1-10.
6. Pierce M, Hope H, Ford T, Hatch S, Hotopf M, John A, et al. Mental health before and during the COVID-19 pandemic: a longitudinal probability sample survey of the UK population. The Lancet Psychiatry. 2020;7(10):883-92.
7. Castellini G, Rossi E, Cassioli E, Sanfilippo G, Innocenti M, Gironi V, et al. A longitudinal observation of general psychopathology before the COVID-19 outbreak and during lockdown in Italy. J Psychosom Res. 2021;141:110328.
8. Fofana NK, Latif F, Sarfraz S, Bilal, Bashir MF, Komal B. Fear and agony of the pandemic leading to stress and mental illness: An emerging crisis in the novel coronavirus (COVID-19) outbreak. Psychiatry Res. 2020;291.
9. Browning M, Larson LR, Sharaievska I, Rigolon A, McAnirlin O, Mullenbach L, et al. Psychological impacts from COVID-19 among university students: Risk factors across seven states in the United States. PLoS One. 2021;16(1):e0245327.
10. Hossain MM, Tasnim S, Sultana A, Faizah F, Mazumder H, Zou L, et al. Epidemiology of mental health problems in COVID-19: a review. F1000Res. 2020;9:636.
11. Ozdin S, Bayrak Ozdin S. Levels and predictors of anxiety, depression and health anxiety during COVID-19 pandemic in Turkish society: The importance of gender. Int J Soc Psychiatry. 2020:20764020927051.
12. Li T, Sun S, Liu B, Wang J, Zhang Y, Gong C, et al. Prevalence and Risk Factors for Anxiety and Depression in Patients With COVID-19 in Wuhan, China. Psychosom Med. 2021;83(4):368-72.
13. Pieh C, Budimir S, Probst T. The effect of age, gender, income, work, and physical activity on mental health during coronavirus disease (COVID-19) lockdown in Austria. J Psychosom Res. 2020;136:110186.
14. 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.

15. Farrokhi 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.
16. 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.
17. 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.
18. Chiang HH, Guo HR, Livneh H, Lu MC, Yen ML, Tsai TY. Increased risk of progression to dialysis or death in CKD patients with depressive symptoms: A prospective 3-year follow-up cohort study. J Psychosom Res. 2015;79(3):228-32.
19. Schouten RW, Nadort E, Harmse V, Honig A, van Ballegooijen W, Broekman BFP, et al. Symptom dimensions of anxiety and their association with mortality, hospitalization and quality of life in dialysis patients. J Psychosom Res. 2020;133:109995.
20. Bonenkamp AA, Druiventak TA, van Eck van der Sluijs A, van Ittersum FJ, van Jaarsveld BC, Abrahams AC, et al. The Impact of COVID-19 on the mental health of dialysis patients. J Nephrol. 2021;34(2):337-44.
21. Lee J, Steel J, Roumelioti M-E, Erickson S, Myaskovsky L, Yabes JG, et al. Psychosocial Impact of COVID-19 Pandemic on Patients with End-Stage Kidney Disease on Hemodialysis. Kidney360. 2020;1(12):1390-7.
22. Yeter HH, Gok Oguz E, Akcay OF, Karaer R, Yasar E, Duranay M, et al. The reliability and success of peritoneal dialysis during the COVID-19 pandemic. Semin Dial. 2021;34(2):147-56.
23. 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.
24. Beck AT, Steer RA, Brown GK. The Beck Depression Inventory. Second edition ed. San Antonio: Psychological Corp; 1996.
25. 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.
26. 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.
27. 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.
28. Muntingh 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.
29. Masson SC, Tejani AM. Minimum clinically important differences identified for commonly used depression rating scales. J Clin Epidemiol. 2013;66(7):805-7.

30. 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.
31. Ware J, Jr., 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.
32. Sinclair A CK, Loncar M, et al. Dialysis Modalities for the Treatment of End-Stage Kidney Disease: A Health Technology Assessment [Internet]. 2017 Mar [Available from: Available from: https://www.ncbi.nlm.nih.gov/books/NBK532011/.
33. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24(4):385-96.
34. Cohen SaW, G. Perceived Stress in a Probability Sample of the United States. In S. Spacapam & S. Oskamp (Eds.). The Social Psychology of Health: Claremont Symposium on Applied Social Psychology 1988;Newbury Park, CA: Sage:(pp. 31-67).
35. LASA. Longitudinal Aging Study Amsterdam: Perceived Stress 2019 [Available from: https://www.lasa-vu.nl/themes/emotional/perceived-stress.htm.
36. Plantinga L, Lim SS, Bowling CB, Drenkard C. Perceived stress and reported cognitive symptoms among Georgia patients with systemic lupus erythematosus. Lupus. 2017;26(10):1064-71.
37. 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.
38. 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.
39. Rancans E, Renemane L, Kivite-Urtane A, Ziedonis D. Prevalence and associated factors of mental disorders in the nationwide primary care population in Latvia: a cross-sectional study. Ann Gen Psychiatry. 2020;19:25.
40. Flythe JE, Assimon MM, Tugman MJ, Chang EH, Gupta S, Shah J, et al. Characteristics and Outcomes of Individuals With Pre-existing Kidney Disease and COVID-19 Admitted to Intensive Care Units in the United States. Am J Kidney Dis. 2021;77(2):190-203 e1.
41. Hilbrands LB, Duivenvoorden R, Vart P, Franssen CFM, Hemmelder MH, Jager KJ, et al. COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. Nephrol Dial Transplant. 2020;35(11):1973-83.
42. van der Willik EM, Terwee CB, Bos WJW, Hemmelder MH, Jager KJ, Zoccali C, et al. Patient-reported outcome measures (PROMs): making sense of individual PROM scores and changes in PROM scores over time. Nephrology (Carlton). 2021;26(5):391-9.
43. Hsu CM, Weiner DE. COVID-19 in dialysis patients: outlasting and outsmarting a pandemic. Kidney Int. 2020;98(6):1402-4.
44. Hsu CM, Weiner DE, Aweh G, Miskulin DC, Manley HJ, Stewart C, et al. COVID-19 Among US Dialysis Patients: Risk Factors and Outcomes From a National Dialysis Provider. Am J Kidney Dis. 2021.

Chapter 7

Treatment of depressive symptoms in dialysis patients: A systematic review and meta-analysis.

Nadort E, Schouten RW, Witte SHS, Broekman BFP, Honig A, Siegert CEH, van Oppen P.

General Hospital Psychiatry; Volume 67, November-December 2020, Pages 26-34

Abstract

Objective: Symptoms of depression are highly prevalent and undertreated in dialysis patients. To aid clinicians in offering treatment to patients with depression, we conducted a systematic review and meta-analysis on the treatment of current depressive symptoms in dialysis patients.

Methods: Nine databases were searched on January 8th 2020 for randomized controlled trials on the treatment of depressive symptoms in dialysis patients. In contradiction to previous reviews, we only included studies who selected patients with a score above a defined cut-off for depressive symptoms and used an inactive control group, to investigate the effectiveness of treatments in currently depressed patients. All interventions aimed to treat depressive symptoms were accepted for inclusion. Standardized mean differences were calculated in a random effect meta-analysis.

Results: Seventeen studies were included in the systematic review (1640 patients). Nine studies could be included in the meta-analysis. A pooled analysis of 7 studies on psychotherapy showed a standardized mean difference of -0.48 [-0.87 ; -0.08], with a moderate heterogeneity (I2 = 52%,, X2 = 12.56, p = 0.05). All studies on psychotherapy performed a per protocol analysis and scored high on potential bias. A pooled analysis of two studies on SSRI's showed no statistically significant improvement of depressive symptoms (SMD -0.57 [-6.17; 5.02], I2=71%,X2 = 0.2474, p=0.06).

Conclusions: Psychotherapy is a promising treatment for currently depressed dialysis patients, although quality of evidence is low. More evidence is needed regarding the efficacy of SSRI's, exercise therapy and dietary supplements in this population.

Introduction

The burden of depressive symptoms among dialysis patients is high, with a prevalence of up to 43% and a marked effect on quality of life (QoL).(1-3) Furthermore, symptoms of depression are associated with several adverse health outcomes, such as an increased risk of mortality, poor treatment adherence, and a higher hospitalization rate.(2, 4-7) Studies on the course of depression in dialysis patients show that depressive symptoms do not remit spontaneously in a substantial proportion of patients if left untreated, with high levels of depressive affect being a predictor for short- and long-term complications of depression.(8-10) Despite this burden there is under-screening and under-treatment of depressive symptoms in dialysis patients.(4, 7, 11)

Antidepressants are a widely used, efficacious and available treatment for depression in various populations. Evidence regarding safety and efficacy of antidepressants in the dialysis population is currently lacking. A systematic review by Palmer et al. (2016), investigating the effects of selective serotonin reuptake inhibitors (SSRI's) for treating depressive symptoms in dialysis patients, could not draw conclusions due to limited availability of studies and short duration of follow-up of the included studies.(12) In addition, the recently published chronic kidney disease (CKD) Antidepressant Sertraline Trial failed to show efficacy of sertraline over placebo for the treatment of major depression disorder (MDD) in patients with non-dialysis CKD (13) In general, willingness to modify or initiate antidepressant medication is often lacking in both chronic dialysis patients and renal care providers.(14).

Psychological interventions are well established and effective treatments for adult depression. Despite lower effect sizes of psychotherapy for depression in patients with medical disorders compared to the general population, psychotherapy still shows relevant improvement of depressive symptoms in the medically ill patient population (hedges g=0,71 vs g=0,57 respectively).(15) Although a recent randomized trial comparing treatment of depression with sertraline versus cognitive behavioral therapy (CBT) in hemodialysis patients showed improvement in depressive symptoms in both treatments arms from baseline, the sertraline group showed modestly better improvement, but an inactive control arm was not included to show if either treatment is better than control.(16) A recently well-performed review by Natale et al. on psychosocial interventions for preventing and treating depression in dialysis patients, concluded that CBT, exercise and relaxation therapy probably reduce depressive symptoms with moderate certainty evidence.(17, 18) This review included both randomized controlled trials (RCT's) and quasi-RCT's, which may increase the risk for selection bias, and included both participants with or without current clinically significant depressive symptoms , which potentially influences the effect sizes of treatments that are developed for depressed patients.

In this article, we present the results of a systematic review and meta-analysis of RCT's with an inactive control group on various treatment options for patients undergoing maintenance

dialysis with a current diagnosis of depression or depressive symptoms above the defined cut off, to better understand the effect sizes of treatments that have been developed for this particular group of patients. These results will better fit clinical practice, where both medications, psychotherapy and alternative therapies are used for treatment of clinically significant depression in dialysis patients.

Methods

This systematic review and meta-analysis is conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.(19) The protocol for this systematic review and meta-analysis was prospectively registered in Prospero under the registration number CRD42018073969.(20)

Search strategy

The search strategy has been conducted in close cooperation with a trained librarian and included terms on depression, dialysis and (randomized) trials. EMBASE, PubMed, PsycINFO/Ebsco, Web of Sciences, Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database for Systematic Reviews, CINAHL/Ebsco, WHO ICTRP and clinicaltrials.gov were searched from inception up to January 8th 2020. The search strategy was optimized for all consulted databases (supplement S1). There were no restrictions in languages or publication dates. References from relevant systematic reviews on treatment of depressive symptoms in dialysis patients were cross-checked for potential missed inclusions. Articles from all databases were combined in Endnote and duplicates were removed using a duplicate removal protocol.(21) Ongoing research or non-published trials were identified through database searching (clinicaltrials.gov and WHO ICTRP).

Study selection

Screening of title and abstract was performed in the online software program Rayyan.(22) Eligible full texts were retrieved and assessed for inclusion. All steps of study screening and selection were done by two independent reviewers (EN, RWS and SW). Disagreements were resolved by discussion with a third author (AH). Articles were included when they 1) included dialysis patients with depressive symptoms, using either a diagnosis of major depression disorder (MDD) or a score above the defined cut-off on self-rating depression scales, 2) patients were randomized in an active treatment and inactive control group. All interventions aimed to treat depressive symptoms were accepted for inclusion. Studies were also considered if depression was a secondary outcome as long as the other inclusion criteria were met. If multiple articles were published on the same dataset, the most relevant publication was included.

Outcomes

The primary outcome was the difference in depressive symptoms measured by a diagnostic interview or a score on a self-rating depression scale between the intervention and control arm after treatment. Secondary outcomes of interest were: 1) anxiety symptoms, 2) QoL, 3) mortality, 4) treatment satisfaction, 5) cost-effectiveness, 6) and hospitalization.

Data extraction

Data extraction from full-text articles was performed independently by two authors (EN and SW) using a preset format. Information regarding the author, year of publication, country, study design, dialysis modality, in- and exclusion criteria, type of intervention, number of participants, outcome measures and outcomes were extracted independently. Articles in languages other than English were translated before data extraction. Authors were contacted in case of missing data.

Assessment of Risk of Bias and Strength of Evidence

Risk of bias was independently assessed by two authors (EN and SW) using the Cochrane risk of bias tool.(23) Disagreements were resolved by discussion with a third author (RWS). The strength of the overall evidence on the outcomes was assessed by two authors (EN and SW) using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.(24) Quality of evidence was graded as high, moderate, low or very low.

Data synthesis and meta-analysis

Data was pooled using the random effects model in R (R Core Team), with the packages meta and metafor.(25) The results of the included studies are displayed by standardized mean differences (SMD), as the primary outcome was measured by different depression scales in the various studies. Negative SMDs indicate an improvement in the reduction of depressive symptoms in the intervention group. The interpretation of effect size as proposed by Cohen is as follow: 0.20 is a small effect size, 0.50 a medium effect size and 0.80 a large effect size.(Cohen 1988)

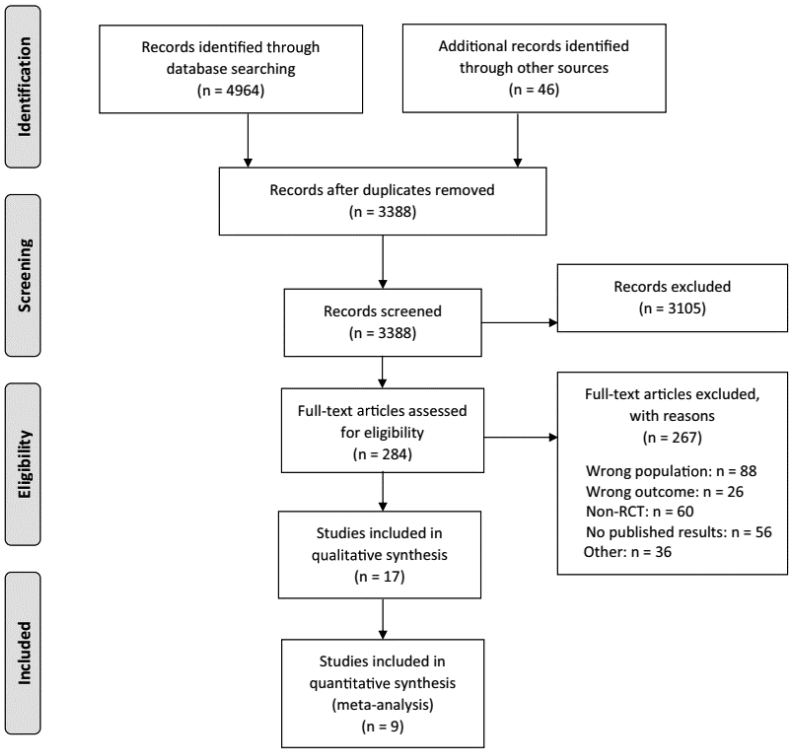
A pooled meta-analysis of continuous variables was conducted using a random effects model with a Sidik-Jonkman estimator with Hartung and Knapp adjustment.(26) Subgroup meta-analysis on different treatment options, such as cognitive therapy and antidepressants, was performed if possible. Statistical heterogeneity was assessed by visual inspection of the forest plot, the chi-squared test and the I2-test whereby the Q statistic was used to test heterogeneity across studies. The I2 index was interpreted as unimportant (0-40%), moderate (30-60%), substantial (50-90%) and considerable heterogeneity (75-100%).(Higgins 2011) Risk of publication bias was based on visual inspection of a funnel plot. The R-code containing the details regarding the meta-analysis are described in **supplementary table S2**.

Results

Search results

In total, 3388 records were screened on title and abstract, 284 full text articles were assessed for eligibility, 17 studies were included in qualitative synthesis (n=1640) and nine studies in the meta-analysis (n=465). See PRISMA flow diagram (**figure1**).

Figure 1: PRISMA flow diagram



RCT = randomized controlled trial.

Study characteristics

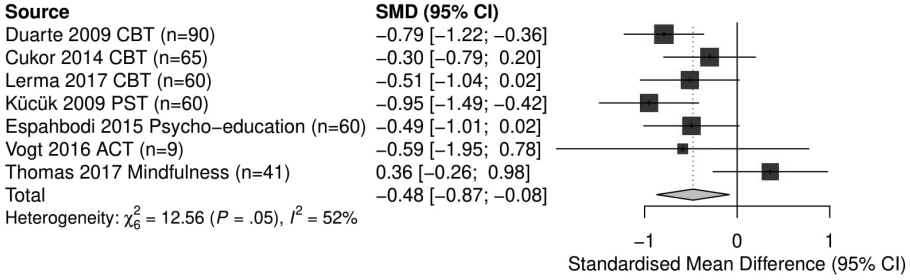
Characteristics of the 17 included RCT's and primary outcomes are provided in **table 1**. Seven studies investigated the effects of psychological interventions, which included three studies on CBT(27-29), one study on problem solving therapy (PST)(30), one study on psycho-education(31), one study on acceptance and commitment therapy (ACT)(32) and one study on brief mindfulness meditation(33). Four studies investigated SSRI's, which included 2 studies on sertraline(34, 35), one study on fluoxetine (36) and one study on escitalopram (37), all versus placebo. Four studies investigated the effects of dietary supplements which included omega-3 fatty acids(38), vitamin D3(39), Radix Bupleuri root (40) and synbiotic and

probiotic supplementation.(41) One study investigated exercise training(42) and one study examined recitation of the Qur'an(43). Control groups consisted of placebo treatment in eight studies, care as usual in seven studies and wait-list in two studies. Detailed information on treatment and control characteristics can be found in **table 2**.

Quantitative analysis

The SMD of the individual study results regarding the effect of treatment compared with the non-active control group is summarized in **table 1**. Meta-analysis of the seven studies on psychological intervention versus control (n=385) showed a statistically significant pooled effect size of -0.48 [-0.87; -0.08] favoring the intervention, with overlapping confidence intervals except for the study on mindfulness and moderate heterogeneity (I2 = 52%, X2 = 12.56, p = 0.05), as shown in **figure 2a**. Except one, all studies are favoring the psychological intervention. The study which examined a brief mindfulness training did not show a significant improvement, with an effect of 0.36 [-0.26; 0.98], favoring the control condition. Sensitivity analysis on the three studies investigating CBT show a comparable effects size of SMD -0.55 [-1.19; 0.08] with low and not significant heterogeneity (I2 = 10%, X2 = 2.21, p = 0.33)(**supplement S3**), which may indicate that the moderate heterogeneity found is likely due to differences in psychotherapeutic interventions.

Figure 2a: Primary analysis: Forest plot of comparison: psychological intervention versus control condition, outcome: standardized mean difference for the degree of depression at posttreatment.



CBT = cognitive behavioral therapy, PST = problem solving therapy, ACT = acceptance and commitment therapy, SMD = standardized mean difference, CI = confidence interval

Table 1: Characteristics of the included studies and the primary outcome on depressive symptoms

First author	Year	Region	Design	HD/ PD	Age	Depression method and cut-off	Exclusion Psychiatric diagnosis or treatment	Other exclusion criteria	Type of intervention	N control	N inter-vention	Outcome SMD (95%CI)
Babamohamadi	2017	Iran	RCT	HD	18-65	BDI≥20	Yes	History or change in medical illness	Qur'an recitation 12 sessions	30	30	-2.30 [-2.96; -1.64]
Blumenfield	1997	USA	RCT	HD	18-70	HAM-D >16	Yes	-	Fluoxetine 20 mg 8 weeks	7	7	-
Cukor	2014	USA	RCT cross-over	HD	>18	BDI>10	Yes	-	CBT individual 10 sessions	38	27	-0.30 [-0.79; 0.20]
Dashti-Khavidaki	2014	Iran	RCT	HD	>18	BDI>16	Yes	Medical illness	Omega-3 16 weeks	18	16	-
Duarte	2009	Brazil	RCT	HD	18-80	MINI≥5, BDI	Yes	Unstable clinical condition	CBT group 12 sessions	46	44	-0.79 [-1.22; -0.36]
Espahbodi	2015	Iran	RCT	HD	-	HADS≥8	Yes	-	Group psycho-ed. 3 sessions	30	30	-0.49 [-1.01; 0.02]
Friedli	2017	UK	RCT feasibility	HD	>18	BDI≥16	Yes	Prognosis <1 year	Sertraline 50mg 24 weeks	15	15	-0.11 [-0.82; 0.61]
Haghighat	2019	Iran	RCT	HD	30-65	HADS-D ≥8	Yes	Medical illness	Synbiotic or probiotic 3 months	15	16/18	-1.74 [-2.59; -0.90], -0.57 [-1.28; 0.13]
Kouidi	2009	Greece	RCT	HD	-	BDI ≥10	Yes	Muscolo- skeletal limitation	Exercise training 1 year	20	24	-1.41 [-2.08; -0.74]
Kücük	2009	Turkey	RCT	HD	18-60	BDI=10-29	Yes	Low education	PST 8 sessions	30	30	-0.95 [-1.49; -0.42]
Lerma	2016	Mexico	RCT	HD	18-60	BDI=10-29	Yes	-	CBT group 5 sessions	38	22	-0.51 [-0.79; 0.20]
Taraz	2013	Iran	RCT	HD	18-80	BDI≥16	Yes	Medical illness	Sertraline 50 mg 12 weeks	25	25	-0.99 [-1.58; -0.40]

Table 1 (continued)

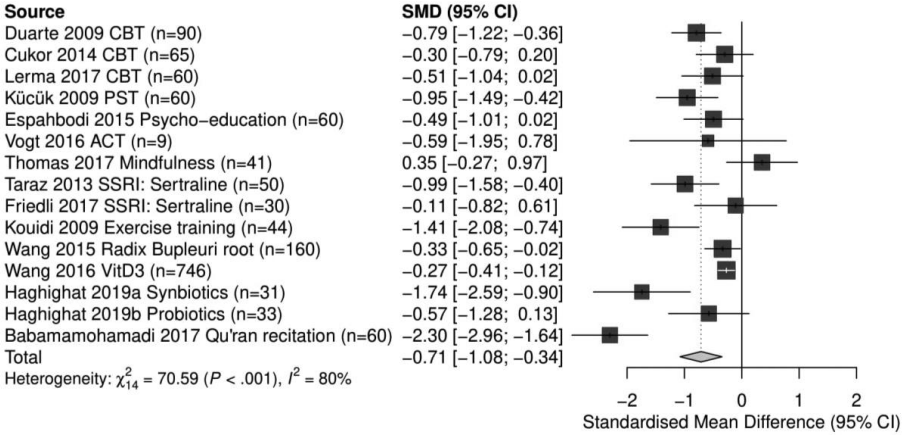
First author	Year	Region	Design	HD/ PD	Age	Depression method and cut-off	Exclusion Psychiatric diagnosis or treatment	Other exclusion criteria	Type of intervention	N control	N inter-vention	Outcome SMD (95%CI)
Thomas	2017	Canada	RCT feasibility	HD	-	PHQ-9≥6	-	-	Mindfulness 13 sessions	21	20	0.36 [-0.26; 0.98]
Vogt	2016	UK	RCT feasibility	HD	>18	PHQ-9 ≥10	Yes	-	ACT 6 sessions	4	5	-0.59 [-1.95; 0.78]
Wang	2015	China	RCT	HD	30-55	Interview MADRS	Yes	-	Radix Bupleuri 12 weeks	80	80	-0.33 [-0.65; -0.02]
Wang	2016	China	RCT	HD PD	>18	BDI≥16	Yes	-	Vitamine D3 52 weeks	373	373	-0.27 [-0.41; -0.12]
Yazici	2012	Turkey	RCT	HD PD	18-65	Zung≥50 HAM-D	Yes	Medical illness	Escitalopram 8 weeks	30	28	-

ACT = Acceptance and Commitment Therapy, BDI = Beck Depression Inventory, CBT = Cognitive Behavioral therapy, HADS = Hospital Anxiety Depression Scale, HAM-D = Hamilton Rating Scale for Depression, HD = hemodialysis, MADRS = Montgomery Asberg Depression Rating Scale, MINI = Mini Neuropsychiatric Interview, PD = peritoneal dialysis, PHQ-9 = Patient Health Questionnaire-9, PST = Problem Solving Therapy, RCT = randomized controlled trial, SMD = Standardized Mean Difference

Meta-analysis comparing two studies on sertraline versus placebo (n=80) shows an effect size of -0.57 [-6.17; 5.02] with a large confidence interval and substantial heterogeneity (I2 = 71%, X2 = 0.2474, p=0.06). The studies on fluoxetine and escitalopram could not be included in the meta-analysis because insufficient data was reported.

As a secondary analysis, SMD calculated from 14 studies are summarized in the forest plot in **figure 2b**. No pooled effect size is given as these treatments were too heterogenic to compare their effects. SMD could be calculated in three out of four studies on dietary supplements.(39, 40) Two studies were performed in China with an SMD of -0.33 [-0.65; -0.02] for Radix Bupleuri root and -0.27 [-0.41; -0.12] for vitamin D3. One study was performed in Iran with an SMD of -1.74 [-2.59; -0.90] for synbiotic supplements and SMD of -0.57 [-1.28; 0.13] for probiotic supplements. For exercise training SMD was -1.41 [-2.08; -0.74](42) and for Qur'an recitation, SMD was -2.30 [-2.96;-1.64] which is considered as an outlier.(43)

Figure 2b: Secondary analysis: Forest plot of comparison: intervention versus control condition, outcome: standardized mean difference for the degree of depression at posttreatment.



CBT = cognitive behavioral therapy, PST = problem solving therapy, ACT = acceptance and commitment therapy, vitD3 = vitamin D3, SMD = standardized mean difference, CI = confidence interval, SSRI = selective serotonin reuptake inhibitor

Table 2: Treatment and control characteristics

First author	Type of intervention	Delivered by	Frequency	Duration	No of sessions	Control
Babamohamadi	Qur'an recitation 12 sessions	MP3 player with headphones	3/week for 20 minutes	4 weeks	12	No intervention
Blumenfield	Fluoxetine 20 mg	-	1/day	8 weeks	-	Placebo
Cukor	CBT individual	Psychologist	1/week for 60 minutes	12 weeks	Max 10	Wait-list
Dashti-Khavidaki	Omega-3	Soft-gel capsules 180 mg EPA and 120 mg DHA	6/day	16 weeks	-	Placebo (paraffin oil)
Duarte	CBT group	Licensed psychologist with extensive specialized training in CBT	1/week for 90 minutes	12 weeks	12	Care as usual: routinely available brief individualized psychological consultation
Espahbodi	Group psychoeducation	Nephrologist and psychiatrist	3/week for 60 minutes	1 week	3	No intervention
Friedli	Sertraline 50-100 mg[a]	-	1/day	24 weeks	-	Placebo
Haghighat	Synbiotic or probiotic supplement	Sachet 5 gr[b]	4/day	3 months	-	Placebo
Kouidi	Exercise training during HD treatment	Exercise trainers specialized in physical rehabilitation[c]	3/week	60-90 min	Min 100	Care as usual
Kücük	PST	-	30-60 minutes	-	8	Care as usual
Lerma	CBT group	Therapist, groups of 3-6 patients	1/week for 120 minutes	5 weeks	5	Wait-list
Taraz	Sertraline 50-100 mg[d]	-	1/day	12 weeks	-	Placebo
Thomas	Mindfulness meditation	Psychologist and senior psychiatry resident during HD session	3/week for 10-15 minutes	8 weeks	Min 13	Care as usual
Vogt	ACT individual	Telephone-supported self-help book	1/week for 30 minutes	6 weeks	6	Care as usual
Wang	Radix Bupleuri root 1 gram	-	1/day	12 weeks	-	Placebo

Table 2 (continued)

First author	Type of intervention	Delivered by	Frequency	Duration	No of sessions	Control
Wang	Vitamine D3 50.000 IU/	-	1/week	52 weeks	-	Placebo
Yazici	Escitalopram[e]	-	-	8 weeks	-	Placebo

[a] possibility of 100 mg at 2 and 4 months follow up.
[b] Synbiotic supplement contained probiotic strains and fibers, the probiotic supplement contained probiotic strains only.
[c] Exercise training session consisted of 5 min warm-up, 30-60 min active cycling session, 20 min strengthening program and a 5 min cool-down period.
[d] 50 mg for 2 weeks, followed by 100 mg for 10 weeks.
[e] Unknown dose

Secondary outcomes

Anxiety was measured in six studies (**supplement S6a**).(28, 31, 33, 40, 44) SMD of the effect size could be calculated in five studies, with a pooled effect of -0.25 [-0.54; 0.05] and small heterogeneity which was not significant (I2 = 7%, X2 = 5.38, p=0.37), shown in **supplement S5a**. Quality of life was measured in six studies (**supplement S6b**).(27-29, 32, 38, 40) SMD could be calculated in four studies, with a pooled effect of 0.40 [0.10; 0.70] and small not-significant heterogeneity (I2 = 14%, X2 = 4.66, p=0.32), shown in **supplement S5b**. Other secondary outcomes mortality, treatment satisfaction, cost-effectiveness and hospitalization, were not reported in the included studies.

Qualitative synthesis

Of the seven studies on psychological interventions, all but the two studies on ACT and on mindfulness meditation showed a significant improvement of depressive symptoms in the intervention group in comparison with the control group. The three studies on CBT assessed treatments of five to twelve individual or group sessions led by a psychologist or therapist, scheduled during hemodialysis sessions or on non-dialysis days. The CBT interventions consisted of psycho-education and different CBT techniques such as self-monitoring of mood-status, cognitive restructuring, behavioral activation and relaxation exercises.(27-29) The PST treatment consisted of 8 sessions of maximum one hour but no further details are given on the content of the sessions.(30) The psycho-education consisted of three group sessions with content on renal failure and dialysis care, problem solving skills, stress management and muscle relaxation.(31) ACT was composed of six individual sessions delivered by a telephone-supported self-help book and the mindfulness meditation was provided three times a week during hemodialysis sessions for 8 weeks by a psychiatry resident or a psychologist.(32, 33)

The four studies on SSRI's show inconsistent results. For Sertraline, in one study no benefit was observed after 24 weeks and in the other study a significant improvement in depression score was seen in the intervention group after 12 weeks.(34, 35) A small study on Fluoxetine showed a significant improvement of depression in the intervention group after 4 weeks but not after 8 weeks and a study on Escitalopram showed a significant improvement compared with the placebo group after 8 weeks.

Three studies on dietary supplements showed a significantly lower depression score after four months of daily omega-3 fatty acids intake, after three months of daily intake of the Chinese herb Radix Bupleuri root and after three months of four-times daily synbiotic or probiotic supplementation, but no significant improvement in depression scores was seen after 52 weeks of weekly Vitamin D3 injection.(38-41) One study on an exercise training program of three times per week for 60-90 minutes during hemodialysis treatment, showed a significant difference in depression scores after one year favoring the intervention group.(42) One religious study on the effect of Holy Qur'an recitation delivered three times a

week by a MP3 player with headphones during dialysis sessions showed a significant effect on depression scores in hemodialysis patients in Iran after four weeks.(43)

Study quality

The Risk of Bias in most of the studies is considerable, as is presented in a risk of bias graph (**supplement S5a**) and a risk of bias summary (**supplement 5b**). Only one study met all quality criteria, sensitivity analysis on studies with low risk of bias was not possible. Publication bias was assessed using a funnel plot which shows a symmetric distribution around the pooled effect, as shown in **supplement S7**. A Baujat plot to detect sources of heterogeneity in meta-analysis shows that the study on recitation of the Qur'an has the largest contribution to overall heterogeneity (**supplement S8**).(45) The certainty of the evidence assessed according to the GRADE criteria is graded as low to very low (**supplement S9**).

Discussion

This study systematically reviewed and meta-analyzed RCT's with an inactive control group studying various treatment options for patients undergoing maintenance dialysis with a current diagnosis of depression or above threshold depressive symptoms. As we displayed the treatment effect of all included studies (see figure 2b), this systematic review makes it possible to compare treatment effects of the different treatment options used in clinical practice, such as psychotherapy, antidepressants, dietary supplements and exercise therapy.

Psychotherapy

The medium effect size found for psychotherapy in this meta-analysis (SMD -0.48 [-0.87; -0.08]) is comparable to the medium effect size found by Cuijpers et al. in a subgroup analysis on adults with a general medical disorder and depression (g=-0.57 [-0.69; -0.44]).(15) Sensitivity analysis on three studies on CBT showed similar results as the main analysis on all psychotherapies (SMD -0.55 [-1.19; 0.08]), with a low heterogeneity of 10% which was not significant ($X2 = 2.21$, $p=0.33$). A recent review by Natale et al. on CBT in dialysis patients found an improvement on the Beck Depression Inventory (BDI) score of mean difference (MD) -6.10 [-8.63; -3.57], which corresponds to a SMD of -0.31.(17, 18) This is a smaller effect size than we found for CBT in our sensitivity analysis, which may be explained by the broader inclusion criteria used by Natale et al., whose study also included quasi-RCT's and studies on patients with and without depressive symptoms which potentially has influenced the effect sizes. The somewhat larger SMD found by our meta-analysis might be explained by CBT having a higher treatment effect in patients with current depressive symptoms, although it should be noted that our 95%CI covers both estimates as well as zero, where the latter indicates no effect of CBT. Hence, the generally similar results on CBT found by Natale et al. and our meta-analysis, which is done on a subset of RCT studies with only clinically

depressed patients reviewed by Natale et al, is an interesting outcome and relevant for clinical practice.

Given the moderate heterogeneity, the use of different control groups, and high risk of bias due to no blinding and per protocol analyses, the effect size found in this meta-analysis may be overestimated and should be interpreted with care.(46) The moderate heterogeneity (I^2 = 52%, X^2 = 12.56, p=0.05) found in our study may be explained by the use of different study designs, different patient characteristics and most importantly different psychotherapeutic treatments, including CBT, PST, third-wave psychotherapies such as ACT and mindfulness-based cognitive therapy. CBT and PST are practical and rational therapies, where CBT focusses on identifying distorted cognitions, moods and behaviors and helps the patient with cognitive restructuring and behavioral activation, and PST focusses on difficulties patients encounter in live and teaches them structured problem-solving techniques to help solve their problems.(27-29, 47) ACT approaches psychopathology as psychological inflexibility which causes experiential avoidance and aims to encourage patients to counter this avoidance by teaching acceptance and mindfulness skills.(32) Mindfulness-based cognitive therapy focusses on meditation techniques where patients are guided to enter into moment-to-moment non-judgmental awareness.(33) Our systematic review did not provide sufficient number of studies on each type of psychotherapy to warrant a further stratification or comparison on the different types of psychotherapies.

SSRI's

RCT's on the use of antidepressants in the dialysis population versus a placebo control group are scarce.(48-50) In this review only 2 out of 4 studies could be included in the meta-analysis, both investigating sertraline in comparison with placebo. Mehrotra et al. recently performed a RCT comparing CBT and sertraline treatment in hemodialysis patients with depression and found a modestly better improvement in depression score with sertraline than with CBT (MD -1.84 [-3.54; -0.13]).(16) However, this study could not be included because of the absence of a placebo group. The relatively low pooled effect of sertraline found in our meta-analysis has a very large confidence interval (-0.57 [-6.17; 5.02]) and more evidence is needed to make any type of conclusion regarding the efficacy of SSRIs in dialysis patients.

Other outcomes

Four studies on dietary supplements show small to moderate effect sizes on depressive symptoms indicating that it might be beneficial to use dietary supplements for depression in dialysis patients. Exercise training is known to have significant beneficial effects in CKD patients on physical fitness, cardiovascular dimensions and quality of life.(51) In comparison to the review of Natale et al., we found no evidence on relaxation therapy and only one study on exercise training in dialysis patients, which shows a promising effect on depression and cardiac autonomic outflow in a relatively young hemodialysis cohort with a mean age of

46.(42) However, these results on dietary supplements and exercise training should be validated in other populations before any conclusion can be drawn.

The pooled effects of studies on secondary outcomes shows a small effect size on anxiety symptoms and a small to moderate effect on quality of life. Data on other secondary outcomes were not reported, hence no conclusions on treatment satisfaction, cost-effectiveness or the effect of treatment on mortality and hospitalization can be drawn.

Future research

Although we included studies from the inception of the searched databases, the first reported study on this topic was in 1997, which might be more recent than expected. The most likely explanation for this is the increased focus on patient-related outcomes and changes in attitudes towards treatment of mental health in dialysis patients during this period.

Considering the known high prevalence of depression in dialysis patients, it is surprising that adequately powered RCT's on treatment of depressive symptoms are relatively scarce in dialysis patients. There are consistently more studies on CBT than for any other therapeutic approach, which makes the relative comparison between different treatment options difficult.

Reasons for the low number of trials on treating current depressive symptoms in this population may be due to the experience that many trials in the dialysis setting have problems with recruitment and retention rates and protocol adherence.(52)

Almost all included studies used per protocol analysis. By not performing an intention to treat analysis, a potential bias due to post-randomization exclusion of patients is created, which most likely will overestimate the true effect and increases the risk of a type I error.(53-55). Seven of the studies in this review excluded patients with medical illnesses other than kidney failure or a life expectancy of less than one year. As most dialysis patients have multiple medical issues and a short life expectancy, this might reduce the generalizability of the results.

Future research should focus on adequately designed RCTs for evaluation of psychotherapy, antidepressants and dietary supplements in dialysis patients with a) an adequate power calculation and sample size, b) an intention to treat analysis, c) blinding where possible, d) a selection of patients on current above threshold depressive symptoms and d) comparing the intervention of interest with a well-defined care as usual group.

Conclusion

This systematic review and meta-analysis suggests that treatment of clinical depression in dialysis patients with psychotherapy, especially practical and rational therapies such as CBT, PST and psycho-education, are most promising, while the effect of antidepressants is

currently inclusive due to lack of studies. Given the large burden of depressive symptoms in dialysis patients and proven effectivity in other medically ill patient populations, it is advisable to offer psychotherapy to dialysis patients with depressive symptoms. Various life style interventions like dietary supplements and exercise programs have shown positive effects as well, but more studies will be needed before definitive conclusions can be made, also in comparison with and in addition to psychotherapy.

References

1. Palmer S, Vecchio M, Craig JC, Tonelli M, Johnson DW, Nicolucci A, Pellegrini F, Saglimbene V, Logroscino G, Fishbane S, Strippoli GF: Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. Kidney Int, 84: 179-191, 2013
2. Farrokhi 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. American journal of kidney diseases : the official journal of the National Kidney Foundation, 63: 623-635, 2014
3. Hedayati SS, Minhajuddin AT, Afshar M, Toto RD, Trivedi MH, Rush AJ: Association between major depressive episodes in patients with chronic kidney disease and initiation of dialysis, hospitalization, or death. JAMA, 303: 1946-1953, 2010
4. 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. American journal of kidney diseases : the official journal of the National Kidney Foundation, 46: 642-649, 2005
5. Lopes AA, Bragg J, Young E, Goodkin D, Mapes D, Combe C, Piera L, Held P, Gillespie B, Port FK, Dialysis O, Practice Patterns S: Depression as a predictor of mortality and hospitalization among hemodialysis patients in the United States and Europe. Kidney Int, 62: 199-207, 2002
6. Cukor D, Rosenthal DS, Jindal RM, Brown CD, Kimmel PL: Depression is an important contributor to low medication adherence in hemodialyzed patients and transplant recipients. Kidney Int, 75: 1223-1229, 2009
7. Schouten RW, Harmse VJ, Dekker FW, van Ballegooijen W, Siegert CEH, Honig A: Dimensions of Depressive Symptoms and Their Association With Mortality, Hospitalization, and Quality of Life in Dialysis Patients: A Cohort Study. Psychosom Med, 81: 649-658, 2019
8. Cukor D, Coplan J, Brown C, Peterson RA, Kimmel PL: Course of depression and anxiety diagnosis in patients treated with hemodialysis: a 16-month follow-up. Clinical journal of the American Society of Nephrology : CJASN, 3: 1752-1758, 2008
9. Schouten RW, Haverkamp GL, Loosman WL, Chandie Shaw PK, van Ittersum FJ, Smets YFC, Vleming LJ, Dekker FW, Honig A, Siegert CEH: Anxiety Symptoms, Mortality, and Hospitalization in Patients Receiving Maintenance Dialysis: A Cohort Study. American journal of kidney diseases : the official journal of the National Kidney Foundation, 2019
10. Soykan A, Boztas H, Kutlay S, Ince E, Aygor B, Ozden A, Nergizoglu G, Berksun O: Depression and its 6-month course in untreated hemodialysis patients: a preliminary prospective follow-up study in Turkey. Int J Behav Med, 11: 243-246, 2004
11. Johnson S, Dwyer A: Patient perceived barriers to treatment of depression and anxiety in hemodialysis patients. Clin Nephrol, 69: 201-206, 2008
12. Palmer SC, Natale P, Ruospo M, Saglimbene VM, Rabindranath KS, Craig JC, Strippoli GF: Antidepressants for treating depression in adults with end-stage kidney disease treated with dialysis. Cochrane Database Syst Rev: CD004541, 2016
13. Hedayati SS, Gregg LP, Carmody T, Jain N, Toups M, Rush AJ, Toto RD, Trivedi MH: Effect of Sertraline on Depressive Symptoms in Patients With Chronic Kidney Disease Without Dialysis Dependence: The CAST Randomized Clinical Trial. JAMA, 318: 1876-1890, 2017

14. Pena-Polanco JE, Mor MK, Tohme FA, Fine MJ, Palevsky PM, Weisbord SD: Acceptance of Antidepressant Treatment by Patients on Hemodialysis and Their Renal Providers. Clinical journal of the American Society of Nephrology : CJASN, 12: 298-303, 2017
15. Cuijpers P, Karyotaki E, Reijnders M, Huibers MJH: Who benefits from psychotherapies for adult depression? A meta-analytic update of the evidence. Cogn Behav Ther, 47: 91-106, 2018
16. Mehrotra R, Cukor D, Unruh M, Rue T, Heagerty P, Cohen SD, Dember LM, Diaz-Linhart Y, Dubovsky A, Greene T, Grote N, Kutner N, Trivedi MH, Quinn DK, Ver Halen N, Weisbord SD, Young BA, Kimmel PL, Hedayati SS: Comparative Efficacy of Therapies for Treatment of Depression for Patients Undergoing Maintenance Hemodialysis: A Randomized Clinical Trial. Ann Intern Med, 170: 369-379, 2019
17. 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, 12: CD004542, 2019
18. Natale P, Palmer S, Ruospo M, Rabindranath K, Hegbrant J, Strippoli G: FP386PSYCHOSOCIAL INTERVENTIONS FOR PREVENTING AND TREATING DEPRESSION IN DIALYSIS PATIENTS. Nephrology Dialysis Transplantation, 34, 2019
19. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol, 62: 1006-1012, 2009
20. Nadort E SR, Honig A, Siegert C, Dekker F, van Oppen P: Treatment of depressive symptoms in dialysis patients: a systematic review. PROSPERO International prospective register of systematic reviews, 2018
21. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T: De-duplication of database search results for systematic reviews in EndNote. J Med Libr Assoc, 104: 240-243, 2016
22. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A: Rayyan-a web and mobile app for systematic reviews. Syst Rev, 5: 210, 2016
23. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, Cochrane Bias Methods G, Cochrane Statistical Methods G: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ, 343: d5928, 2011
24. McMaster University: GRADEpro Guideline Development Tool,. (gradepro.org),, developed by Evidence Prime Inc., 2015
25. Viechtbauer W: Conducting Meta-Analyses in R with The metafor Package. Journal of Statistical Software, 36, 2010
26. Rover C, Knapp G, Friede T: Hartung-Knapp-Sidik-Jonkman approach and its modification for random-effects meta-analysis with few studies. BMC Med Res Methodol, 15: 99, 2015
27. Cukor D, Ver Halen N, Asher DR, Coplan JD, Weedon J, Wyka KE, Saggi SJ, Kimmel PL: Psychosocial intervention improves depression, quality of life, and fluid adherence in hemodialysis. J Am Soc Nephrol, 25: 196-206, 2014
28. Lerma A, Perez-Grovas H, Bermudez L, Peralta-Pedrero ML, Robles-Garcia R, Lerma C: Brief cognitive behavioural intervention for depression and anxiety symptoms improves quality of life in chronic haemodialysis patients. Psychol Psychother, 90: 105-123, 2017
29. Duarte PS, Miyazaki MC, Blay SL, Sesso R: Cognitive-behavioral group therapy is an effective treatment for major depression in hemodialysis patients. Kidney Int, 76: 414-421, 2009
30. Kucuk L, Işil Ö: The Effects of Problem Solving Education on Depression Level and Problem Solving Skills on Dialysis Patients, 2009

31. Espahbodi F, Hosseini H, Mirzade MM, Shafaat AB: Effect of Psycho Education on Depression and Anxiety Symptoms in Patients on Hemodialysis. Iran J Psychiatry Behav Sci, 9: e227, 2015
32. W. V: Acceptance and Commitment Therapy self-help intervention for depression in
1. haemodialysis patients: A feasibility randomised controlled trial. College of Social Science, School of Psychology. Lincoln, University of Lincoln, 2016 pp 176
33. Thomas Z, Novak M, Platas SGT, Gautier M, Holgin AP, Fox R, Segal M, Looper KJ, Lipman M, Selchen S, Mucsi I, Herrmann N, Rej S: Brief Mindfulness Meditation for Depression and Anxiety Symptoms in Patients Undergoing Hemodialysis: A Pilot Feasibility Study. Clinical journal of the American Society of Nephrology : CJASN, 12: 2008-2015, 2017
34. Friedli K, Guirguis A, Almond M, Day C, Chilcot J, Da Silva-Gane M, Davenport A, Fineberg NA, Spencer B, Wellsted D, Farrington K: Sertraline Versus Placebo in Patients with Major Depressive Disorder Undergoing Hemodialysis: A Randomized, Controlled Feasibility Trial. Clinical journal of the American Society of Nephrology : CJASN, 12: 280-286, 2017
35. Taraz M, Khatami MR, Dashti-Khavidaki S, Akhonzadeh S, Noorbala AA, Ghaeli P, Taraz S: Sertraline decreases serum level of interleukin-6 (IL-6) in hemodialysis patients with depression: results of a randomized double-blind, placebo-controlled clinical trial. Int Immunopharmacol, 17: 917-923, 2013
36. Blumenfield M, Levy NB, Spinowitz B, Charytan C, Beasley CM, Jr., Dubey AK, Solomon RJ, Todd R, Goodman A, Bergstrom RF: Fluoxetine in depressed patients on dialysis. Int J Psychiatry Med, 27: 71-80, 1997
37. Yazici A, Erdem P, Erdem A, Yazici K, Acar S, Basterzi A: Efficacy and tolerability of escitalopram in depressed patients with end stage renal disease: an open placebo-controlled study. Klinik psikofarmakoloji bulteni. 2012 pp 23-30
38. Dashti-Khavidaki S, Gharekhani A, Khatami MR, Miri ES, Khalili H, Razeghi E, Hashemi-Nazari SS, Mansournia MA: Effects of omega-3 fatty acids on depression and quality of life in maintenance hemodialysis patients. Am J Ther, 21: 275-287, 2014
39. Wang Y, Liu Y, Lian Y, Li N, Liu H, Li G: Efficacy of High-Dose Supplementation With Oral Vitamin D3 on Depressive Symptoms in Dialysis Patients With Vitamin D3 Insufficiency: A Prospective, Randomized, Double-Blind Study. J Clin Psychopharmacol, 36: 229-235, 2016
40. Wang X, Feng Q, Xiao Y, Li P: Radix Bupleuri ameliorates depression by increasing nerve growth factor and brain-derived neurotrophic factor. Int J Clin Exp Med, 8: 9205-9217, 2015
41. Haghighat N, Rajabi S, Mohammadshahi M: Effect of synbiotic and probiotic supplementation on serum brain-derived neurotrophic factor level, depression and anxiety symptoms in hemodialysis patients: a randomized, double-blinded, clinical trial. Nutr Neurosci: 1-10, 2019
42. Kouidi E, Karagiannis V, Grekas D, Iakovides A, Kaprinis G, Tourkantonis A, Deligiannis A: Depression, heart rate variability, and exercise training in dialysis patients. Eur J Cardiovasc Prev Rehabil, 17: 160-167, 2010
43. Babamohamadi H, Sotodehasl N, Koenig HG, Al Zaben F, Jahani C, Ghorbani R: The Effect of Holy Qur'an Recitation on Depressive Symptoms in Hemodialysis Patients: A Randomized Clinical Trial. J Relig Health, 56: 345-354, 2017
44. Yazıcı AE, Erdem P, Erdem A, Yazıcı K, Acar ŞT, Başterzi AD, Taşdelen B: Depresyonu Olan Son Dönem Böbrek Yetmezliği Hastalarında Essitalopramın Etkinliği ve Tolerabilitesi: Bir Açık Plasebo Kontrollü Çalışma. Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology, 22: 23-30, 2016

45. Baujat B, Mahe C, Pignon JP, Hill C: A graphical method for exploring heterogeneity in meta-analyses: application to a meta-analysis of 65 trials. Stat Med, 21: 2641-2652, 2002
46. Cuijpers P, Karyotaki E, Reijnders M, Ebert DD: Was Eysenck right after all? A reassessment of the effects of psychotherapy for adult depression. Epidemiol Psychiatr Sci, 28: 21-30, 2019
47. Mynors-Wallis L: Problem solving treatment for anxiety and depression: A practical guide., New York, Oxford University Press, 2005
48. Afzal A HA, Ali N, Zafar F, Ayub F, Zafar A, Lillah A: Dealing with Depression in End Stage Renal Disease, Escitalopram vs Nortryptyline. Pakistan journal of medical and health sciences, Vol. 11: pp 38-40, 2017
49. Hosseini SH, Espahbodi F, Mirzadeh Goudarzi SM: Citalopram versus psychological training for depression and anxiety symptoms in hemodialysis patients. Iran J Kidney Dis, 6: 446-451, 2012
50. Zhao C, Ma H, Yang L, Xiao Y: Long-term bicycle riding ameliorates the depression of the patients undergoing hemodialysis by affecting the levels of interleukin-6 and interleukin-18. Neuropsychiatr Dis Treat, 13: 91-100, 2017
51. Heiwe S, Jacobson SH: Exercise training for adults with chronic kidney disease. Cochrane Database Syst Rev: CD003236, 2011
52. Flythe JE, Narendra JH, Hilliard T, Frazier K, Ikeler K, Amolegbe A, Mitchell D, Dorough A, Lee SD, Ordish A, Wilkie C, Dember LM, Building Research Capacity in the Dialysis Community at the Local Level Stakeholder Workshop P: Cultivating a Research-Ready Dialysis Community. J Am Soc Nephrol, 2019
53. Fergusson D, Aaron SD, Guyatt G, Hebert P: Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. BMJ, 325: 652-654, 2002
54. Gupta SK: Intention-to-treat concept: A review. Perspect Clin Res, 2: 109-112, 2011
55. Hernan MA, Hernandez-Diaz S: Beyond the intention-to-treat in comparative effectiveness research. Clin Trials, 9: 48-55, 2012

Supplementary tables and files

Supplement S1: Search strategies in different databases

Pubmed search 9-1-2019:
"Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR "Mood Disorders"[Mesh:NoExp] OR "Adjustment Disorders"[Mesh] OR depress*[tiab] OR melanchol*[tiab] OR mdd[tiab] OR anxiety[tiab] OR "Anxiety"[Mesh] OR "Anxiety Disorders"[Mesh]
AND
"Kidney Failure, Chronic"[mesh] OR "Renal Dialysis"[Mesh] OR "Hemofiltration"[Mesh] OR Dialys*[tiab] OR hemodialys*[tiab] OR haemodialys*[tiab] OR Renal Replacement Therap*[tiab] OR Hemofiltration*[tiab] OR Hemodiafiltration*[tiab] OR Haemodiafiltration*[tiab] OR haemofiltration*[tiab] OR chronic kidney disease[tiab] OR chronic kidney failure[tiab] OR chronic renal disease[tiab] OR chronic renal failure[tiab] OR end stage kidney [tiab] OR end stage renal [tiab] OR endstage kidney[tiab] OR endstage renal[tiab] OR ESRD[tiab] OR ESKD[tiab] OR ESRF[tiab] OR ESKF[tiab] OR CAPD[tiab] OR CCPD[tiab] OR APD[tiab] OR CKD[tiab] OR CRD[tiab] OR CKF[tiab]
AND
randomized controlled trial[pt] OR controlled clinical trial[pt] OR random*[tiab] OR placebo[tiab] OR drug therapy[sh] OR trial[tiab] OR groups[tiab]

EMBASE search 9-1-2019:
'depression'/exp OR 'mood disorder'/de OR 'adjustment disorder'/exp OR 'anxiety'/exp OR 'anxiety disorder'/exp OR depress*:ab,ti OR melanchol*:ab,ti OR mdd:ab,ti OR anxiety:ab,ti
AND
'depression'/exp OR 'mood disorder'/de OR 'adjustment disorder'/exp OR 'anxiety'/exp OR 'anxiety disorder'/exp OR depress*:ab,ti OR melanchol*:ab,ti OR mdd:ab,ti OR anxiety:ab,ti
AND
random* OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR ((tripl* OR trebl*) AND blind*) OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'controlled clinical trial'/de OR 'single blind procedure'/exp OR 'placebo'/exp OR 'randomization'/exp

The Cochrane Library (CENTRAL, Cochrane reviews) search 9-1-2019:
(depress* OR melanchol* OR mdd OR anxiety):ti,ab,kw
AND
(Dialys* OR hemodialys* OR haemodialys* OR (Renal Replacement NEXT Therap*) OR Hemofiltration* OR Hemodiafiltration* OR Haemodiafiltration* OR haemofiltration* OR "chronic kidney disease" OR "chronic kidney failure" OR "chronic renal disease" OR "chronic renal failure" OR "end stage kidney" OR "end stage renal" OR "endstage kidney" OR "endstage renal" OR ESRD OR ESKD OR ESRF OR ESKF OR CAPD OR CCPD OR APD OR CKD OR CRD OR CKF):ti,ab,kw

PsycInfo via EBSCOhost search 9-1-2019:
DE "Depression Emotion" OR DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Endogenous Depression" OR DE "Late Life Depression" OR DE "Postpartum Depression" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression" OR DE "Atypical Depression" OR DE "Affective Disorders" OR DE "Anxiety" OR DE "Anxiety Disorders" OR DE "Acute Stress Disorder" OR DE "Death Anxiety" OR DE "Generalized Anxiety Disorder" OR DE "Obsessive Compulsive Disorder" OR DE "Panic Disorder" OR DE "Phobias" OR DE "Post-Traumatic Stress" OR DE "Posttraumatic Stress Disorder" OR DE "Separation Anxiety Disorder" OR DE "Adjustment Disorders" OR (TI (depress* OR melanchol* OR mdd OR anxiety) OR AB (depress* OR melanchol* OR mdd OR anxiety))

AND
DE "Dialysis" OR DE "Hemodialysis" OR (TI (Dialys* OR hemodialys* OR haemodialys* OR Renal-Replacement-Therap* OR Hemofiltration* OR haemofiltration* OR Hemodiafiltration* OR haemodiafiltration* OR "chronic kidney disease" OR "chronic kidney failure" OR "chronic renal disease" OR "chronic renal failure" OR "end stage kidney" OR "end stage renal" OR "endstage kidney" OR "endstage renal" OR ESRD OR ESKD OR ESRF OR ESKF OR CAPD OR CCPD OR APD OR CKD OR CRD OR CKF) OR AB (Dialys* OR hemodialys* OR haemodialys* OR Renal-Replacement-Therap* OR Hemofiltration* OR haemofiltration* OR Hemodiafiltration* OR haemodiafiltration* OR "chronic kidney disease" OR "chronic kidney failure" OR "chronic renal disease" OR "chronic renal failure" OR "end stage kidney" OR "end stage renal" OR "endstage kidney" OR "endstage renal" OR ESRD OR ESKD OR ESRF OR ESKF OR CAPD OR CCPD OR APD OR CKD OR CRD OR CKF))
AND
DE "Treatment Effectiveness Evaluation" OR DE "Clinical Trials" OR DE "Mental Health Program Evaluation" OR DE "Placebo" OR TI placebo* OR AB placebo* OR AB randomly OR TX randomi* OR TI trial OR AB trial OR TX ((singl* OR doubl* OR trebl* OR tripl*) N3 (blind* OR mask* OR dummy)) OR TI (control* N3 (trial* OR study OR studies OR group*)) OR AB (control* N3 (trial* OR study OR studies OR group*)) OR TI factorial* OR AB factorial* OR TI allocat* OR AB allocat* OR TI assign* OR AB assign* OR TI volunteer* OR AB volunteer* OR TI (crossover* OR "cross over*") OR AB (crossover* OR "cross over*") OR TX (quasi N5 (experimental OR random*))

Web Of Science search 9-1-2019 (Databases searched: SCI-EXPANDED, SSCI, A&HCI, ESCI):
TOPIC: (depress* OR melanchol* OR mdd OR anxiety)
AND
TOPIC: (Dialys* OR hemodialys* OR haemodialys* OR Renal-Replacement-Therap* OR Hemofiltration* OR Hemodiafiltration* OR Haemodiafiltration* OR haemofiltration* OR "chronic kidney disease" OR "chronic kidney failure" OR "chronic renal disease" OR "chronic renal failure" OR "end stage kidney" OR "end stage renal" OR "endstage kidney" OR" endstage renal" OR ESRD OR ESKD OR ESRF OR ESKF OR CAPD OR CCPD OR APD OR CKD OR CRD OR CKF)
AND
TOPIC: (random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)

CINAHL via EBSCOhost search 9-1-2019:
(MH "Depression+") OR (MH "Affective Disorders") OR (MH "Anxiety Disorders+") OR (MH "Adjustment Disorders+") OR (TI (depress* OR melanchol* OR mdd OR anxiety) OR AB (depress* OR melanchol* OR mdd OR anxiety))
AND
(MH "Dialysis+") OR (MH "Hemofiltration+") OR (MH "Hemodialysis+") OR (MH "Peritoneal Dialysis+") OR (MH "Kidney Failure, Chronic+") OR (TI (Dialys* OR hemodialys* OR haemodialys* OR Renal Replacement Therap* OR Hemofiltration* OR haemofiltration* OR Hemodiafiltration* OR haemodiafiltration* OR "chronic kidney disease" OR "chronic kidney failure" OR "chronic renal disease" OR "chronic renal failure" OR "end stage kidney" OR "end stage renal" OR "endstage kidney" OR "endstage renal" OR ESRD OR ESKD OR ESRF OR ESKF OR CAPD OR CCPD OR APD OR CKD OR CRD OR CKF) OR AB (Dialys* OR hemodialys* OR haemodialys* OR Renal Replacement Therap* OR Hemofiltration* OR haemofiltration* OR Hemodiafiltration* OR haemodiafiltration* OR "chronic kidney disease" OR "chronic kidney failure" OR "chronic renal disease" OR "chronic renal failure" OR "end stage kidney" OR "end stage renal" OR "endstage kidney" OR "endstage renal" OR ESRD OR ESKD OR ESRF OR ESKF OR CAPD OR CCPD OR APD OR CKD OR CRD OR CKF))
AND
(MH "Clinical Trials+") OR (PT (Clinical trial)) OR (MH "Random Assignment") OR (MH "Quantitative Studies") OR (TX ((clini* N1 trial*) OR (singl* N1 blind*) OR (singl* N1 mask*) OR (doubl* N1 blind*) OR (doubl* N1 mask*) OR (tripl* N1 blind*) OR (tripl* N1 mask*) OR (trebl* n1 blind*) or (trebl* n1

mask*) OR (random* N1 allocat*) OR placebo* OR (MH "Placebos") OR (control* N3 (trial* OR study OR studies OR group*)) OR randomized OR randomised))

WHO ICTRP search 9-1-2019:
Title: renal OR kidney OR dialysis OR hemodialysis OR haemodialysis OR Hemofiltration OR haemofiltration OR Hemodiafiltration OR haemodiafiltration. Condition: depression OR depressive OR anxiety OR melancholia OR melancholic OR mdd. Recruitment status: all
OR
Title: depression OR depressive OR anxiety OR melancholia OR melancholic OR mdd. Condition: renal OR kidney OR dialysis OR hemodialysis OR haemodialysis OR Hemofiltration OR haemofiltration OR Hemodiafiltration OR haemodiafiltration. Recruitment status: all

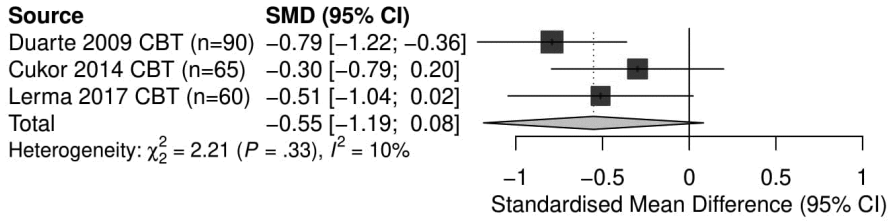
Clinicaltrials.gov search 9-1-2019:
Condition or disease: renal OR kidney OR dialysis OR hemodialysis OR haemodialysis OR Hemofiltration OR haemofiltration OR Hemodiafiltration OR haemodiafiltration
AND
Other terms: depression OR depressive OR anxiety OR melancholia OR melancholic OR mdd. Trial Status: all

Supplement S2: R-code

```
#Meta-analysis code for R, performed by R. Schouten

#packages used
install.packages("meta")
install.packages("metafor")

#load packages
library("meta")
library("metafor")

#set workingdirectory
setwd

#load dataset
Data1 <- All studies
Data2 <- Psychotherapy only
Data3 <- CBT only
Data4 <- SSRI only
Data5 <- Anxiety studies
Data6 <- QoL studies

#meta-analysis using all studies
meta1 <- metacont(Ne, Me, Se, Nc, Mc, Sc, data=Data1, studlab=paste(Subgroup, Author, Year),
comb.fixed=FALSE, comb.random=TRUE,method.tau="SJ",hakn=TRUE,sm = "SMD")
forest(meta1, layout= "JAMA", text.predict="95% PI", col.predict="black")
funnel(meta1, studlab=TRUE)
baujat(meta1)

#meta-analysis psychotherapy only
meta2 <- metacont(Ne, Me, Se, Nc, Mc, Sc, data=Data2, studlab=paste(Subgroup, Author, Year),
comb.fixed=FALSE, comb.random=TRUE,method.tau="SJ",hakn=TRUE,sm = "SMD")
forest(meta2, layout= "JAMA", text.predict="95% PI", col.predict="black")
funnel(meta2, studlab=TRUE)
baujat(meta2)

#meta-analysis CBT only
meta3 <- metacont(Ne, Me, Se, Nc, Mc, Sc, data=Data3, studlab=paste(Subgroup, Author, Year),
comb.fixed=FALSE, comb.random=TRUE,method.tau="SJ",hakn=TRUE,sm = "SMD")
forest(meta3, layout= "JAMA", text.predict="95% PI", col.predict="black")
funnel(meta3, studlab=TRUE)
baujat(meta3)

#meta-analysis SSRI only
meta4 <- metacont(Ne, Me, Se, Nc, Mc, Sc, data=Data4, studlab=paste(Subgroup, Author, Year),
comb.fixed=FALSE, comb.random=TRUE,method.tau="SJ",hakn=TRUE,sm = "SMD")
forest(meta4, layout= "JAMA", text.predict="95% PI", col.predict="black")
funnel(meta4, studlab=TRUE)
baujat(meta4)

#meta-analysis Anxiety
```

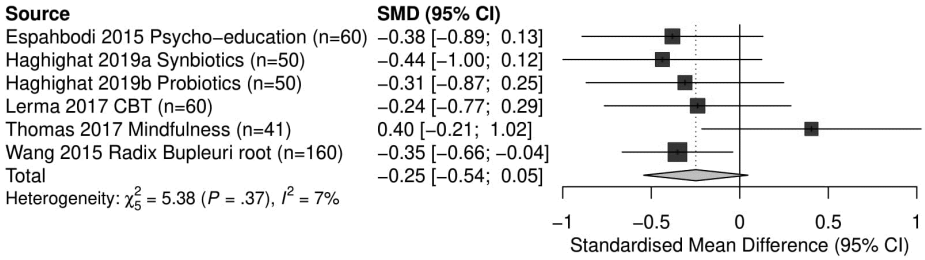
```
meta5 <- metacont(Ne, Me, Se, Nc, Mc, Sc, data=Data5, studlab=paste(Subgroup, Author, Year),
comb.fixed=FALSE, comb.random=TRUE,method.tau="SJ",hakn=TRUE,sm = "SMD")
forest(meta5, layout= "JAMA", text.predict="95% PI", col.predict="black")
funnel(meta5, studlab=TRUE)
baujat(meta5)

#meta-analysis QoL
meta6 <- metacont(Ne, Me, Se, Nc, Mc, Sc, data=Data6, studlab=paste(Subgroup, Author, Year),
comb.fixed=FALSE, comb.random=TRUE,method.tau="SJ",hakn=TRUE,sm = "SMD")
forest(meta6, layout= "JAMA", text.predict="95% PI", col.predict="black")
funnel(meta6, studlab=TRUE)
baujat(meta6)
```

Supplementary table S3: Forest plot including CBT only



CBT = cognitive behavioral therapy, SMD = standardized mean difference, CI = confidence interval.

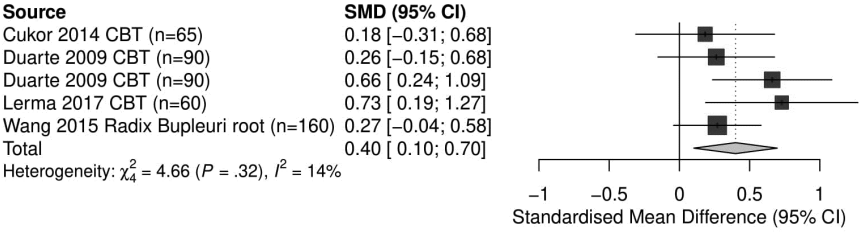
Supplementary table S4a: Forest plot with anxiety symptoms as the outcome



CBT = cognitive behavioral therapy, SMD = standardized mean difference, CI = confidence interval

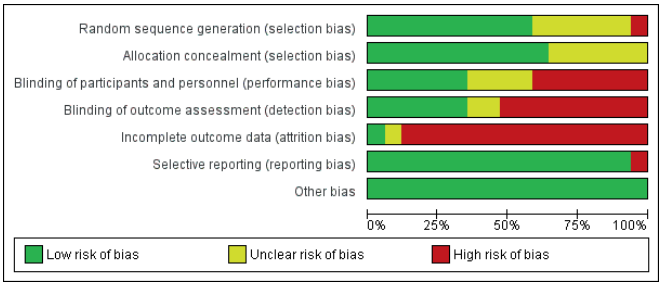
7

Supplementary figure S4b: Forest plot with quality of life as the outcome

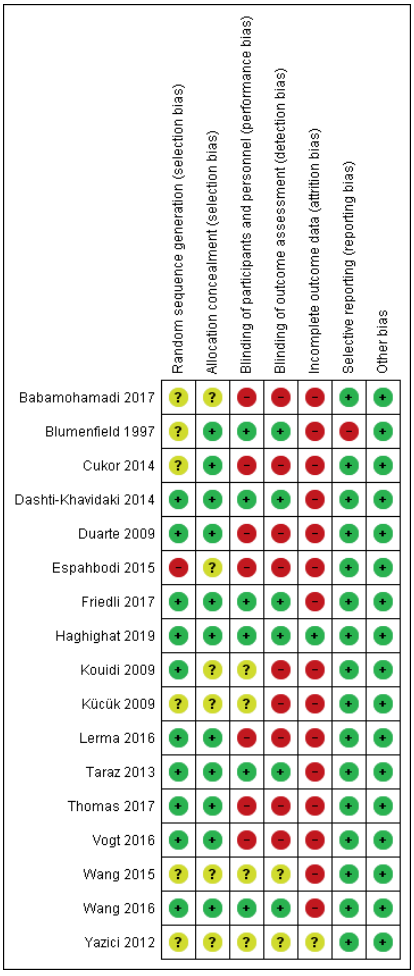


CBT = cognitive behavioral therapy, SMD = standardized mean difference, CI = confidence interval

Supplementary figure S5a. Risk of Bias of included studies



Supplementary figure S5b. Risk of bias summary per type of bias



Supplement S6:

Table S6a: Effectivity of treatment for symptoms of Anxiety

First author	Type of intervention	Anxiety scale	Outcome SMD (95%CI)
Espahbodi	Group psycho-ed. 3 sessions	HADS-A	-0.38 [-0.89; 013]
Haghighat	Synbiotic Probiotic 3 months	HADS-A	-0.44 [-1.00; 0.12] -0.31 [-0.87; 0.25]
Lerma	CBT group 5 sessions	BAI	-0.24 [-0.77; 0.29]
Thomas	Mindfulness 13 sessions	GAD-7	0.40 [-0.21; 1.02]
Wang	Radix Bupleuri 12 weeks	HADS-A	-0.35 [-0.66; -0.04]
Yazici	Escitalopram 8 weeks	HAM-A	-

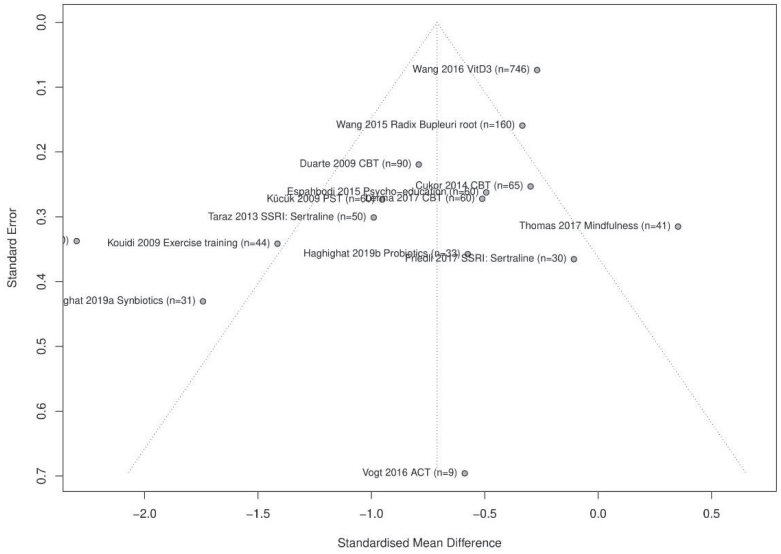
BAI = Beck Anxiety Inventory , CBT = cognitive behavioral therapy, CI = confidence interval, GAD-7 = General Anxiety Disorder-7, HADS-A = Hospital Anxiety Depression Scale – Anxiety, HAM-A = Hamilton Rating Scale for Anxiety , SMD = standardized mean difference.

Table S6b: Effectivity of treatment for quality of life

First author	Type of intervention	QoL	Outcome SMD (95%CI)
Cukor	CBT individual 10 sessions	KDQOL-SF	0.18 [-0.31; 0.68]
Dashti-Khavidaki	Omega-3 16 weeks	SF-36	-
Duarte	CBT group 12 sessions	KDQoL-SF	0.26 [-0.15; 0.68] 0.66 [0.24; 1.09]
Lerma	CBT group 5 sessions	QoL Scale	0.73 [0.169; 1.27]
Vogt	ACT 6 sessions	EQ-5D-5L	-
Wang	Radix Bupleuri 12 weeks	SF-36	0.27 [-0.04; 0.58]

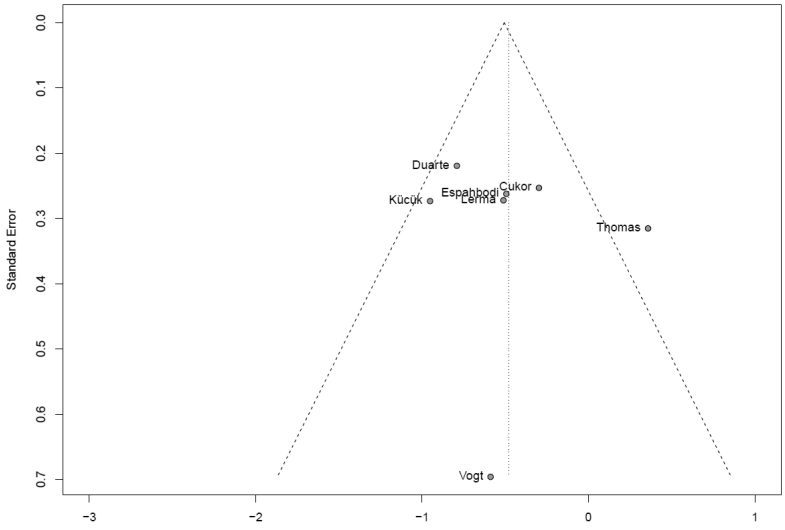
CBT = cognitive behavioral therapy, CI = confidence interval, EQ-5D-5L = 5 level EuroQol five dimension scale, KDQOL-SF = Kidney Disease Quality of Life Scale, SF-36 = Medical Outcome Study 36-item Short Form Health Survey, SMD = standardized mean difference, QoL scale = QoL Profile in the Chronically Ill scale.

Supplement S7a: Funnel plot including all studies from the pooled analysis

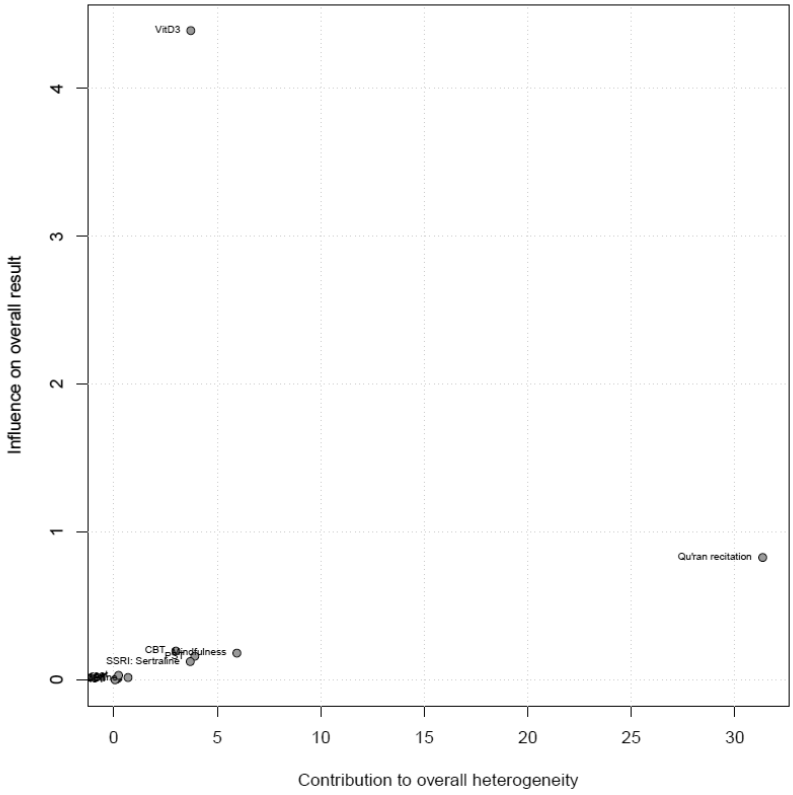


ACT = Acceptance and commitment therapy, CBT = Cognitive behavioural therapy, PST = Problem solving therapy, SSRI = selective serotonin reuptake inhibitor,VitD3 = Vitamine D3

S7b: Funnel plot including studies on psychotherapy only



Supplement S8: Baujat plot for exploring heterogeneity in the meta-analyses.



ACT = Acceptance and commitment therapy, CBT = Cognitive behavioral therapy, PST = Problem solving therapy, SSRI = selective serotonin reuptake inhibitor,VitD3 = Vitamin D3

Supplement S9: Quality of evidence of included studies using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Outcome	No of studies	Quality assessment (GRADE)					Quality of the evidence
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	
Psychotherapy on depression	8	Serious (-1)*	None (0)	None (0)	Serious (-1)**	None (0)	Low
Antidepressants on depression	4	Serious (-1)***	None (0)	None (0)	Very serious (-2)**	None (0)	Very low
Anxiety	4	Serious (-1)*	None (0)	None (0)	Very serious (-2)**	None (0)	Very low
Quality of Life	4	Serious (-1)*	None (0)	None (0)	Serious (-1)**	None (0)	Low

No = number, GRADE = Grading of Recommendations Assessment, Development, and Evaluation

*No blinding of participants, personnel and outcome assessment and per protocol analysis.
**Confidence intervals include both no effect and appreciable benefit and harm.
***Per protocol analysis.

Supplement S10: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6, 30-31
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9, 27
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9, 23
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10-11, 36
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	23, 28
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10, 28
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	35
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	33-34
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

Chapter 8

The (cost) effectiveness of internet-based self-help CBT for dialysis patients with symptoms of depression: study protocol of a randomized controlled trial.

Nadort E, Schouten RW, Dekker FW, Honig A,
van Oppen P, Siegert CEH.

BMC Psychiatry; 27 November 2019; Article number 372

Abstract

Background: Only a minority of dialysis patients with depressive symptoms are diagnosed and receive treatment. Depressive symptoms are highly prevalent in this population and are associated with adverse clinical outcomes. Underlying factors for this undertreatment may be the lack of evidence for the safety and effectivity of antidepressant medication, the reluctance of patients to adhere to antidepressant medication, the lack of mental healthcare provision in somatic healthcare environments and end-stage renal disease (ESRD) related physical limitations that complicate face-to-face psychotherapy. Guided Internet-based self-help treatment has demonstrated to be effective for depressive symptoms in other chronic patient populations and may overcome these barriers. The aim of this study is to investigate the (cost) effectiveness of a guided Internet-based self-help intervention for symptoms of depression in dialysis patients.

Methods: This study is a cluster randomized controlled trial (RCT) that investigates the effectiveness of a 5-week Internet-based self-help Problem Solving Therapy (PST) for depressive symptoms in dialysis patients. Depressive symptoms will be measured using the Beck Depression Inventory – second edition (BDI-II), with a cut-off score of ≥10. We aim to include 206 dialysis patients with depressive symptoms who will be cluster randomized to the intervention or the Care as Usual (CAU) control group. Secondary outcomes will include anxiety symptoms, quality of life, economic costs and clinical outcomes, such as inflammatory factors and hair cortisol levels. Assessments will take place at baseline (T0), 2 weeks after intervention (T1) and 6 months (T2), 12 months (T3) and 18 months (T4) after intervention. The control group will be measured at the same time points. Analysis will be based on the intention-to-treat principle. Mixed models will be used to assess the changes within each condition between pre-treatment and post-treatment.

Discussion: If demonstrated to be (cost) effective, Internet-based PST will offer new possibilities to treat dialysis patients with depressive symptoms and to improve their quality of care.

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

Background

Only in a minority of dialysis patients, depressive symptoms are diagnosed and treated.(1) However, depressive symptoms are highly prevalent in this population and are associated with adverse clinical outcomes.(2) These symptoms are a major burden to the individual dialysis patient causing decreased quality of life and are associated with decreased adherence to dialysis prescription and lifestyle advice, increased hospitalization and decreased survival.(1, 3, 4) Furthermore, the social and economic costs related to depression in the dialysis population are substantial. The effect of depressive symptoms on the increase of health care costs seem to be independent of other factors, such as comorbidities, dialysis aspects and demographic variables.(1, 4)

Depressive symptoms and its impairments do not remit spontaneously if left untreated.(5, 6) Underlying factors for under-treatment of depressive symptoms with medication are a lack of evidence for the safety and effectivity of antidepressant medication in dialysis patients(7, 8) and the reluctance of patients to adhere to antidepressant medication(9, 10). Psychotherapy could be a safe alternative, with promising results in the few published trials in the end-stage renal disease (ESRD) population.(11-13) However, barriers to receive psychotherapy are the lack of mental healthcare provision in somatic healthcare environments and ESRD related physical limitations such as fatigue and other physical impairments that may reduce the ability of patients to attend face-to-face psychotherapy.

Guided online self-help cognitive behavioral treatment tailored to dialysis patients may be a promising tool for treatment of depression in this population. A guided cognitive-behavioral internet-based self-help intervention can overcome various barriers with respect to face-to-face interventions as it is easy accessible, home or dialysis-based and can be followed in one's own limited time.(14) Self-help treatment has been proven effective in psychological distress in people with and without chronic physical health conditions.(15-19) These self-help interventions have proven equally effective in terms of reducing depressive symptoms and adherence compared to face-to-face psychological interventions, when they are guided by a therapist.(20) Feasibility trials with online self-help cognitive behavioral treatment in dialysis patients show promising results but, to the best of our knowledge, no adequately powered randomized controlled trial (RCT) has yet been performed.(16, 21-24)

A commonly used brief, structured, psychological intervention adapted for use in the medical setting is Problem Solving Therapy (PST). PST is based on the assumption that depressive symptoms are caused by difficulties patients encounter in life. The goals are to teach a structured problem-solving technique to help solve the patients' current problems and to provide a sense of mastery and self-control by providing a positive experience of problem-solving.(25, 26)

Besides the lack of evidence for the effectiveness of treatment on improving depressive symptoms in dialysis patients, more insight is needed in the possible mechanisms that are

involved between somatic markers and depressive symptoms in this patient population. Numerous studies have suggested a parallel inflammatory pathway between depression and ESRD via elevated levels of inflammatory cytokines(27) or a relation between hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and depressive symptoms(28). These pathways are not yet fully understood and are founded on associations found in observational studies. Monitoring changes in stress and inflammatory markers pre- and post-treatment may provide insight in the direction of the hypothesized causal pathways.

There are no adequately powered studies that have examined the effectiveness of guided Internet-based self-help treatment in dialysis patients. Data from applying PST in other medical settings and from smaller feasibility trials in dialysis patients show promising results in improving depressive symptoms. We hypothesize that this intervention will lead to lower depressive symptoms, is better accessible and can be offered at low costs.(29, 30) The aims of this RCT are therefore multiple. First, we will evaluate clinical and cost-effectiveness of a guided internet-based self-help PST for dialysis-patients on the primary outcome measure of depressive symptoms. Secondly, we will examine the effect on the secondary outcome measures anxiety and quality of live. And thirdly, we will examine biochemical mechanisms of depression by investigating changes in inflammatory parameters and hair cortisol levels pre- and post-treatment.

Methods

Study design

This study is a multicenter, cluster RCT with an active intervention arm and a Care as Usual (CAU) control arm. The intervention is a guided 5-week Internet-based self-help PST treatment, offered on tablet-computers during dialysis sessions. The internet-based treatment is based on face-to-face PST and is guided by a therapist, who gives individual feedback to the patients via the online portal. Eligible and consenting patients will be assessed at baseline (T0), within 2 weeks after the intervention (T1), at 6 months (T2), at 12 months (T3) and at 18 months (T4) after intervention. The control group will be assessed at the same time points. Data will be collected by self-reported questionnaires during dialysis sessions. In parallel we will conduct an economic evaluation in order to assess cost-effectiveness and monitor changes in stress and inflammatory markers pre- and post-treatment to examine biochemical mechanisms of depression.

The study protocol, information brochure and informed consent were approved by the Medical Ethics Committee of MEC-U, Nieuwegein, the Netherlands (registration number: NL58520.100.17). Protocol modifications will be reported to and approved by the Medical Ethics Committee before implementation in the trial. Written informed consent is obtained from all participants. **Figure 1** displays the flow diagram of the study design. This protocol is written in accordance with the SPIRIT guidelines.

Recruitment

Dialysis patients will be recruited from 18 participating dialysis centers in 10 cities in the Netherlands. A list of study sites can be found in supplement 1. We will approach and inform all eligible dialysis patients in the participating centers about the study in close collaboration with all stakeholders, such as nephrologists, nurses and social workers. The treating nephrologist will inform the patient on the trial and introduces the research assistant in the dialysis center. If patients are willing to participate, written informed consent will be obtained by the research assistant. The attending nephrologist will be informed about participation. After giving consent, patients will be requested to complete a self-assessment questionnaire (T0) on depressive symptoms, anxiety symptoms, quality of life, dialysis symptoms and several socio-demographic questions. Blood and hair samples will be taken and stored for analysis of inflammatory parameters and cortisol levels.

Trial inclusion criteria

Chronic, adult dialysis patients, defined as being (i) 18 years or older and (ii) >90 days on dialysis treatment, who are (iii) able to fill in a questionnaire in Dutch and have (iii) a depressive symptoms score of 10 or higher on the Beck Depression Inventory – second edition (BDI-II)(31), will be randomized to the intervention or control arm. This cut-off value of 10 showed promising results in earlier feasibility trials.(21, 23)

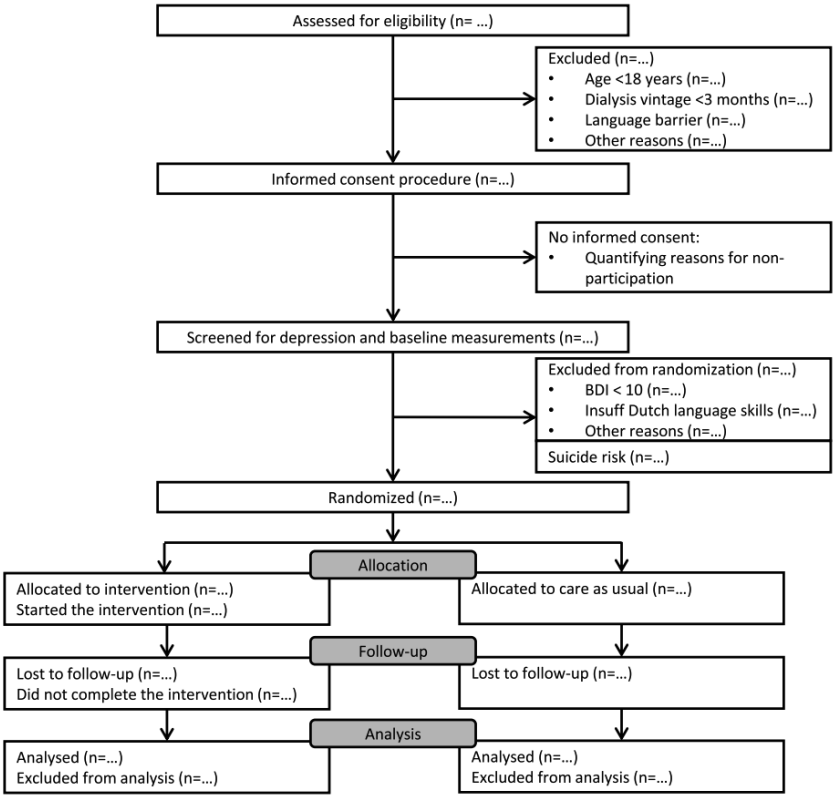
Observational cohort inclusion criteria

Chronic, adult dialysis patients who are excluded from the randomization because of a low score on the BDI-II or patients who have insufficient Dutch language skills, are offered to participate in a parallel observational cohort study. Questionnaires will also be available in Arabic, English and Turkish. In this manner we will gain information on the excluded patients and thus the generalizability of the results, which could aid in the implementation in clinical practice.

Exclusion criteria

Patients will be excluded if they are actively suicidal. If patients report suicidal ideations on item 9 of the BDI-II “suicidal thoughts and wishes” by scoring ‘2’ (“I would like to kill myself”) or ‘3’ (“I would kill myself if I had the chance”), suicide risk will be further assessed by a study doctor under supervision of a psychiatrist. If the patient is actively suicidal, the patient will be excluded from the study and the attending nephrologist will be informed and advised to refer the patients for adequate safety and treatment.

Figure 1: CONSORT flow diagram



Randomization

Cluster randomization will be applied to reduce possible contamination between both arms of the trial. Participants will be cluster-randomized in a 1:1 allocation to the intervention or CAU after baseline measurements (T0). Clusters will be based on the shift of the dialysis session per dialysis center. The average dialysis center has 4 major shifts: Monday morning, Monday afternoon, Tuesday morning and Tuesday afternoon. A total of 72 clusters of average 3 patients in 18 participating dialysis centers will be present in our study. Clusters will be randomized using stratified blocks per participating dialysis center.

Randomization will be performed and registered by an automated computer software program to ensure independent allocation. Baseline measurements will be completed prior to randomization. The coordinating researcher assigns the intervention to participants. Although the treating nephrologist will not be actively informed about the depression score and allocation, we do not consider them blinded as patients and investigators will not be blinded. Outcome assessors are blinded and data analysts will be blinded until primary analysis will be performed.

Intervention

The internet-based self-help intervention examined in this study is an online psychotherapy, based on PST principles.(26) PST focusses on developing coping skills and is concentrated on practical problems which people face in their daily lives. An existing evidence based internet version of PST, which has proven to be effective in similar somatically ill patient populations,(30), was adjusted for use in the dialysis population, while conserving the intent of the original PST-based intervention. Modifications concerned additional information about dialysis treatment and its psychosocial consequences, real-life examples from dialysis patient focus groups and transforming the written information into easily understandable animations. The text and animations were rewritten to comply with a 'B1' language reference level.(32)

The intervention consists of five modules with explanatory text, animations, figures and exercises and is called 'Worry Less for Dialysis Patients' (in Dutch: "Minder Zorgen voor Dialyse Patiënten"). Patients are requested to complete 1 session each week and to finish the module within 6 weeks. However, there will be a possibility to extend this period up to 10 weeks, which will be documented. Patients are offered to complete the sessions on a tablet computer provided by this trial during dialysis sessions, but if preferred it can also be done from home on a private tablet or computer. If patients are unfamiliar with tablet computers, they are offered the opportunity to receive a printed booklet of the intervention. If patients have problems with the use of the tablet due to unfamiliarity, physical limitations, shunt use in the dominant arm of Dutch writing problems, they will be supported by a member of the research team, which will be documented. Supported care within the module is provided by a trained therapist and consists of weekly online feedback on their assignments. Patients have the possibility to request their therapist for additional support via the website. Treatment non-adherence and drop-outs will be discussed with the patients. Reasons for not completing the modules and patient satisfaction will be obtained via a short evaluation questionnaire. If a patient expresses suicidal ideations in the assignments of the intervention, suicide risk will be assessed over telephone by the supporting therapist under supervision of a psychiatrist. If the patient is actively suicidal, the patient will be excluded from the study and the attending nephrologist will be informed and advised to refer the patient for adequate safety and treatment.

Control

Patients randomized to the control group do not receive Internet-based PST during standard hemodialysis treatment. Both patients in the intervention and in the control group are free to accept any medical or psychological intervention during the study (CAU). The received mental healthcare will be monitored through electronic patient records and self-reported healthcare utilization.

Feasibility

In 2016 we conducted a feasibility test with 15 patients from different age categories in the dialysis clinic of the OLVG-West hospital in Amsterdam. Every patient was given a tablet computer with one of the modules of the PST intervention. Patients evaluated the course with a grade of 7 out of 10. The instruction and lay-out was clear for most of the patients, respectively 75% and 90%. The introduction and several explanatory texts were adjusted according to suggestions from participants in the feasibility test and patient focus groups.

Initially we used BDI>13 as inclusion criteria. Due to new available research in feasibility trials we amended the protocol to BDI >10 which has been approved by the Medical Ethics Committee MEC-U.(21, 23)

Outcome measures

Patient characteristics

Demographic self-reported items in the questionnaire will include postal code, marital status, number of children, education, profession, ethnicity, payed labor hours, smoking, alcohol usage and psychiatric disorders in the family. Data extracted from patient files will include gender, age, dialysis vintage, vascular entrance, registration on transplantation list, somatic and psychiatric comorbidities according to Davies Comorbidity Index, body mass index (BMI), primary cause of kidney failure, medication, routine laboratory measurements and change in dialysis modality. Psychotherapy and medication usage will be registered between follow-ups. The self-reported measurements will be conducted with printed self-reported questionnaires handed out during the dialysis session of the participants. **Table 1** describes the measures used at each assessment point.

Primary outcomes

Depressive symptoms are assessed using a self-questionnaire, the BDI-II.(33, 34) Respondents are asked to rate how much each of these symptoms bothered them in the past week, on a scale ranging from 0 (not at all) tot 3 (severely). The total score has a minimum of 0 and a maximum of 63. Treatment response will be based on the change in depressive symptoms defined by a change in the sum score of the BDI-II. The BDI-II has been validated and extensively used in the dialysis setting.(2, 31, 35) Furthermore, the Quick Inventory of Depressive Symptomatology (QIDS-SR16) self-report questionnaire will be used to assess the specific depressive symptoms, its severity and its symptom domains.(36)

Secondary outcomes

Secondary outcome assessment based on self-report will include measures of anxiety, quality of life, health care utilization and the prevalence, severity and impact of symptoms in dialysis patients. Anxiety will be assessed with the Beck Anxiety Inventory (BAI).(37) Quality of life will be measured using the Short Form-12 (SF-12). The 12-item Short Form Health

Survey was developed for patients with chronic conditions. The SF-12 has been validated and frequently used in the dialysis patient groups.(38) Prevalence, severity and impact of symptoms of dialysis will be assessed with the Dialysis Symptom Index (DSI).(39) Clinical outcomes include mortality and hospitalization. Mortality is measured using the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) coding system to make differences between cardiovascular and non-cardiovascular mortality. Hospitalization is defined as the number and reason of hospital admissions from baseline till end of the study period.

Table 1: Summary of measures

Measure	T0: baseline	T1: 2 weeks posttreatment	T2: 6 months posttreatment	T3-T4: 12-18 months posttreatment
Self-report measures				
Demographics	x			
BDI-II	x	x	x	x
BAI	x	x	x	x
QIDS-SR16	x	x	x	x
SF-12	x	x	x	x
EQ-5D	x	x	x	x
DSI	x	x	x	x
Short Tic-P	x	x	x	x
Hair questionnaire	x	x	x	
Evaluation of intervention		x		
Other				
Data extraction from patients files	x	x	x	x
Biochemical parameters	x	x	x	x
Hair cortisol	x	x	x	

Economic evaluation

A validated health-related quality of life instrument will be used to assess quality-adjusted life years (QALY) health gains. For this purpose, we will use the Dutch version of the 5 level EuroQol five dimension scale (EQ-5D), a generic quality of life instrument which comprises of five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D index is obtained by applying predetermined tariffs (utility weights) to the five domains. The Dutch tariffs of the EQ-5D will be used for computing the QALYs.(40) This index provides a societal-based global quantification of the patient's health status. Furthermore, the EQ-5D will be compared with the SF-12 health related quality of health questionnaire, which is used often in patients on chronic dialysis therapy. Healthcare usage will be measured using part one of the Tic-P self-report together with data from patient files.(41)

Inflammatory factors and cortisol

Besides data on biochemical parameters extracted from patient files, blood samples will be taken to measure cytokines interleukin 1-beta (IL-1B), IL-6, IL-10, high sensitivity C-reactive protein (Hs-CRP) and tumor necrosis factor alpha (TNFa). Peripheral blood before dialysis will be collected in anticoagulant-free EDTA and serum tubes. All samples will be immediately centrifuged at 1200g for 10 min and stored in aliquots at −80 °C until analysis. Hair samples will be taken from the back of the head as close as possible to the scalp to measure mean cortisol concentrations from the past 3 months.(42)

Data management and monitoring

Patient flow in the participating centers will be organized using a secured tailor-made Access database. The decoding list will be kept in the Investigator Site File in a secured place in the dialysis department. Data-entry will be coded and entered in Castor.(43) Range limitations will be built into Castor to prevent misclassification and measurement error. Research assistants will be trained in data collection and data entry to enhance data quality.

The risk of this trial is classified as 'negligible' and a study specific monitoring plan is created in close corporation with the data monitoring committee which includes double data entry checks. If deemed necessary by the monitoring committee, monitoring can be intensified. No adverse events are to be expected specifically related to this intervention. Actively suicidal participants will be excluded from the trial as described above.

Sample size

The power calculation is based on the comparison between T1 to T0 between the intervention and the control group. We took the conservative small to medium effect size (Cohen's d=0.4) on the primary outcome measure, while using a power 0.80, with alpha set on .05. Therefore, a total set of N=99 patients is required in each arm. The design effect of cluster-randomization is estimated to be 1.04. After adjustment for cluster randomization, sample size is calculated to be N=206 in total (103 per arm).

Statistical analysis

We will quantify the flow of participants through the study using frequencies and percentages in accordance with the SPIRIT flow diagram shown in figure 1. Missing data will be reported and discussed in the manuscripts on the trial. Depending on the type of missing data, multiple imputation will be used to handle missing data. Descriptive statistics will be used to describe non-consent, treatment adherence and completion, drop-out and exclusion. The main analysis to assess the effectiveness of the intervention will test differences in the change in depression scores pre-and post-treatment between the intervention and control arms. Analysis will be done per intention to treat principle. Differences in change in depressive symptoms and other continuous secondary outcomes

between intervention and control will be assessed using mixed models with the respective clusters, centers and baseline scores as covariates. The analyst will be blinded to the treatment group allocation. Treatment effect over time will be tested by adding a group*time interaction term into the model. Regression models will be used to explore (biochemical) mechanisms. Multivariable adjustment will be done deliberately within the causal pathway in order to explain potential mechanisms.

Economic analysis

The economic evaluation will be conducted in two ways. First, we will conduct a cost-effectiveness analysis (CEA) with treatment response as the clinical outcome of interest. Second, we will conduct a Cost-Utility Analysis (CUA) using QALYs as a generic measure of health gains. Both CEA and CUA will be conducted from both the societal perspective (including indirect costs) and the health care perspective (direct healthcare costs). Analysis will be conducted using an intention to treat principle.

The Incremental Cost-Effectiveness Ratio (ICER) will be computed to obtain costs per treatment response and the costs per QALY gained. For decision-making purposes, the ICER acceptability curve will be plotted for various Willingness-To-Pay (WTP) ceilings, which helps to making judgements whether the intervention offers good value for money relative to CAU or no treatment.

Trial status

Enrolment for the trial started in January 2018. At the moment of submission of this manuscript, recruitment of participants is still open.

Dissemination policy

Trial results will be published as manuscripts in international peer reviewed journals and information bulletins to participants and personnel of participating dialysis centers. In close corporation with the Dutch Kidney Patient organization, we will disseminate the trial results among dialysis patients throughout the Netherlands. No professional writers will be used during the writing of the manuscripts. Authorship eligibility guidelines according to the international committee of medical journal editors (ICMJE) will be applied to all submitted manuscripts.

Discussion

There is a need for adequately powered RCT's to assess the effectiveness of treatment options for depressive symptoms in dialysis patients, as evidence is currently lacking. In order to conduct a high-quality trial, a multidisciplinary team with various experts related to dialysis and depression was involved in the development of the intervention and the study design. This trial may provide insights on the effectiveness, feasibility and applicability of Internet-based self-help PST in the dialysis population.

This study has several limitations. First, the intervention may not be applicable for patients with cognitive impairment, illiteracy, other cultural background or insufficient Dutch language skills. Second, Internet-based treatment on tablet-computers might not be suitable for dialysis patients who are not familiar with the Internet or tablet-use, or who suffer from vascular disease related problems such as impaired vision or polyneuropathy of their hands. Both of these problems will be solved by offering assistance by the study team during the intervention which will be documented, furthermore patients can be provided with a printed version of the intervention. Third, drop-out rates are high for internet-based self-help interventions in other populations(29, 30), to cope with this problem we embed the intervention in routine care in the dialysis departments during dialysis treatment with frequent face-to-face interaction with the participants, which will make it easier to prevent early termination. Furthermore, we aim to provide insight in the reasons for termination or non-participation in this study.

If demonstrated to be (cost) effective, Internet-based PST offers new possibilities to treat many dialysis patients with symptoms of depression and to improve the quality of care. This RCT is aimed at contributing to better recognition and adequate treatment of symptoms of depression in dialysis patients in the future.

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. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2005;46(4):642-9.
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.
3. Farrokhi 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. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2014;63(4):623-35.
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.
5. 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. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2019.
6. 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.
7. 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.
8. 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. Clinical journal of the American Society of Nephrology : CJASN. 2017;12(2):280-6.
9. Winter SE, Barber JP. Should treatment for depression be based more on patient preference? Patient Prefer Adherence. 2013;7:1047-57.
10. Pena-Polanco JE, Mor MK, Tohme FA, Fine MJ, Palevsky PM, Weisbord SD. Acceptance of Antidepressant Treatment by Patients on Hemodialysis and Their Renal Providers. Clinical journal of the American Society of Nephrology : CJASN. 2017;12(2):298-303.
11. Cukor D, Ver Halen N, Asher DR, Coplan JD, Weedon J, Wyka KE, et al. Psychosocial intervention improves depression, quality of life, and fluid adherence in hemodialysis. J Am Soc Nephrol. 2014;25(1):196-206.
12. 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.
13. Kucuk L, Işil Ö. The Effects of Problem Solving Education on Depression Level and Problem Solving Skills on Dialysis Patients2009. 1638-49 p.

14. Gellatly J, Bower P, Hennessy S, Richards D, Gilbody S, Lovell K. What makes self-help interventions effective in the management of depressive symptoms? Meta-analysis and meta-regression. Psychol Med. 2007;37(9):1217-28.
15. 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.
16. 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.
17. Dickens C, Cherrington A, Adeyemi I, Roughley K, Bower P, Garrett C, et al. Characteristics of psychological interventions that improve depression in people with coronary heart disease: a systematic review and meta-regression. Psychosom Med. 2013;75(2):211-21.
18. 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.
19. 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.
20. Andersson G, Cuijpers P, Carlbring P, Riper H, Hedman E. Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis. World Psychiatry. 2014;13(3):288-95.
21. 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.
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.
23. 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.
24. Hudson JL, Moss-Morris R, Game D, Carroll A, Chilcot J. Improving Distress in Dialysis (iDiD): A tailored CBT self-management treatment for patients undergoing dialysis. J Ren Care. 2016;42(4):223-38.
25. 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.
26. Mynors-Wallis L. Problem solving treatment for anxiety and depression: A practical guide. New York: Oxford University Press; 2005.
27. Taraz M, Taraz S, Dashti-Khavidaki S. Association between depression and inflammatory/anti-inflammatory cytokines in chronic kidney disease and end-stage renal disease patients: a review of literature. Hemodial Int. 2015;19(1):11-22.
28. Staufenbiel SM, Penninx BW, Spijker AT, Elzinga BM, van Rossum EF. Hair cortisol, stress exposure, and mental health in humans: a systematic review. Psychoneuroendocrinology. 2013;38(8):1220-35.

29. 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.
30. 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.
31. 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.
32. Council of Europe. Common European Framework of Reference for Languages: Learning, Teaching, Assessment (CEFR) 2018 [Available from: https://www.coe.int/en/web/common-european-framework-reference-languages/home.
33. Beck AT, Steer RA, Brown GK. The Beck Depression Inventory. Second edition ed. San Antonio: Psychological Corp; 1996.
34. 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.
35. Chilcot J, Wellsted D, Farrington K. Screening for depression while patients dialyse: an evaluation. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2008;23(8):2653-9.
36. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry. 2003;54(5):573-83.
37. 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.
38. 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? Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2015;30(7):1170-6.
39. 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.
40. Lamers LM, Stalmeier PF, McDonnell J, Krabbe PF, van Busschbach JJ. [Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff]. Ned Tijdschr Geneeskd. 2005;149(28):1574-8.
41. Bouwmans C, De Jong K, Timman R, Zijlstra-Vlasveld M, Van der Feltz-Cornelis C, Tan Swan S, et al. Feasibility, reliability and validity of a questionnaire on healthcare consumption and productivity loss in patients with a psychiatric disorder (TiC-P). BMC Health Serv Res. 2013;13:217.
42. Noppe G, de Rijke YB, Dorst K, van den Akker EL, van Rossum EF. LC-MS/MS-based method for long-term steroid profiling in human scalp hair. Clin Endocrinol (Oxf). 2015;83(2):162-6.
43. EDC C. Security Statement 2019 [Available from: https://www.castoredc.com/security-statement/.

Supplementary tables and files

Supplementary table S1: List of participating dialysis centers, corresponding cities and local investigator

Dialysis centres	City	Local investigator
OLVG West	Amsterdam	C.E.H. Siegert, internist-nephrologist
OLVG Oost	Amsterdam	
Amsterdam University Medical Centres, location VUmc	Amsterdam	F. van Ittersum, internist-nephrologist
Diapriva	Amsterdam	
Niercentrum aan de Amstel	Amstelveen	
Haaglanden Medisch Centrum, Westeinde	The Hague	P. Chandie-Shaw, internist-nephrologist
Haaglanden Medisch Centrum, Antoniushove	The Hague	
HagaZiekenhuis Leyweg	The Hague	L.J. Vleming, internist-nephrologist
HagaZiekenhuis Sportlaan	The Hague	
HagaZiekenhuis DialyseCentrum Zoetermeer	Zoetermeer	
Jeroen Bosch Ziekenhuis	Den Bosch	E. Hoogeveen, internist-nephrologist
St. Antonius Ziekenhuis	Nieuwegein	W.J.W. Bos, internist-nephrologist
St. Antonius Dialysecentrum Tiel	Tiel	
Maasstad Ziekenhuis	Rotterdam	M. Dekker-de Bie, internist-nephrologist
Franciscus Gasthuis	Rotterdam	M. Westerman, internist-nephrologist
Franciscus Vlietland	Schiedam	
Tergooi Ziekenhuis	Hilversum	M. Schouten, internist-nephrologist
Dialysecentrum ‘t Gooi	Hilversum	

*Local investigators are responsible for the coordination of the trial in the corresponding dialysis centres. Research assistants will work in close cooperation with the local investigators to implement this study and improve uniform inclusion and data collection.

Chapter 9

Internet-based self-help Cognitive Behavioral Therapy for depressive symptoms in hemodialysis patients: a cluster randomized controlled trial.

Nadort E, Schouten RW, Boeschoten RE, Smets YFC, Chandie Shaw P, Vleming LJ, Dekker MJE, Westerman M, Hoogeveen EK, Bos WJW, Schouten M, Farhat K, Dekker FW, van Oppen P, Broekman BFP, Siegert CEH.

Submitted

Abstract

Background and objectives: Depressive symptoms are highly prevalent in the hemodialysis population and are associated with adverse clinical outcomes. There is a need for safe and effective treatment of depressive symptoms in these patients. The aim of this study is to investigate the effectiveness of a guided internet-based self-help intervention for hemodialysis patients with symptoms of depression.

Design, setting, participants, and measurements: 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-week guided internet-based self-help intervention based on problem solving therapy or a parallel care-as-usual control group. Clusters were based on hemodialysis shift to prevent contamination. The primary outcome depression was measured with the BDI-II. Secondary outcomes were anxiety symptoms, quality of life and dialysis symptoms. Analysis was done 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 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 the 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.

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 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, there is a need for save and effective treatment of depressive symptoms.(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 persons with depression in general as well as in patients with medical conditions.(12-14) CBT seems promising in decreasing depressive symptoms as well as improving quality of life in dialysis patients based on limited evidence from small trials with per protocol analysis.(15-17)

CBT treatment protocols are not yet part of routine dialysis care and research regarding optimal delivery methods are required.(18) 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.(16, 18) A possible alternative for face-to-face treatment is Internet delivered self-help CBT (ICBT) as it is easy accessible and of proven effectiveness, also in populations with other chronic somatic conditions.(19-24), Two non-controlled feasibility trials on ICBT in dialysis patients provide encouragement that this is a feasible and innovative option for effective psychological treatment for depression.(25, 26) Up to now, no randomized controlled trials have been performed on ICBT in dialysis patients.

A cognitive behavioral method that is commonly used to develop sufficient coping skills in patients with depressive symptoms is problem solving therapy (PST).(27-29) An Internet-based version of PST (IPST) has already been developed and is effective in reducing depressive symptoms in the general population.(30) 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.

Materials and methods

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). The extensive description of the study has been published earlier.(31) 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 is carried out in accordance with de declaration of Helsinki and the CONSORT 2010 statement: extension to cluster randomized trials.(32)

Participants

Hemodialysis patients were recruited from 18 participating dialysis centers affiliated with nine hospitals across the Netherlands. All patients were assessed for eligibility. Chronic, adult 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.(33, 34) 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.

Intervention

All participants in the clusters allocated to the intervention were offered an individual evidence based guided IPST.(30) While the intent of the original PST-based intervention was conserved, the IPST was adjusted for use in the hemodialysis population and real-life examples from dialysis patient focus groups were added (**Supplemental file 1**). The intervention consisted of five modules that participants had to finish within 10 weeks on tablet-computers during hemodialysis sessions or at home if preferred. 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 treatment completers because the core concepts of the IPST were covered in the first three modules.(35)

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.(36) The Davies comorbidity index was used to define the level of comorbidity.(37)

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 mild symptoms of depression.(33, 38) The BDI-II has been validated and extensively used in the dialysis setting.(39, 40) The minimal clinically important difference of the BDI-II is defined as a 17.5% reduction in BDI-II score.(41)

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.(42) 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.(43-46) 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 = bothers very much).(47, 48)

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, while using a power 0.80, with alpha set on .05 and an attrition rate of 30% (as seen in other internet-based therapies for patients with depressive symptoms).(27) 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.

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.

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, adjusted for baseline scores, center and cluster (**supplemental file 2**). 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. Post-hoc exploratory subgroup analyses were performed on sex, age, immigrant status, education level, depression severity (mild, moderate and severe) and computer literacy. The analyst was blinded to the treatment group allocation. All statistical analyses were performed using SPSS for Windows, version 27 (IBM Corp).

Results

Participant flow

The participant flow is presented in **Figure 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%).

Baseline characteristics

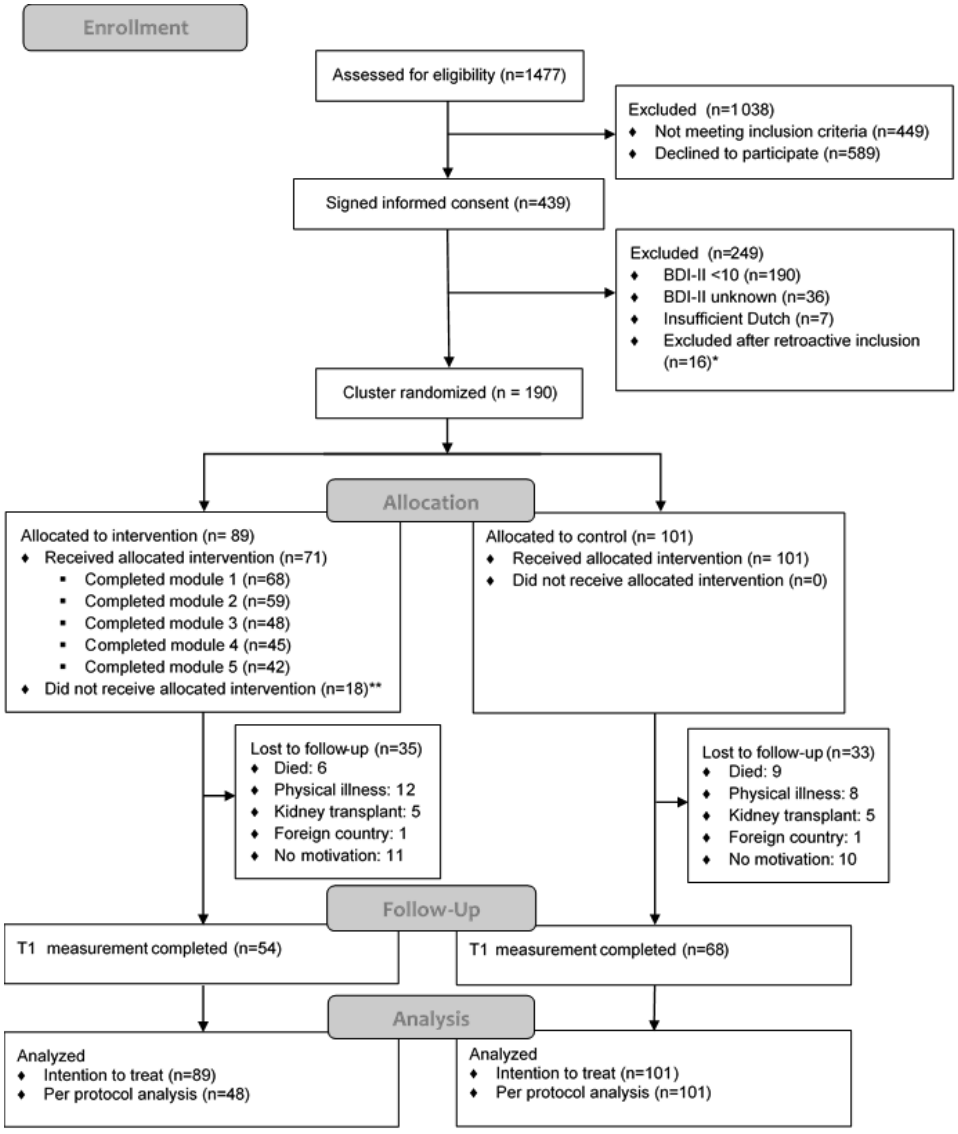
Baseline demographics and clinical characteristics of included patients are shown in **Table 1**. Patients who were lost to follow-up were more likely to be of migration background (52% versus 39%, p=0.09), to be married (52% versus 35%, p=0.14) and to be on the waiting list for a kidney transplant (38% vs 27%, p=0.30) (**Supplemental Table S3**).

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 treatment completers (**Figure 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 S3**).

Figure 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).

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 ≥100ml/24h	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 psychopharmic use			
Antidepressants	37 (20%)	20 (23%)	17 (17%)
Benzodiazepine	38 (20%)	21 (24%)	17 (17%)

Table 1 (continued)
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.

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**). Post-hoc analyses showed no significant differences in pre-specified subgroups (**Supplemental Table S4**). Possible trends in favor of the intervention are seen in women, age <65 year, in moderate baseline depression scores of BDI-II between 19-28 and also in computer literate patients. 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.

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%).

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				
	T1	14.7 ± 8.5	15.2 ± 7.7	-0.2 (-2.8;2.4)	0.87	-0.1 (-3.0;2.7)	0.94
Secondary outcomes* **							
Anxiety (BAI)	T0	13.0 ± 9.9	14.6 ± 11.0				
	T1	11.9 ± 9.0	11.2 ± 8.5	2.0 (-0.5;4.5)	0.12	2.1 (-0.7;4.8)	0.15
HRQoL (SF-12), PCS	T0	27.0 ± 7.9	28.4 ± 9.2				
	T1	33.4 ± 8.6	34.2 ± 9.7	-1.0 (-4.0;2.0)	0.50	-1.3 (-4.7;2.1)	0.45
HRQoL (SF-12), MCS	T0	48.5 ±10.0	49.0 ± 10.1				
	T1	50.2 ± 9.4	48.0 ± 9.4	1.0 (-2.4;4.4)	0.55	0.1 (-3.7;3.9)	0.96
Dialysis symptoms (DSI), Presence score	T0	15.5 ± 6.6	14.6 ± 5.9				
	T1	13.9 ± 7.3	14.7 ± 5.6	-1.4 (-3.2;0.5)	0.14	-1.2 (-3.2;0.8)	0.24
Dialysis symptoms (DSI), Bothersome score	T0	46.0 ± 23.6	44.6 ± 22.5				
	T1	39.5 ± 24.2	42.0 ± 18.3	-1.4 (-7.5;4.7)	0.65	-1.3 (-7.9;5.4)	0.71

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.
*Linear Mixed Model analysis with baseline scores as covariate.
**Linear Mixed Model analysis with the respective clusters, centers and baseline scores as covariates.
***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				
	T1	13.4 ± 8.4	15.2 ± 7.7	-0.9 (-3.5;1.8)	0.53	-1.0 (-4.0;1.9)	0.50
Secondary outcomes* **							
Anxiety (BAI)	T0	12.8 ± 10.9	14.6 ± 11.0				
	T1	11.5 ± 9.1	11.2 ± 8.5	1.5 (-1.2; 4.3)	0.27	1.5 (-1.5; 4.6)	0.32
HRQoL (SF-12), PCS	T0	28.9 ± 7.5	28.4 ± 9.2				
	T1	34.8 ± 8.8	34.2 ± 9.7	-0.4 (-3.7; 3.0)	0.83	-0.5 (-4.2; 3.2)	0.79
HRQoL (SF-12), MCS	T0	48.0 ± 9.6	49.0 ± 10.1				
	T1	50.6 ± 9.7	48.0 ± 9.4	1.4 (-2.3; 5.1)	0.46	0.4 (-3.7; 4.5)	0.85
Dialysis symptoms (DSI), Presence score	T0	15.9 ± 7.3	14.6 ± 5.9				
	T1	13.9 ± 7.4	14.7 ± 5.6	-1.5 (-3.5; 0.5)	0.13	-1.2 (-3.4; 0.9)	0.55
Dialysis symptoms (DSI), Bothersome score	T0	46.2 ± 25.6	44.6 ± 22.5				
	T1	39.6 ± 24.3	42.0 ± 18.3	-1.8 (-8.4; 4.8)	0.58	-1.6 (-8.8; 5.6)	0.67

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.
*Linear Mixed Model analysis with baseline scores as covariate.
**Linear Mixed Model analysis with the respective clusters, centers and baseline scores as covariates.
***Naïve model without random intercept for center because convergence was not achieved.

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. Exploratory subgroup analyses showed possible trends in favor of the intervention group related to female sex, younger age, computer literacy and moderate severity of depression. 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 there is evidence of its effectiveness in other chronic patient populations and because of promising results from feasibility trials in dialysis patients 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.(22-24) 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.(19, 49) 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.

Exploratory subgroup analysis on patients aged <65 year showed an effect of -2.4 (95%CI -6.1; 1.3, p=0.21) and subgroup analysis in patients who did not need help with the use of the tablet-computer showed an effect of -1.3 BDI-II points (95%CI -4.6; 2.0, p=0.43. As the minimal clinically important difference of 3.3 BDI-II points falls within these confidence intervals, it is possible that a clinically relevant effect might be found in a larger cohort of younger dialysis patients who are computer literate. 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.

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(27), 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 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. Although this is common practice in other 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 advices 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, 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.

Fifth, 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.

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 there was a decrease in depression scores of 21% over time. 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.

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.
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.
3. Farrokhi 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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.

15. Cukor D, Ver Halen N, Asher DR, Coplan JD, Weedon J, Wyka KE, et al. Psychosocial intervention improves depression, quality of life, and fluid adherence in hemodialysis. J Am Soc Nephrol. 2014;25(1):196-206.
16. 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.
17. Lerma A, Perez-Grovas H, Bermudez L, Peralta-Pedrero ML, Robles-Garcia R, Lerma C. Brief cognitive behavioural intervention for depression and anxiety symptoms improves quality of life in chronic haemodialysis patients. Psychol Psychother. 2017;90(1):105-23.
18. Chilcot J, Hudson JL. Is successful treatment of depression in dialysis patients an achievable goal? Semin Dial. 2018.
19. Barak A, Hen L, Boniel-Nissim M, Shapira Na. 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.
20. 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.
21. 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.
22. 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.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. Mynors-Wallis L. Problem solving treatment for anxiety and depression: A practical guide. New York: Oxford University Press; 2005.
29. 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.
30. 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.

31. 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.
32. Campbell MK, Piaggio G, Elbourne DR, Altman DG, Group C. Consort 2010 statement: extension to cluster randomised trials. BMJ. 2012;345:e5661.
33. Beck AT, Steer RA, Brown GK. The Beck Depression Inventory. Second edition ed. San Antonio: Psychological Corp; 1996.
34. 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.
35. 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.
36. 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.
37. 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.
38. 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.
39. 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.
40. Chilcot J, Wellsted D, Farrington K. Screening for depression while patients dialyse: an evaluation. Nephrol Dial Transplant. 2008;23(8):2653-9.
41. 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.
42. 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.
43. Ware J, Jr., 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.
44. 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.
45. 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.
46. Muntingh 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.

47. 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.
48. 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.
49. 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.

Supplementary files and tables

Supplemental File S1: Additional information on the adjustments of the IPST intervention for use in the hemodialysis population

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 and real-life example cases from dialysis patient focus groups were added Furthermore, written information was 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"). 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.

Supplemental File S2: Additional information on the Linear Mixed Model analysis

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.

SPSS syntax of main analyses (BDI-II):

```
*naive model (without adjusting for center or cluster).
**-2LL 824,487.
MIXED bdi_t1_analyse WITH bdi_t0 randomization
  /CRITERIA=CIN(95) MXITER(100) MXSTEP(10) SCORING(1) SINGULAR(0.000000000001)
HCONVERGE(0,
    ABSOLUTE) LCONVERGE(0, ABSOLUTE) PCONVERGE(0.000001, ABSOLUTE)
  /FIXED=bdi_t0 randomization | SSTYPE(3)
  /METHOD=REML
  /PRINT=SOLUTION.

*Adjusted model (adjusted for center and cluster).
** -2LL 812.427. This model is significantly better than the model without random intercept for
center.
*** difference in df=4. Critical value for chi2 with 4 df is 9.488. Difference is 12.06, hence significant.
MIXED bdi_t1 BY cluster WITH bdi_t0 randomization
  /CRITERIA=CIN(95) MXITER(100) MXSTEP(10) SCORING(1) SINGULAR(0.000000000001)
HCONVERGE(0,
    ABSOLUTE) LCONVERGE(0, ABSOLUTE) PCONVERGE(0.000001, ABSOLUTE)
  /FIXED= randomization cluster bdi_t0 | SSTYPE(3)
  /METHOD=REML
  /PRINT=DESCRIPTIVES  SOLUTION
  /RANDOM=INTERCEPT | SUBJECT(center) COVTYPE(VC).

* ICC.
compute ICC=1.537056/(50.653127+1.537056).
alter type ICC (f5.3).
fre ICC.
* ICC is 0.029.
```

Supplemental Table S3: Patient characteristics of patients who completed T1, who were lost to follow-up at T1, who completed the intervention and who did not complete the intervention.

Characteristic	T1 complete (n=122)	T1 missing (n=68)	Intervention completers (n=48)	Intervention non-completers (n=41)
Demographic				
Age (year)	65 ± 14	63 ± 16	63 ± 15	64 ± 14
Male sex	78 (64%)	39 (57%)	29 (60%)	28 (68%)
Immigrant*	48 (39%)	35 (52%)	22 (46%)	16 (39%)
Country of birth				
The Netherlands	82 (67%)	42 (62%)	31 (65%)	30 (73%)
Social				
Married/in a relationship	43 (35%)	35 (52%)	20 (42%)	19 (46%)
Has Children	82 (67%)	52 (77%)	33 (69%)	30 (73%)
Education**				
Low	46 (38%)	29 (43%)	17 (35%)	16 (39%)
Middle	52 (43%)	29 (43%)	26 (54%)	19 (46%)
High	24 (20%)	9 (13%)	5 (10%)	6 (15%)
Employed	11 (9%)	3 (4%)	3 (6%)	4 (10%)
Renal and dialysis				
Dialysis vintage (months)	26 [8-50]	28 [9-46]	18 [7-38]	26 [8-48]
Primary kidney disease				
Renal vascular disease	28 (23%)	11 (16%)	10 (21%)	10 (24%)
Diabetic nephropathy	38 (31%)	18 (27%)	15 (31%)	9 (22%)
Glomerulonephritis	9 (7%)	6 (9%)	3 (6%)	3 (7%)
Other	37 (30%)	23 (34%)	13 (27%)	16 (39%)
Kt/V_{urea} at baseline	3.9 ± 1.2	3.9 ± 1.1	3.9 ± 1.2	3.9 ± 1.2
On waiting list for kidney transplant	33 (27%)	26 (38%)	16 (33%)	12 (29%)
Residual diuresis of ≥100ml/24h	76 (62%)	38 (56%)	28 (58%)	29 (71%)
Clinical				
Davies comorbidity score				
Low comorbidity	21 (17%)	13 (19%)	10 (21%)	6 (15%)
Moderate comorbidity	76 (62%)	38 (56%)	29 (60%)	25 (61%)
High comorbidity	26 (21%)	17 (25%)	9 (19%)	10 (24%)
Comorbid conditions				
Diabetes mellitus	54 (44%)	34 (50%)	23 (48%)	22 (54%)
Cardiovascular disease***	105 (86%)	57 (84%)	39 (81%)	34 (83%)
Laboratory				
Hb (g/dL)	11.1 ± 1.3	11.3 ± 1.3	11.0 ± 1.3	11.0 ± 1.3
Phosphate (mg/dL)	5.0 ± 1.6	5.3 ± 1.9	5.3 ± 1.9	4.7 ± 1.6
Albumin (g/L)	3.7 ± 0.5	3.6 ± 0.4	3.8 ± 0.4	3.7 ± 0.4
PTH (pg/mL)	38 ± 30	39 ± 33	36 ± 26	42 ± 33
Psychiatric				
Psychiatric diagnosis in medical history	93 (76%)	55 (81%)	38 (79%)	29 (71%)
None	12 (10%)	4 (6%)	3 (6%)	3 (7%)
Major depressive disorder	3 (2%)	2 (3%)	3 (6%)	2 (5%)
Anxiety disorder	21 (17%)	11 (16%)	8 (17%)	10 (24%)
Other				
BDI-II score	18.7 ± 7.0	19.5 ± 8.7	18.1 ± 5.9	20.1 ± 8.4
BAI score	13.7 ± 10.2	14.1 ± 11.0	12.8 ± 10.9	13.1 ± 8.6

Supplemental Table S3 (continued)

Characteristic	T1 complete (n=122)	T1 missing (n=68)	Intervention completers (n=48)	Intervention non-completers (n=41)
Current psychotherapy	11 (9%)	7 (10%)	6 (13%)	6 (15%)
Current psychopharmic use	23 (19%)	14 (21%)	11 (23%)	9 (22%)
Antidepressants	23 (20%)	13 (19%)	8 (17%)	9 (22%)
Benzodiazepine	20 (16%)	19 (28%)	14 (29%)	7 (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.

Supplemental Table S4: Intention to treat Linear Mixed Model subgroup analyses for primary outcome depression (BDI-II scores) for the intervention and control group.

Subgroup		Intervention	Control	Adjusted MD (95%CI)*	p-value
Sex					
Women		**n=32**	**n=41**		
	T0	20.4 ± 8.5	20.2 ± 7.5		
	T1	13.5 ± 8.4	16.6 ± 8.2	-2.6 (-7.7; 2.5)	0.60
Men		**n=57**	**n=60**		
	T0	18.2 ± 6.3	18.1 ± 8.4		
	T1	15.1 ± 8.7	14.1 ± 7.2	1.5 (-2.0; 5.1)	0.40
Age					
<65 year		**n=42**	**n=49**		
	T0	19.1 ± 6.2	20.4 ± 9.2		
	T1	14.5 ± 8.9	16.7 ± 8.6	-2.4 (-6.1; 1.3)	0.21
≥65 year		**n=47**	**n=52**		
	T0	18.8 ± 8.0	17.6 ± 6.7		
	T1	14.8 ± 8.4	13.8 ± 6.6	1.4 (-2.7; 5.6)	0.50
Immigrant status					
Native		**n=51**	**n=55**		
	T0	18.3 ± 7.2	18.0 ±7.2		
	T1	14.2 ± 8.4	14.1 ± 6.5	1.0 (-2.8; 4.7)	0.61
Immigrant		**n=38**	**n=45**		
	T0	20.0 ± 7.1	20.1 ±9.1		
	T1	15.4 ± 9.0	16.9 ± 9.1	0.5 (-5.2; 4.2)	0.84
Education					
Low formal education**		**n=33**	**n=42**		
	T0	20.1 ± 7.2	19.5 ± 8.2		
	T1	14.7 ± 8.4	14.8 ± 7.7	-0.14 (-5.2; 4.9)	0.95
Middle and high formal		**n=56**	**n=58**		
education	T0	18.4 ± 7.2	18.6 ± 8.1		
	T1	14.6 ± 8.7	15.4 ± 7.7	0.2 (-3.3; 4.9)	0.92
Depression severity					
BDI-II T0 ≥ 13		**n=76**	**n=77**		
	T0	20.4 ± 6.9	21.4 ± 7.8		
	T1	15.1 ± 8.4	16.6 ± 8.1	-0.4 (-3.7; 3.0)	0.82
BDI-II T0 ≥ 16		**n=53**	**n=57**		
	T0	23.1 ± 6.7	23.9 ± 7.5		
	T1	14.7 ± 8.9	18.3 ± 8.0	-1.4 (-5.4; 2.5)	0.47
Mild depression**		**n=58**	**n=66**		
(BDI-II 10-19)	T0	14.8 ± 2.7	14.1 ± 2.9		
	T1	13.5 ± 7.5	12.4 ± 6.1	0.8 (-2.7; 4.2)	0.66
Moderate depression**		**n=21**	**n=21**		
(BDI-II 19-28)	T0	23.1 ± 2.9	23.0 ± 2.4		
	T1	14.8 ± 9.6	17.6 ± 5.7	-1.9 (-7.3; 3.5)	0.48
Severe depression**		**n=10**	**n=14**		
(BDI-II 29-63)	T0	34.7 ± 4.6	35.6 ± 3.3		
	T1	27.3 ± 5.7	24.1 ± 9.4	-0.8 (-15.8; 14.3)	0.90
Intervention					
Computer literate		**n=26**	**n=101**		
	T0	20.2 ± 5.6	19.0 ± 8.1		
	T1	15.4 ± 7.5	15.2 ± 7.7	-1.3 (-4.6; 2.0)	0.43
Computer illiterate		**n=45**	**n=101**		
	T0	19.1 ± 8.2	19.0 ± 8.1		
	T1	14.9 ± 9.4	15.2 ± 7.7	0.5 (-3.0; 4.1)	0.76

Supplemental Table S4 (continued)

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 score range 0-63.
Abbreviations: CI, confidence interval; BDI-II; Beck Depression Inventory – Second edition; MD, mean difference.
*Linear Mixed Model analysis with the respective clusters, centers and baseline scores as covariates.
**Naïve model without random intercept for center because convergence was not achieved.

Chapter 10

General Discussion

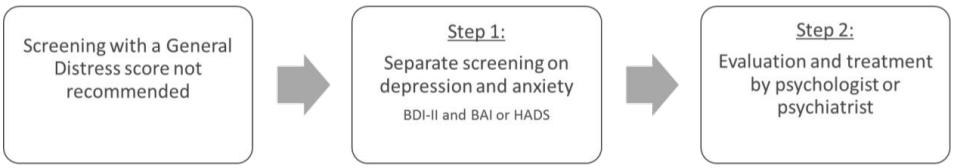
This thesis examines symptoms of depression and anxiety in dialysis patients. In this final chapter, the results of the performed studies will be summarized and discussed per subject. First, two studies that focused on screening for anxiety and depression will be discussed. Second, two studies on symptom dimensions of anxiety and depression will be deliberated. Third, one study on the impact of COVID-19 on depression and anxiety will be discussed. Fourth, in three studies treatments of depression in dialysis patients will be addressed. Finally, clinical implications of the results and suggestions for future research will be made.

Main findings and discussion per aim

Aim 1: Screening

Chapter 2 described the results of a study aimed at exploring the concept of 'General distress' in dialysis patients. General distress includes symptoms of both depression and anxiety and may potentially be useful for screening purposes. In this study, we combined both symptoms of anxiety and depression measured by the Beck Anxiety Inventory (BAI) and Beck Depression Inventory – Second edition (BDI-II) to investigate three concepts: 1) a General distress score, 2) an overarching Somatic distress score and 3) an overarching Cognitive distress score. In addition, the concept of General distress was examined in the Hospital Anxiety and Depression Scale (HADS) in a different cohort. For both BAI/BDI-II and HADS, the strictly unidimensional factor of General distress did not show a good fit (Confirmatory Fit Indices (CFI) with 0.690 for BAI/BDI-II and 0.699 for HADS). Moderate performance was found with a multidimensional bi-factor tripartite model including a General Distress score, a Depression score and an Anxiety score (CFI of BAI/BDI-II was 0.873 and HADS 0.839). Our results showed that both the BAI/BDI-II as well as the HADS are not sufficiently unidimensional to warrant the use of a General Distress score in dialysis patients, without investigating anxiety and depression separately. A General Distress score may be used as a first step in screening of dialysis patients for anxiety and depression, if these concepts are further assessed in a second step with separate screening tools for anxiety and depression or evaluation by a psychologist or a psychiatrist (**Figure 1**).

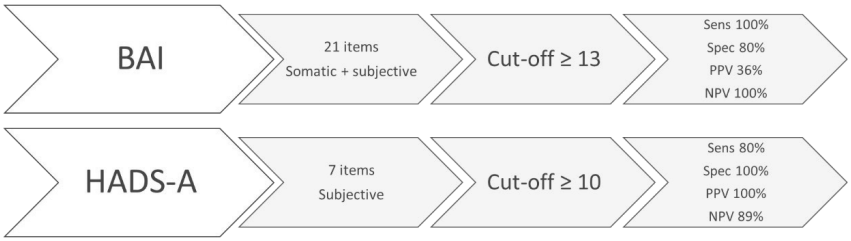
Figure 1: Schematic display of the conclusion of Chapter 2.



Chapter 3 reported on the results of a validation study of two widely used screening tools for symptoms of anxiety, the BAI and the HADS – Anxiety subscale (HADS-A) by the MINI-international neuropsychiatric interview (MINI). In this validation cohort, 20% of hemodialysis

patients had a diagnosis of an anxiety disorder by the MINI. Interrater reliability was almost perfect (Kappa 0.82, p<0.001). ROC curves showed good diagnostic accuracy of the BAI and HADS-A. The optimal cutoff value for the BAI was ≥ 13 and for the HADS-A, optimal cutoff value was ≥ 10 (**Figure 2**). These data showed that both the BAI and the HADS-A are valid screening instruments for anxiety in hemodialysis patients that can easily be administered in routine dialysis care. In clinical practice, the HADS-A might be more useful than the BAI due to less items, the exclusion of somatic symptoms of anxiety and high predictive value. Future research should focus on validation of anxiety screening tools in hemodialysis populations from different health systems to strengthen the current evidence on this topic and to further improve the identification of hemodialysis patients who are in need for treatment of anxiety disorders.

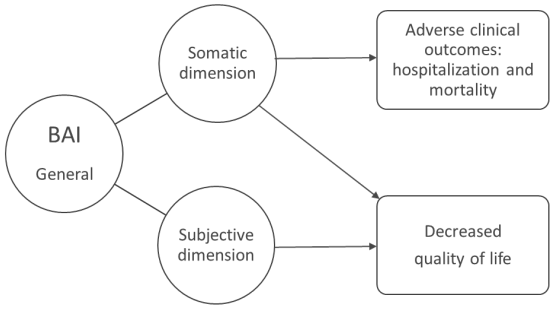
Figure 2: Schematic display of the results and conclusion of Chapter 3.



Aim 2: Symptom dimensions

Chapter 4 stated the results of an investigation on symptom dimensions of anxiety and the association with adverse clinical outcomes. By using confirmatory factor analysis on the BAI, we identified a Somatic, Subjective and General anxiety dimension. A further subdivision of the Somatic dimension can be made using Autonomic, Neurophysiologic and Panic symptoms dimensions. All symptom dimensions were associated with a substantial decrease in quality of life. Only the Somatic symptom dimensions was associated with hospitalization (Rate Ratio 1.7, 95%CI 1.5-2.1) and all-cause mortality (Hazard Ratio 1.7, 95%CI 1.2-2.4). These associations were independent of somatic comorbidity and other confounding factors. These results can lead to better understanding of the clinical presentation of anxiety, more personalized treatment of anxiety and ultimately improve outcomes for dialysis patients.

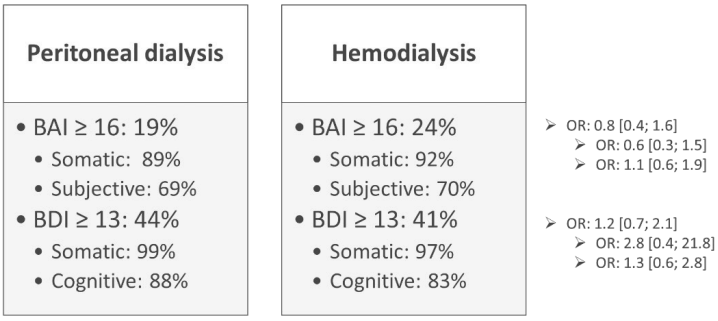
Figure 3: Schematic display of the results and conclusion of Chapter 4.



Note: Associations with adverse outcomes were assessed with multivariable regression models, adjusted for social characteristics, dialysis characteristics and laboratory measures.

Chapter 5 described the association between dialysis modality and the prevalence and symptom dimensions of depression and anxiety, analyzed with regression models adjusted for potential confounders. Clinically significant anxiety and depression were highly prevalent in both peritoneal dialysis and hemodialysis patients, but no differences in prevalence or severity were found between these groups. In both groups, the somatic symptom dimensions of both anxiety and depression were more prevalent and more severe than the subjective anxiety symptom dimension or cognitive depression symptom dimension, which is possibly related to the high comorbidity level and the impact on general health status in both samples. Almost all patients experienced symptoms related to loss of energy, fatigue and insomnia. Insomnia is not only a symptom of depression but can at the same time be a risk factor to develop symptoms of depression, and further impact mental health of dialysis patients. These results underscore the need for early recognition, prevention and treatment of symptoms of anxiety and depression in dialysis patients regardless of treatment modality.

Figure 4: Schematic display of the results of Chapter 5.

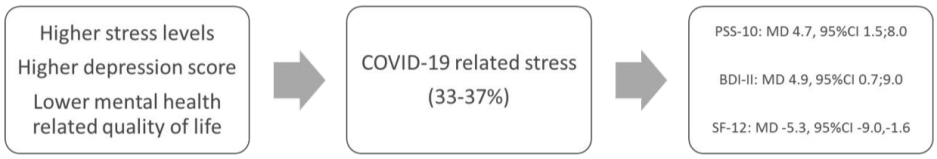


Note: Odds Ratios (OR) are assessed with multivariable logistic regression models, adjusted for age, sex, ethnicity, social characteristics and comorbidities.

Aim 3: Impact of COVID-19

Chapter 6 reported on the findings from a longitudinal study on the impact of COVID-19 on depression, anxiety and quality of life in hemodialysis patients. This is relevant as patients with kidney failure on hemodialysis treatment have many somatic comorbidities besides their chronic kidney disease, which makes them at risk of experiencing symptoms of stress, depression and anxiety related to the pandemic. Data of hemodialysis patients from the first and second COVID-19 lockdown in the Netherlands were compared to data prior to the pandemic with linear mixed models. Interestingly, no significant differences were found in depression, anxiety and quality of life (measured with the Short Form 12 (SF-12)) between before and during the pandemic). During the first lockdown, 33% of participants reported COVID-19 related stress and in the second lockdown 37%. Patients who reported COVID-19 related stress had higher stress levels on the Perceived Stress Scale-10 (PSS-10), higher BDI-II scores and lower SF-12 mental component summary scores than patients who did not experienced COVID-19 related stress. However, these differences were already present before the pandemic, which indicates that a substantial subgroup of patients with pre-existent mental health problems seems to be more susceptible to experience COVID-19 related stress. These results underscore the need for screening and treatment of depression and mental health related quality of life in hemodialysis patients to prevent increase of stress symptoms in this group during pandemics and other major stressful events in the future.

Figure 5: Schematic display of the results of Chapter 6.



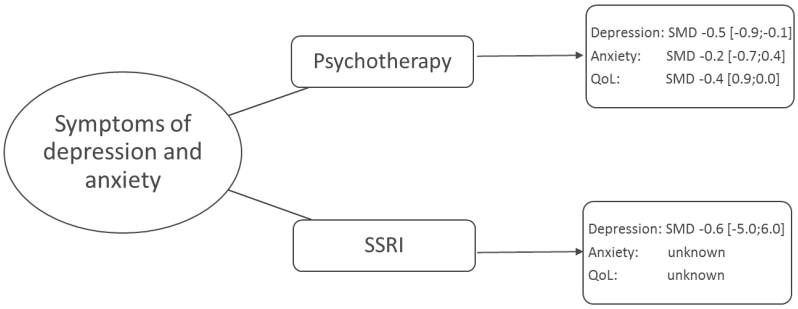
Note: Mean difference are in comparison with patients who did not experience COVID-19 related stress. Analyzed with linear mixed model, adjusted for age, sex, immigrant status, high formal education, dialysis vintage and high comorbidity score.

Aim 4: Treatment

Chapter 7 stated the results of a systematic review and meta-analysis of randomized controlled trials investigating various treatment options for depression in dialysis patients. Multiple databases were searched and studies which included patients who had a diagnosis of depression or scored above a cutoff for depression on a screening tool were included. This resulted in 17 studies with a total of 1640 participants. A meta-analysis of seven studies on psychotherapy versus care as usual showed a standardized mean difference (SMD) on depressive symptoms of -0.5 [-0.9;-0.1], with a moderate heterogeneity of 52%. Although these results indicate that psychotherapy might be an effective treatment option for depression in dialysis patients, this is based on 'low quality evidence' due to per protocol analysis of the included studies and high scores of potential bias. Two studies on selective serotonin reuptake inhibitors (SSRI's) showed a SMD of -0.6 [-5.0; 6.0] but due to the very

wide confidence interval no conclusions can be drawn. Few studies were found on exercise therapy and dietary supplements. More evidence is needed regarding the efficacy of SSRI's, exercise therapy and dietary supplements in this population. Given the large burden of depressive symptoms in dialysis patients and proven effectivity in other medically ill patient populations, we suggest to offer psychotherapy to dialysis patients with depressive symptoms.

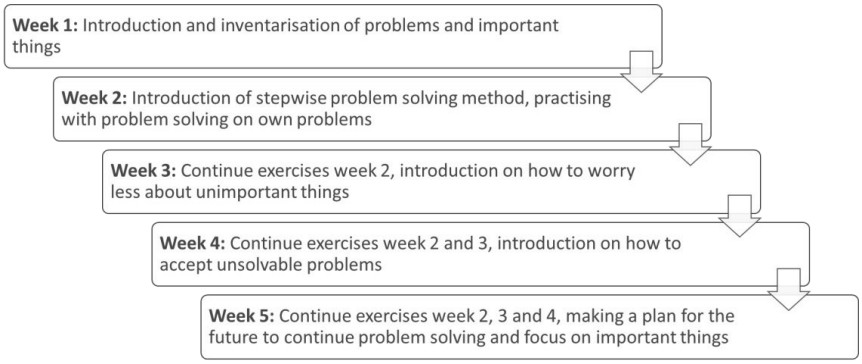
Figure 6: Schematic display of the results of Chapter 7.



Note: Treatment effects are compared to a care as usual or placebo control arm. Pooled analysis on psychotherapy included 7 studies on depression, 3 on anxiety and 4 on quality of life (QoL). Pooled analysis on Selective Serotonin Reuptake Inhibitors (SSRI's) included 2 studies on depression and no studies on anxiety and QoL.

Chapter 8 described the study protocol of the Depression Related Factors and Outcomes in Dialysis Patients With Various Ethnicities and Races Study – Internet Intervention (DIVERS-II). This is the first large cluster randomized controlled trial on the effectiveness of guided internet-based self-help cognitive behavioral intervention based on problem solving therapy (PST) for depressive symptoms in hemodialysis patients versus care as usual. Inclusion criteria were adult patients on maintenance dialysis with adequate Dutch language skills and a BDI-II score of $\geq$ 10. Clusters were based on dialysis shift within each center. An existing evidence-based internet version of PST was adjusted for use in the dialysis population by converting written information into easily understandable animations and by adding real-life examples from dialysis patients focus groups. The intervention consisted of five modules, one per week, and could be completed on a tablet computer during dialysis sessions or at home if preferred by the participant. The research team assisted in the use tablet of the tablet computers if needed. Supported care within the intervention was provided by trained therapists and consisted of weekly online feedback on assignments. Main outcome was the difference in symptoms of depression (BDI-II) adjusted for baseline symptoms between the treatment and control group after treatment and secondary outcomes were symptoms of anxiety (BAII), quality of life (SF-12) and dialysis symptoms (Dialysis Symptom Index). Analysis was done per intention to treat principle with linear mixed models to account for missing data.

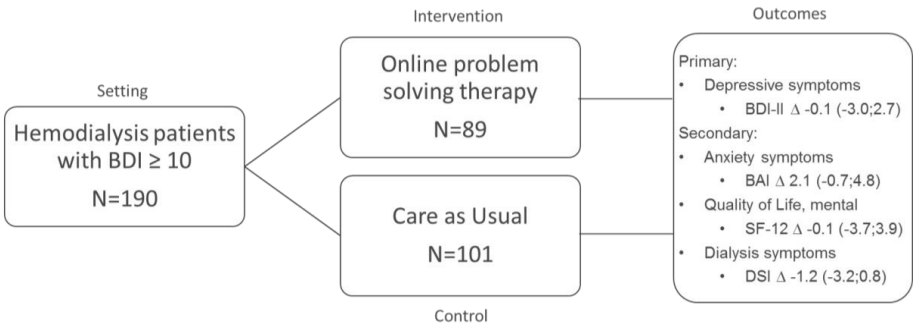
Figure 7: Schematic display of the content of the guided online self-help intervention for dialysis patients as used in the DIVERS-II study as described in Chapter 8.



Note: The intervention is based on problem solving treatment for anxiety and depression by Mynors-Wallis and the online version of PST made by Warmerdam and collegues.(1, 2)

Chapter 9 reported the outcomes of the DIVERS-II study. 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%). In the intervention group, more than half of the participants (54%) completed the intervention and the majority of the participants (63%) needed help with the use of the tablet computer or filling out the exercises. 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 (mean difference -0.1, 95%CI -3.0; 2.7). Explorative subgroup analyses showed possible trends in favor of the intervention group related to female sex, younger age, computer literacy and moderate severity of depression. No differences were seen between the groups in secondary outcomes. Per protocol sensitivity analysis showed comparable results. Although recruitment rates were low, dropout rates were high and there were no differences in outcomes between the intervention and control group. These results are an addition to the limited evidence on treatment of depression in hemodialysis patients. Future research is needed to provide insight in for which patients these interventions might be effective which may lead to the development of more personalized treatment of depression in hemodialysis patients.

Figure 8: Schematic display of the results of Chapter 9.



Note: Results are based on the intention to treat linear mixed model analysis and are displayed as mean difference. A positive number represents a higher value in the intervention group, a negative number represents a lower value in the intervention group.

Clinical implications and future research

In general, the results of this thesis underline the high burden of symptoms of depression and anxiety in dialysis patients and the impact on the lives of these patients due to poor recognition and limited evidence on effective treatment options. Several factors may play a role in these complex clinical problems and implementation strategies for adequate screening and treatment of symptoms of depression and anxiety in dialysis patients is needed. In the following paragraphs, the clinical implications of the results, suggestions for implementation strategies and future research are presented.

Screening and treatment of symptoms of depression and anxiety in dialysis patients

Despite the recommendation of biannual screening for depression in international guidelines since 2005, routine screening is still not part of clinical practice in nephrology departments.(3) The complexity of this problem and the current gaps in the literature might be better understood by looking further into the ten criteria by Wilson and Jungner for successful screening strategies.(4)

The **first criterion** for screening is that the condition should be an important health problem. The high prevalence and symptom burden of depression and anxiety in dialysis patients and the association with adverse clinical outcomes underscore the importance of this health problem.(3, 5-9) Furthermore, the scientific agenda of the Dutch Kidney Foundation explicitly states the need of more support for patients with kidney failure in coping with psychological consequences of their disease.(10)

The **second criterion** of screening is that there should be an accepted treatment for patients with the recognized disease. The results of this thesis show that adequately powered clinical trials on treatment of depression and anxiety in dialysis patients are scarce and guided

internet-based self-help PST is not more effective than care as usual in lowering depressive symptoms. Psychotherapy is an effective and widely used treatment for persons with depression in general as well as in patients with medical conditions.(11-13) Although evidence is limited, CBT seems promising in decreasing depressive symptoms as well as improving quality of life in dialysis and there is no indication that psychotherapy is not effective in dialysis patients.(14, 15)

In theory, the maintenance dialysis setting seems ideal for efficient implementation of research as patients have frequent and predictable health care encounters where copious data could be generated within a system of strong infrastructure and governance.(16) Despite this, clinical trials in dialysis patients in general are scarce, have low recruitment and retention rates and have challenges with protocol adherence.(17) Barriers for engagement of different stakeholders in the research process include knowledge gaps, mistrust, competing priorities and misaligned clinical and research activities.(18) These problems with recruitment and retention are described in chapter 7 and 9 of this thesis. In chapter 7 we found that evidence on the effective treatment of depression and anxiety in dialysis patients is scarce and sample sizes of studies are small. In chapter 9, we report the same experience in conducting the DIVERS-II trial where we experienced low recruitment rates. Only 13% of all patients who were assessed for eligibility could be randomized and we needed 18 participating dialysis centers and an extension of the inclusion period of 12 months to be able to complete inclusion. In comparison, recruitment rate for the DIVERS-I observational cohort study was 30%. It seems that the willingness of dialysis patients to participate in a non-experimental study is higher than the willingness to participate in clinical trials. A recent randomized vignette-based study on the willingness of hospitalized patients to participate in research also found that patients were more likely to participate in a hypothetical observational study than in a hypothetical intervention study.(19) Factors associated with lower participation in de intervention study were higher self-rated health and clinical equipoise of the intervention, whereas higher participation was associated with a positive attitude towards research, previous participation in clinical studies and being a blood or organ donor (as an indicator of altruism).(19)

An additional explanation in dialysis patients might be the reluctance to initiate yet another treatment. For instance, it is found that the willingness to modify or initiate antidepressant medication is often lacking in chronic dialysis patients. Reasons for not starting treatment are the attribution of depression to a recent acute event, chronic disease or dialysis, lack of interest, refusal to take medication and concerns about medication side effects.(20) Another study showed that the presence of concomitant borderline, narcissistic, factitious and avoidant personality disorders was responsible for 38% of antidepressant treatment failure in dialysis patients.(21)

Additional reasons for the low recruitment and retention rates in clinical trials in dialysis patients could be the high hospitalization and mortality rates in this population due to the unstable health status of dialysis patients and frequent side effects and complications of dialysis treatment that interfere with study visits.(22) Also, somatic symptoms related to dialysis and depression like fatigue, lack of energy and difficulty with concentration increase subject burden of patients to fill out questionnaires or to participate in or complete an online

self-help intervention.(23) Due to high numbers of patients from immigrant background, language and cultural factors may also play a role.(24)

Furthermore, stigmas on mental health might play an additional role in the scarcity of psychosocial trials in dialysis patients. Although data on mental health stigma's in the dialysis setting is limited, one study showed that 55% of patients scoring above a cut-off on the BDI-II refused further assessment and treatment of possible major depressive disorder.(21) Reasons for this refusal were denial of being depressed and unwillingness to consider taking additional medication. Despite education about depression, some patients in this study regarded mental illness as weakness and were afraid to be stigmatized if they were to acknowledge symptoms of depression. Our own experiences from the DIVERS-II study were similar, where despite our efforts to inform patients about the well-known impact of kidney failure and dialysis on mood and mental health, some patients did not want to discuss this subject with us or indicated that they were not 'crazy', a word they associated themselves with feelings of sadness or a depressed mood.

To overcome the barriers for engagement of different stakeholders in research mentioned in the first paragraph of this subchapter, it is suggested that interdisciplinary partnerships are needed to implement education and training on research, to promote a culture of trust and transparency, to enhance communication with all stakeholders throughout the research process and to develop a sustainable infrastructure for research.(17) Strategies we used to enhance inclusion rates in DIVERS-II were, first, the formation of a consortium of 18 participating dialysis centers affiliated to 9 hospitals with fast involvement of the local principal investigators who were all nephrologist with interest in psychosocial research. Second, we provided education and training of nephrologist, nurses and social workers in all centers before the start of research activities. Third, we engaged treating nephrologists and nurses in informing patients about the study and in introducing the researchers individually to each eligible patient to enhance trust. Fourth, we aligned research practice with clinical workflows by informing patients with the treating nephrologists during ward rounds, so that research was prioritized without comprising on clinical care delivery. Fifth, to make sure we involved diverse stakeholders at all stages of research, we discussed the content and lay-out of the online self-help intervention with patient focus groups, dialysis nurses and social workers and we expanded our multidisciplinary research team with two patient researchers in order to receive input on research protocols and implementation processes. Sixth, to fight stigma, we provided information on psychosocial consequences of kidney failure and dialysis therapy during research presentations for nephrologist, dialysis nurses and social workers and to patients during the inclusion process. There are two main possibilities why we did not find an effect of guided internet-based self-help PST for depressive symptoms in hemodialysis patients compared to care as usual in the DIVERS-II trial. The first possibility is that PST itself is not effective to treat depressive symptoms in dialysis patients despite promising findings in the literature in other patients with chronic diseases.(25, 26) It could be that dialysis patients have too many unsolvable problems to benefit from learning problem solving skills and that only one module on acceptance and processing dialysis related losses is not sufficient enough for these patients to lower their depressive symptoms.

The second possibility is that internet-based self-help therapy is not feasible in dialysis patients although feasibility trials showed promising results. In the DIVERS-II trial, we experienced that a high number of participants needed help with the use of the tablet-computer because they could only use one arm or could not use their dominant hand due to cannulation during dialysis. Also, due to the mean age of 64, a high percentage of participants with low formal education level (40%) and high numbers of unemployment (93%), computer skills were not sufficient in a substantial proportion of patients to perform the intervention on the tablet-computers without assistance. Furthermore, because of negative effects of kidney failure and dialysis treatment on social relationships which often leads to social isolation, having a patient-therapist relationship or social contacts in a group-based therapy could have beneficial effects on treatment outcomes compared to self-help therapy.(27, 28)

Future research should further investigate how to optimize the implementation of research protocols in routine dialysis care and should focus on the role of stigma on mental health in both healthcare professionals and patients in the dialysis settings. Additionally, it would be interesting to examine in which subgroups of patients internet-based interventions might be effective as this may aid in the development of more personalized treatment of depression in hemodialysis patients. A recent small feasibility trial on psychotherapy sessions via video-conference during hemodialysis showed that this delivery method was feasible and well-accepted by dialysis patients although sample size was too small to detect treatment effect.(29) It would be interesting to further assess video-conference treatment and privacy issues on a hemodialysis ward, also in light of the COVID-19 and possible future pandemics. Research on treatment could also focus more on somatic symptoms of depression and anxiety such as fatigue and insomnia, as these are not only consequences of depression and anxiety but can also be a risk factor to develop symptoms of depression and anxiety.(30, 31) Overwhelming exhaustion can lead to the depletion of the sense of control and capacity to do daily activities due to lack of energy, which might lead to feelings of sadness, guilt and frustration.(23) Another alternative treatment approach could be interventions based on positive psychology. Positive psychology interventions are primarily aimed at increasing positive feelings, positive behaviors and positive cognitions as opposed to improving negative thoughts or maladaptive behavior patterns.(32) A recent quasi-experimental study showed promising effects on stress, anxiety and quality of life of a positive thinking intervention in hemodialysis patients.(33) A meta-analysis has shown that positive affect and life-satisfaction are associated with a small but significant effect on recovery and survival in physically ill patients.(34) It would be interesting to investigate the effect of interventions enhancing emotional well-being on the prognosis of dialysis patients besides symptoms of depression and anxiety. Finally, it could be interesting to focus qualitative research on dialysis patients without symptoms of depression and anxiety to gain more insight in their coping strategies in dealing with the burden of kidney failure and dialysis therapy. This could aid in formulating new strategies on how to better activate and socialize dialysis patients with symptoms of depression and anxiety.

The **third criterion** for screening is that facilities for diagnosis and treatment of depression and anxiety should be available. If screening instrument on depression and anxiety were to be implemented in the dialysis setting, there should be enough capacity in medical psychology

and psychiatry departments to be able to evaluate and possibly treat all patients that need further assessment by scoring above a cutoff value.

The **fourth criterion** for screening is that there should be a recognizable latent or early symptomatic stage. In patients with a life-threatening disease such as kidney failure, there is a gradual transition from feeling sad, depressed or anxious to an adjustment disorder with depressive or anxious features to a major depressive disorder or anxiety disorder that causes significant distress or impairment according to the DSM-5 criteria.(35, 36) These feelings of sadness and anxiety could be seen as an early symptomatic stage in the development of depressive and anxiety disorders an can be measured overtime by a validated self-report screening tool.

The **fifth criterion** is that there should be a suitable test or examination. The results of this thesis show that screening with a general distress score based on the BDI-II/BAI or the total HADS in dialysis patients is not recommended, and that separate investigations of depression and anxiety are needed in order to identify patients in need for further assessment and treatment. A recent systematic review on depression screening tools in patients with kidney failure included a total of 16 studies with limitations related to methodological quality and generalizability.(37) Although the BDI-II was by far the best studied screening tool, a wide range of thresholds were reported from ≥10 to ≥19.(38-42) Two studies that examined the performance characteristics of the HADS depression sub score (HADS-D), found a cutoff of ≥6 and ≥8 for clinically relevant depression.(43, 44)

It is suggested that screening with the BDI-II in dialysis patients may lead to overestimation of prevalence of depression due to overlap in somatic symptoms of depression and somatic symptoms of hemodialysis treatment.(45, 46) In other severely ill patients groups receiving palliative care, factor analysis showed that screening with the BDI-II could measure three different constructs of current conceptualizations of depression: anhedonia, demoralization, and grief.(47) Anhedonia is characterized by a loss of the ability to experience pleasure in things accompanied by a loss of interest and is one of the two key symptoms of major depressive disorder. The central concepts of demoralization are considerable loss of meaning, hope and purpose, together with being unable to cope, feelings of failure and feeling alone.(48) Grief is characterized by feelings of loss. These concepts are often difficult to differentiate and may overlap. It is known that antidepressant therapy is not effective in demoralization and it is suggested to treat these patients with psychotherapy that focusses on attitudes towards hope and meaning in life.(49) It would be interesting if future research would look further into the concept of demoralization in dialysis patients to aid in better understanding and recognition of depression versus demoralization to be able to provide the right treatment in these patients.

The literature on screening instruments for anxiety in dialysis patients is even more limited. In this thesis, we reported on a validation study of the BAI and HADS anxiety sub score (HADS-A) and found cutoff scores of ≥13 and ≥10, respectively, for anxiety in hemodialysis patients, with a preference for the HADS-A due to lower number of items and equal diagnostic discrimination (area under the curve = 0.95). It is suggested that even shorter screening tools may be appropriate as an initial screen of all dialysis patients. In the US, the Patient Health

Questionnaire 2 (PHQ-2) for instance is the most commonly used short screen for depression in medical settings. This questionnaire exists of only two items measuring 1) diminished interest or pleasure and 2) feeling down, depressed or hopeless. An equivalent for anxiety is the Generalized Anxiety Disorder 2-item (GAD-2), this questionnaire exist of two items measuring 1) feeling nervous, anxious or on edge and 2) not being able to stop or control worry. These short screens, however, have not been evaluated in the dialysis setting yet. Future research should focus on the validation of short screening tools in dialysis patients and on further validation of anxiety screening tools in dialysis populations from different healthcare systems.

Based on the results of this thesis and the current literature, the most suitable test for screening on anxiety and depression in clinical practice would be the HADS, as it is a quick screening tool that is validated and of proven diagnostic accuracy for both depression and anxiety in dialysis patients.(43, 44) (50) For research purposes, however, the use of the BDI-II and BAI could be recommended as these 21-item questionnaires also collect data on somatic symptoms of depression and anxiety which are associated with adverse clinical outcomes such as hospitalization and mortality in dialysis patients. The integration of both somatic and cognitive/subjective symptoms of depression and anxiety in research is important as this might lead to better understanding of clinical presentations of depression and anxiety in dialysis patients and may also be helpful to develop more personalized treatment for specific symptom dimensions in dialysis patients.

The **sixth criterion** for screening is that the test should be acceptable to the target population. However, data on acceptability and effective implementation strategies of screening for depression and anxiety is scarce. In terms of implementation, several issues should be kept in mind. First of all, timing of screening is important. Among patients who were depressed, a high level of agreement has been found between screening during or before/after hemodialysis treatment. However, non-depressed hemodialysis patients score significantly higher on somatic symptoms as well as on total BDI-II score when screened during a dialysis session compared to off dialysis. (40) This creates a potential for overdiagnosis and overtreatment of depression. Furthermore, the perception of privacy should be taken into account with implementation or discussing results of screening for depression and anxiety on a dialysis ward due to possible stigma.

In the Netherlands, the national implementation of online patient-reported outcome measures (PROMs) in routine dialysis care has been challenging. A recent pilot study on the evaluation of two PROMs, the short from 12 (SF-12) that consists of 12 items and the Dialysis Symptom Index (DSI) that consists of 36 items, found a low average response rate of 36% with high variability among dialysis centers.(51) Average duration of completing these PROMs was 12 minutes and 33% of patients needed support with reading questions out load and filling out answers. Additional findings were the importance of communication about the content and purpose of the PROMs with patients and the association between engagement of professionals and response rates. Furthermore, individual feedback on PROM scores was crucial for patients and discussing these scores with a healthcare professional was rated as highly insightful and valuable. As stated by van der Willik and colleagues, the implementation

of an extra PROM on depression and anxiety should be accompanied by clear communication on the content and purpose to both health care providers and dialysis patients to make it acceptable.(51) Future research should focus on the acceptability of adding screening instruments on depression and anxiety to the current PROM's in the Netherlands and on optimal implementation strategies in the dialysis setting.

The **seventh criterion** is that the natural history of the condition should be adequately understood. There are studies on the clinical course of symptoms of depression and anxiety in dialysis patients that show that these symptoms do not remit spontaneously if left untreated.(52, 53) However, other studies report that high depression scores in dialysis patients may also be temporary due to the high rates of intermittent, distressing events like cardiovascular events or hospitalization.(45) In chapter 9 of this thesis, we saw a clinically important decrease in depression symptoms in both the treatment and control group after the intervention. Besides other explanations, this could be caused by regression to the mean. In chapter 6 we investigated the impact of a major stressful event like a pandemic on symptom levels of depression and anxiety. We found that patients with high levels of COVID-19 related stress also reported high depression scores and decreased mental health related quality of life. Yet, de pandemic did not seem to have further increased their symptom severity compared to pre-pandemic levels. This finding is in accordance with a large cohort study on patients with depressive, anxiety and obsessive-compulsive disorders from the general population. The pandemic caused a detrimental effect on mental health in these patients with preexistent mental health disorders, but no greater increase in symptoms was reported during the pandemic.(54) More research on the natural course of symptoms of depression and anxiety in dialysis patients is needed before this criterion is met.

The **eighth criterion** is that there should be an agreed policy on whom to treat as patients. As stated in the introduction of this thesis, self-report scales are generally preferred for screening in both clinical and research settings for pragmatic reasons such as time and costs.(40, 55) However, high depression scores in dialysis patients may also be temporary due to the high rates of intermittent, distressing events like cardiovascular events or hospitalization.(27) It is suggested that indication for treatment should be defined by a diagnosis of depressive of anxiety disorder made by a psychologist or psychiatrist, or sustained high depression and anxiety symptom scores over multiple assessments.(33) On the other hand, treating symptoms of depression and anxiety in an earlier stage might prevent worsening of symptoms and the development of major depressive disorders and anxiety disorders.

The **ninth criterion** is that there should be an economical balance in the costs of case-finding. As previously said, clinical trials on psychotherapy are scarce and evidence on cost-effectiveness is even scarcer. More research is needed into the cost-effectiveness of treatments of depression and anxiety in dialysis patients and on the effect of health outcomes such as hospitalization and mortality.

The **tenth criterion** is that case-finding should be a continuing process. Screening for depression is recommended biannually in International guidelines which would meet this criterion.(3) During the implementation of the PROM's in the Netherlands it was found that a frequency of two to four times a year is preferred by most patients.(56)

In summary, despite the additional evidence on depression and anxiety in dialysis patients presented in this thesis, there are still gaps in the current literature that prevent successful implementation of screening for depression and anxiety in dialysis patients in the near future. It is important to be reserved in implementing screening and treatment strategies without sufficient scientific evidence to promote these strategies. More research is needed on cost-effective treatment options and optimal implementation strategies of screening and treatment for symptoms of depression and anxiety in dialysis patients.

Main conclusion

This thesis aimed to gain more insight in symptoms of depression and anxiety in dialysis patients. Various studies on screening, symptom dimensions, the impact of the COVID-19 pandemic and on treatment of depression and anxiety were performed and enabled this thesis to emphasize the interaction between soma and psyche, which increases the complexity of identifying and treating symptoms of depression and anxiety in dialysis patients

Taken together, this thesis indicates that there is a large burden of symptoms of depression and anxiety in dialysis patients. The somatic symptom dimension of anxiety is highly common and is associated with adverse clinical outcomes such as hospitalization and mortality, independent of comorbidity. We did not find a difference in symptom dimensions of depression and anxiety between hemodialysis and peritoneal dialysis patients but we did find that almost all patients experienced symptoms related to loss of energy, fatigue and insomnia. This underscores the complex interplay between mental and physical health in this population. Also, patients with pre-existent mental health symptoms are vulnerable to experience increased levels of stress during major stressful events like pandemics.

Furthermore, in screening for depression and anxiety in dialysis patients the use of a general distress score is not recommended and separate tools for depression and anxiety are needed. Symptoms of anxiety can be identified with the use of appropriate screening tools and cutoff scores validated in the dialysis population. However, successful implementation of screening protocols for depression and anxiety in the near future is not possible due existing gaps in the literature on cost-effective treatment options and optimal implementation strategies. Finally, we did not find an additional effect of guided internet-based self-help problem solving therapy for depressive symptoms in dialysis patients compared to care as usual. Development of personalized treatment options of symptoms of depression and anxiety is needed in order to adequately treat patients suffering from these symptoms and ultimately improve health outcomes and quality of life of dialysis patients.

References

1. Mynors-Wallis L. Problem solving treatment for anxiety and depression: A practical guide. New York: Oxford University Press; 2005.
2. 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.
3. National Kidney F. KDOQI Clinical Practice Guideline for Hemodialysis Adequacy: 2015 update. Am J Kidney Dis. 2015;66(5):884-930.
4. Wilson JMG, Jungner G, World Health O. Principles and practice of screening for disease / J. M. G. Wilson, G. Jungner. Geneva: World Health Organization; 1968.
5. 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.
6. Cukor D, Coplan J, Brown C, Friedman S, Cromwell-Smith A, Peterson RA, et al. Depression and Anxiety in Urban Hemodialysis Patients. Clin J Am Soc Nephrol. 2007;2(3):484-90.
7. Reckert A, Hinrichs J, Pavenstadt H, Frye B, Heuft G. Prevalence and correlates of anxiety and depression in patients with end-stage renal disease (ESRD). Z Psychosom Med Psychother. 2013;59(2):170-88.
8. Preljevic VT, Osthus TB, Os I, Sandvik L, Opjordsmoen S, Nordhus IH, et al. Anxiety and depressive disorders in dialysis patients: association to health-related quality of life and mortality. Gen Hosp Psychiatry. 2013;35(6):619-24.
9. Farrokhi 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.
10. Dutch Kidney Foundation, Dutch Federation for Nephrology, Dutch Kidney Patients Association. Beating kidney disease. A joint agenda for research and innovation., (2018).
11. Richards SH, Anderson L, Jenkinson CE, Whalley B, Rees K, Davies P, et al. Psychological interventions for coronary heart disease. Cochrane Database Syst Rev. 2017;4:CD002902.
12. 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.
13. 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.
14. 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.
15. Nadort E, Schouten RW, Witte SHS, Broekman BFP, Honig A, Siegert CEH, et al. Treatment of current depressive symptoms in dialysis patients: A systematic review and meta-analysis. Gen Hosp Psychiatry. 2020;67:26-34.
16. Dember LM, Archdeacon P, Krishnan M, Lacson E, Jr., Ling SM, Roy-Chaudhury P, et al. Pragmatic Trials in Maintenance Dialysis: Perspectives from the Kidney Health Initiative. J Am Soc Nephrol. 2016;27(10):2955-63.

17. Flythe JE, Narendra JH, Hilliard T, Frazier K, Ikeler K, Amolegbe A, et al. Cultivating a Research-Ready Dialysis Community. J Am Soc Nephrol. 2019.
18. Flythe JE, Narendra JH, Dorough A, Oberlander J, Ordish A, Wilkie C, et al. Perspectives on Research Participation and Facilitation Among Dialysis Patients, Clinic Personnel, and Medical Providers: A Focus Group Study. Am J Kidney Dis. 2018;72(1):93-103.
19. Gayet-Ageron A, Rudaz S, Perneger T. Study design factors influencing patients' willingness to participate in clinical research: a randomised vignette-based study. BMC Med Res Methodol. 2020;20(1):93.
20. Pena-Polanco JE, Mor MK, Tohme FA, Fine MJ, Palevsky PM, Weisbord SD. Acceptance of Antidepressant Treatment by Patients on Hemodialysis and Their Renal Providers. Clin J Am Soc Nephrol. 2017;12(2):298-303.
21. Wuerth D, Finkelstein SH, Finkelstein FO. The identification and treatment of depression in patients maintained on dialysis. Semin Dial. 2005;18(2):142-6.
22. Collins AJ, Foley RN, Gilbertson DT, Chen SC. The state of chronic kidney disease, ESRD, and morbidity and mortality in the first year of dialysis. Clin J Am Soc Nephrol. 2009;4 Suppl 1:S5-11.
23. Cheng E, Evangelidis N, Guha C, Hanson CS, Unruh M, Wilkie M, et al. Patient experiences of sleep in dialysis: systematic review of qualitative studies. Sleep Med. 2021;80:66-76.
24. Haverkamp GL, Loosman WL, van den Beukel TO, Hoekstra T, Dekker FW, Chandie Shaw PK, et al. The association of acculturation and depressive and anxiety symptoms in immigrant chronic dialysis patients. Gen Hosp Psychiatry. 2016;38:26-30.
25. Kucuk L, Işil Ö. The Effects of Problem Solving Education on Depression Level and Problem Solving Skills on Dialysis Patients2009. 1638-49 p.
26. 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.
27. Ma R, Mann F, Wang J, Lloyd-Evans B, Terhune J, Al-Shihabi A, et al. The effectiveness of interventions for reducing subjective and objective social isolation among people with mental health problems: a systematic review. Soc Psychiatry Psychiatr Epidemiol. 2020;55(7):839-76.
28. Gómez Penedo JM, Rubel J, Krieger T, Alalú N, Babl AM, Roussos A, et al. Effects of patient–therapist interpersonal complementarity on alliance and outcome in cognitive–behavioral therapies for depression: Moving toward interpersonal responsiveness. J Couns Psychol. 2020:No Pagination Specified-No Pagination Specified.
29. Jakubowski KP, Jhamb M, Yabes J, Gujral S, Oberlin LE, Bender FH, et al. Technology-assisted cognitive-behavioral therapy intervention for end-stage renal disease. Transl Behav Med. 2020;10(3):657-63.
30. Neckelmann D, Mykletun A, Dahl AA. Chronic insomnia as a risk factor for developing anxiety and depression. Sleep. 2007;30(7):873-80.
31. Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disord. 2011;135(1-3):10-9.
32. Sin NL, Lyubomirsky S. Enhancing well-being and alleviating depressive symptoms with positive psychology interventions: a practice-friendly meta-analysis. J Clin Psychol. 2009;65(5):467-87.

33. Shokrpour N, Sheidaie S, Amirkhani M, Bazrafkan L, Modreki A. Effect of positive thinking training on stress, anxiety, depression, and quality of life among hemodialysis patients: A randomized controlled clinical trial. J Educ Health Promot. 2021;10:225.
34. Lamers SM, Bolier L, Westerhof GJ, Smit F, Bohlmeijer ET. The impact of emotional well-being on long-term recovery and survival in physical illness: a meta-analysis. J Behav Med. 2012;35(5):538-47.
35. Bannink M, Monster J. Richtlijn Depressie. Palliatieve zorg Richtlijnen voor de praktijk. 2010:227-44.
36. Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed. Arlington, VA, US: American Psychiatric Publishing, Inc.; 2013. xliv, 947-xliv, p.
37. Kondo K, Antick JR, Ayers CK, Kansagara D, Chopra P. Depression Screening Tools for Patients with Kidney Failure: A Systematic Review. Clin J Am Soc Nephrol. 2020;15(12):1785-95.
38. 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.
39. Bautovich A, Katz I, Loo CK, Harvey SB. Beck Depression Inventory as a screening tool for depression in chronic haemodialysis patients. Australas Psychiatry. 2018;26(3):281-4.
40. Chilcot J, Wellsted D, Farrington K. Screening for depression while patients dialyse: an evaluation. Nephrol Dial Transplant. 2008;23(8):2653-9.
41. Grant D, Almond MK, Newnham A, Roberts P, Hutchings A. The Beck Depression Inventory requires modification in scoring before use in a haemodialysis population in the UK. Nephron Clin Pract. 2008;110(1):c33-8.
42. van den Beukel TO, Siegert CE, van Dijk S, Ter Wee PM, Dekker FW, Honig A. Comparison of the SF-36 Five-item Mental Health Inventory and Beck Depression Inventory for the screening of depressive symptoms in chronic dialysis patients. Nephrol Dial Transplant. 2012;27(12):4453-7.
43. 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.
44. Preljevic VT, Osthus TB, Sandvik L, Opjordsmoen S, Nordhus IH, Os I, et al. Screening for anxiety and depression in dialysis patients: comparison of the Hospital Anxiety and Depression Scale and the Beck Depression Inventory. J Psychosom Res. 2012;73(2):139-44.
45. 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.
46. Gregg LP, Hedayati SS. Screening for Depression in People with Kidney Failure. Clin J Am Soc Nephrol. 2020;15(12):1702-4.
47. Clarke DM, Kissane DW, Trauer T, Smith GC. Demoralization, anhedonia and grief in patients with severe physical illness. World Psychiatry. 2005;4(2):96-105.
48. Kissane DW. Demoralization: a life-preserving diagnosis to make for the severely medically ill. J Palliat Care. 2014;30(4):255-8.
49. Rzeszut M, Assael R. Differentiating Depression From Demoralization in Organ Transplantation Recipients. Prog Transplant. 2021;31(1):88-90.

50. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
51. van der Willik EM, Hemmelder MH, Bart HAJ, van Ittersum FJ, Hoogendijk-van den Akker JM, Bos WJW, et al. Routinely measuring symptom burden and health-related quality of life in dialysis patients: first results from the Dutch registry of patient-reported outcome measures. Clin Kidney J. 2021;14(6):1535-44.
52. 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.
53. 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.
54. Pan K-Y, Kok AAL, Eikelenboom M, Horsfall M, Jörg F, Luteijn RA, et al. The mental health impact of the COVID-19 pandemic on people with and without depressive, anxiety, or obsessive-compulsive disorders: a longitudinal study of three Dutch case-control cohorts. The Lancet Psychiatry. 2021;8(2):121-9.
55. Hedayati SS, Bosworth HB, Kuchibhatla M, Kimmel PL, Szczech LA. The predictive value of self-report scales compared with physician diagnosis of depression in hemodialysis patients. Kidney Int. 2006;69(9):1662-8.
56. 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.

Appendices

English summary

General introduction

This focus of this thesis is on depression and anxiety in dialysis patients. **Chapter 1** introduces the topic of depression and anxiety in patients with chronic kidney disease. These patients are dependent on dialysis therapy; a chronic, intensive and time-consuming treatment with high physical and mental burden. Symptoms of depression and anxiety are common in dialysis patients and develop in a complex interaction between biological, psychological and social factors. These symptoms are associated with adverse outcomes such as decreased quality of life and increased risk of hospital admission and mortality. Despite the high burden and negative consequences, symptoms of depression and anxiety are often not identified or treated in dialysis patients. In this thesis, data from two large cohort studies in dialysis patients in the Netherlands are used to answer the following questions:

- Which screening tools can be used to identify hemodialysis patients who are in need for further assessment and treatment of anxiety?
- What symptom dimensions of anxiety can be identified in dialysis patients and how are these symptom dimensions associated with adverse clinical outcomes and dialysis modality?
- What is the impact of the COVID-19 pandemic on anxiety and depression in hemodialysis patients?
- What is the effectivity of treatment of depression in dialysis patients?

Screening

Diagnosing depression and anxiety in dialysis patients is challenging as symptoms of depression and anxiety overlap with symptoms of kidney failure and dialysis therapy itself. Furthermore, symptoms of depression and anxiety often coexist. The psychological concept of 'general distress' includes symptoms of both depression and anxiety and may potentially be useful for screening purposes. In **Chapter 2** we assess this concept of 'general distress' by combining scores of depression and anxiety. Our findings show that the concept of general distress in dialysis patients is not suitable for screening. It is recommended to investigate depression and anxiety separately in dialysis patients. Screening tools for depression have been studied in dialysis patients, however, the few studies on screening tools for anxiety are indecisive. In **Chapter 3** we assess the accuracy of two widely used screening instruments for anxiety in dialysis patients by a diagnosis of anxiety disorder based on a psychiatric interview. Both instruments show good distinction between anxious and non-anxious patients and could be used in clinical or research practice for the detection of symptoms of anxiety in dialysis patients.

Symptom dimensions

Insight in symptom dimensions could aid in the understanding of symptoms of depression and anxiety and their treatments. Symptom dimensions of depression have been studied in dialysis

patients, but whether symptom dimensions of anxiety exist in dialysis patients remains largely unknown. Furthermore, due to differences in autonomy, therapy burden and complications between hemodialysis and peritoneal dialysis treatment, this could influence symptom dimensions in patients treated with these different dialysis modalities. In **Chapter 4** we examine symptom dimensions of anxiety and identified a 'somatic' and 'subjective' symptom dimension. Interestingly, only the somatic symptom dimension is related to hospital admissions and mortality while the subjective dimension is not. Both symptom dimensions are related to decreased quality of life. In **Chapter 5** we assess the relation between dialysis modality and symptom dimensions of depression and anxiety. Depression and anxiety and in particular their somatic symptoms dimensions are highly common in both peritoneal and hemodialysis patients. No differences are seen between these groups.

Impact of COVID-19

In the general population, symptoms of depression, anxiety and stress are common reactions to the COVID-19 pandemic due to fear of the contagious disease itself, loss of employment and financial insecurity, deaths of loved ones, forced quarantine and social isolation. Although chronic disease is a risk factor for symptoms of stress, depression and anxiety during COVID-19, the impact in dialysis patients remains largely unknown. In **Chapter 6** we examine symptoms of stress, depression, anxiety and quality of life before and during the COVID-19 pandemic in dialysis patients in the Netherlands. These symptoms do not increase during the pandemic. However, one third of dialysis patients report to experience COVID-19 related stress and have higher stress and depression levels and lower quality of life. Yet, de pandemic did not seem to have further increased their symptom severity compared to pre-pandemic levels.

Treatment

Although dialysis patients experience a high burden of symptoms of depression and anxiety, much is still unknown regarding the effect of treatment for these symptoms. In **Chapter 7** we systematically searched and summarized all studies on treatment for depression and anxiety in dialysis patients. While there were few studies investigating this topic with methodological issues, we found promising evidence for psychotherapy as a treatment of depressive symptoms in dialysis patients. However, more research is need before a definite answer to this question can be provided. **Chapter 8** describes the study protocol of a large study in 18 dialysis centers in the Netherlands investigating the effect of an online self-help psychotherapy treatment on tablet-computers during hemodialysis sessions on symptoms of depression, supported online by a therapist. The results of this study are presented in **Chapter 9**. Depression scores improved in both the treatment and control group by 21%, but no indication was found for an additional positive effect of online self-help psychotherapy in dialysis patients compared to usual care. It could be possible that this intervention is more suitable for younger dialysis patients with adequate computer skills.

General discussion

Chapter 10 is the final chapter of this thesis and aims to interpret and explore the implications in clinical practice of all presented results and provides suggestions for future research. Despite the additional evidence on depression and anxiety in dialysis patients presented in this thesis, there are still gaps in the current literature that prevent successful implementation of screening for depression and anxiety in dialysis patients in the near future. Future research should try to fill in these gaps and examine how to best design the content and accessibility of an intervention for symptoms of depression and anxiety in hemodialysis patients.

Nederlandse samenvatting

Introductie

Hoofdstuk 1 introduceert het onderwerp van dit proefschrift: depressie en angst bij dialysepatiënten. Patiënten met chronisch nierfalen zijn afhankelijk van dialysetherapie. Dit is een chronische, intensieve en tijdrovende behandeling waar patiënten een hoge lichamelijke en mentale last door ervaren. Symptomen van depressie en angst komen veel voor bij dialysepatiënten en ontstaan door een complexe interactie tussen biologische, psychologische en sociale factoren. Deze symptomen zijn geassocieerd met verminderde kwaliteit van leven en verhoogde kans op ziekenhuisopnames en sterfte. Ondanks de grote last die patiënten ervaren en de negatieve consequenties, worden symptomen van depressie en angst bij dialysepatiënten vaak niet herkend en behandeld. In dit proefschrift worden de data van twee grote studies in Nederland gebruikt om de volgende vragen te beantwoorden:

- Welke screeningsinstrumenten kunnen gebruikt worden om dialysepatiënten te identificeren die verdere beoordeling van en hulp nodig hebben voor hun angstklachten?
- Welke symptoomdimensies van angst kunnen er worden geïdentificeerd in dialysepatiënten en hoe zijn deze symptoomdimensies geassocieerd aan negatieve consequenties en dialysemodaliteit?
- Wat is de impact van de COVID-19 pandemie op angst en depressie bij hemodialysepatiënten?
- Wat is de effectiviteit van behandeling van depressie bij dialysepatiënten?

Screenen

Doordat symptomen van depressie en angst overlappen met de symptomen van nierfalen en dialysetherapie en vaak samen voor komen, kan het diagnosticeren van depressie en angst bij dialysepatiënten lastig zijn. Het psychologische concept ‘algemene smart’ (*general distress*) bevat zowel symptomen van depressie als angst en zou mogelijk nuttig kunnen zijn voor screeningsdoeleinden. In **Hoofdstuk 2** onderzoeken we dit concept door het combineren van depressie- en angstscores. Onze bevindingen laten zien dat het concept van algemene smart niet geschikt is voor het screenen van dialysepatiënten. In **Hoofdstuk 3** hebben we de nauwkeurigheid van twee veelgebruikte screeningsinstrumenten voor angstklachten onderzocht bij dialysepatiënten door deze te vergelijken met diagnoses van angststoornissen vastgesteld door een psychiatrisch interview. Beide instrumenten kunnen goed onderscheid maken tussen patiënten met en zonder angst en zouden kunnen worden gebruikt in de praktijk of in onderzoek naar angstsymptomen bij dialysepatiënten.

Symptoom dimensies

Inzicht in symptoomdimensies zou kunnen helpen bij het beter begrijpen en behandelen van depressie- en angstsymptomen bij dialysepatiënten. Symptoomdimensies van angst zijn nog niet eerder onderzocht. Doordat hemodialyse (filtering door een kunstnier) en peritoneaal

dialyse (filtering door het buikvlies) verschillen in autonomie, ervaren last van de behandeling en in complicaties, zou de dialysemodaliteit invloed kunnen hebben op symptoomdimensies van depressie en angst. In **Hoofdstuk 4** hebben we een 'somatische' en 'subjectieve' symptoomdimensie van angst gevonden. Alleen de somatische symptoomdimensie is gerelateerd aan ziekenhuisopnames en sterfte en beide symptoomdimensies zijn gerelateerd aan verminderde kwaliteit van leven. In **Hoofdstuk 5** hebben we gekeken naar de relatie tussen dialysemodaliteit en symptoomdimensies. Hierbij zien we dat van zowel depressie als angst vooral de somatische symptoomdimensies veel voorkomen in zowel hemodialyse als peritoneaal dialyse patiënten. We vinden geen verschillen tussen de groepen.

Impact van COVID-19

In de algemene populatie zijn symptomen van depressie, angst en stress veelvoorkomende reacties op de COVID-19 pandemie door angst voor de ziekte zelf, werkloosheid en financiële onzekerheid, overlijden van naasten, quarantaineplicht en sociale isolatie. Ondanks dat chronische ziektes een risicofactor zijn voor het ontwikkelen van symptomen van depressie, angst en stress tijdens COVID-19, is de impact van de pandemie nog niet goed onderzocht bij dialysepatiënten. In **Hoofdstuk 6** hebben we symptomen van stress, depressie en angst en kwaliteit van leven in dialysepatiënten tijdens de pandemie vergeleken met daarvoor. We hebben geen toename van deze symptomen gevonden tijdens de pandemie. Echter, een derde van de dialysepatiënten gaf aan COVID-19 gerelateerde stress te ervaren en deze patiënten rapporteerden meer symptomen van stress en depressie en slechtere kwaliteit van leven dan patiënten zonder COVID-19 gerelateerde stress.

Behandeling

Ondanks dat dialysepatiënten een hoge last ervaren van depressie- en angstsymptomen, is er nog veel onduidelijk over de effectiviteit van de behandelingen voor deze symptomen. In **Hoofdstuk 7** hebben we een systematische literatuurstudie gedaan naar de behandeling van depressie en angst bij dialysepatiënten. Ondanks dat we maar weinig kwalitatief goede studies hebben gevonden, zagen we veelbelovend bewijs voor psychotherapeutische behandeling voor depressie bij dialysepatiënten. **Hoofdstuk 8** beschrijft het onderzoeksprotocol van een grote studie uitgevoerd in 18 dialysecentra in Nederland, waarin het effect van een online zelfhulp psychotherapie op symptomen van depressie bij dialysepatiënten werd onderzocht. De resultaten van deze studie worden gepresenteerd in **Hoofdstuk 9**. Depressiescores verbeterden met 21% in zowel de behandel- als de controlegroep. Er werd geen bewijs gevonden dat er een aanvullend positief effect was van de online zelfhulp psychotherapie in dialysepatiënten naast de gewone zorg. Deze behandeling zou mogelijk meer geschikt kunnen zijn voor jonge dialysepatiënten met computervaardigheden.

Discussie

Hoofdstuk 10 is het laatste hoofdstuk van dit proefschrift en hier worden alle resultaten geïnterpreteerd, de klinische gevolgen van deze resultaten uiteengezet en worden suggesties

gedaan voor toekomstig onderzoek. Ondanks de aanvullende kennis over depressie en angst bij dialysepatiënten in dit proefschrift, zijn er nog steeds onduidelijkheden in de literatuur waardoor succesvolle implementatie van screening voor depressie en angst bij dialysepatiënten op korte termijn nog niet mogelijk is. Toekomstig onderzoek zal moeten proberen deze gaten in de kennis over dit onderwerp te dichten en onderzoeken hoe de inhoud en toegankelijkheid van een interventie voor depressie en angst bij dialysepatiënten het best ontworpen zouden kunnen worden.

List of Publications

Published

1. Nadort E, Schouten RW, Witte SHS, Broekman BFP, Honig A, Siegert CEH, van Oppen P. Treatment of current depressive symptoms in dialysis patients: A systematic review and meta-analysis. *Gen Hosp Psychiatry.* 2020 Nov-Dec;67:26-34. Epub 2020 Aug 5.
2. Schouten RW, Nadort E, van Ballegooijen W, Loosman WL, Honig A, Siegert CEH, Meuleman Y, Broekman BFP. General distress and symptoms of anxiety and depression: A factor analysis in two cohorts of dialysis patients. *Gen Hosp Psychiatry.* 2020 Jul-Aug;65:91-99. Epub 2020 Apr 25.
3. Schouten RW, Nadort E, Harmse V, Honig A, van Ballegooijen W, Broekman BFP, Siegert CEH. Symptom dimensions of anxiety and their association with mortality, hospitalization and quality of life in dialysis patients. *J Psychosom Res*. 2020 Jun;133:109995. Epub 2020 Mar 26.
4. 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 Nov 27;19(1):372.

Submitted

1. Nadort E, Schouten RW, van Geenen NJK, Boeschoten RE, Chandie Shaw P, Vleming LJ, Schouten M, Farhat K, Dekker FW, van Oppen P, Siegert CEH, Broekman BFP. Validation of two screening tools for anxiety in hemodialysis patients. *Submitted*
2. Nadort E, Schouten RW, Luijkx X, Chandie Shaw P, van Ittersum FJ, Smets YFC, Vleming LJ, Dekker FW, Broekman BFP, Siegert CEH. Symptom dimensions of anxiety and depression in patients on Peritoneal dialysis compared to Hemodialysis. *Submitted*
3. Nadort E, Rijkers N, Schouten RW, Hoogeveen EK, Bos WJW, Vleming LJ, Westerman M, Schouten M, Dekker MJE, Smets YFC, Chandie Shaw P, Farhat K, Dekker FW, van Oppen P, Siegert CEH, Broekman BFP. Depression, anxiety and perceived stress of hemodialysis patients before and during the COVID-19 pandemic. *Submitted*
4. Nadort E, Schouten RW, Boeschoten RE, Smets YFC, Chandie Shaw P, Vleming LJ, Dekker MJE, Westerman M, Hoogeveen EK, Bos WJW, Schouten M, Farhat K, Dekker FW, van Oppen P, Broekman BFP, Siegert CEH. Internet-based self-help Cognitive Behavioral Therapy for depression in hemodialysis patients: a cluster randomized controlled trial. *Submitted*

Not related to this Thesis

1. Nadort E, Stam B, Teeuw AH. Signaling and tackling child abuse. *Ned Tijdschr Geneeskd*. 2010;154:A1450.

Dankwoord

Dit proefschrift is ontstaan door de inzet van vele mensen. Een aantal wil ik hier in het bijzonder bedanken.

Allereerst de deelnemers van de DIVERS-I en DIVERS-II studies: zonder jullie was dit proefschrift er nooit gekomen. Ik heb genoten van het contact met jullie, dat ik altijd even aan het bed mocht komen zitten tijdens de dialyse om te vertellen over mijn onderzoek of om (alweer) een vragenlijst af te geven. Bedankt voor jullie deelname.

Mijn promotieteam:

Em.prof.dr. Honig, Adriaan, ik wil je bedanken voor de kans en het vertrouwen dat je me hebt gegeven om dit promotietraject met jou te starten. Je was een betrokken promotor en je deur stond altijd open voor overleg. Je hebt een fantastische opvolger gevonden in Birit en me in goede handen achtergelaten.

Prof.dr. van Oppen, Patricia, bedankt voor de soepele overname van het promotorschap van Adriaan en je fijne begeleiding gedurende mijn hele traject. Naast de wetenschap was alles met je bespreekbaar en mijn werkplezier stond altijd hoog op je agenda. Dat heb ik zeer gewaardeerd.

Prof.dr. Dekker, Friedo, jouw passie voor de wetenschap, de epidemiologie en het onderwijs hebben me geïnspireerd en veel geleerd. Bedankt voor je betrokkenheid bij mijn traject vanuit het LUMC en je luisterend oor als ik dat nodig had.

Dr. Broekman, Birit, jouw ambities zijn net zo groot als je toewijding aan je promovendi. Bedankt voor je leuke en goede onderzoeksideeën, de veilige sfeer die je creëert overal waar je bent en de aandacht die je hebt voor iedereen, van stagiair tot de Koningin.

Dr. Siegert, Carl, jouw charmante overredingskracht en grote netwerk hebben zowel DIVERS-II als mij naar een hoger niveau gebracht de afgelopen 4 jaar. Als ik het even niet zag zitten was er altijd wel ergens een kop koffie te halen of een nieuw dialysecentrum toe te voegen om onze inclusies te behalen. Bedankt voor je begeleiding en inzet tijdens mijn promotietraject.

Een van bovenstaande promomotieteamleden heeft wel eens gezegd dat je een beetje gek moet zijn om een multicenter RCT op te zetten vanuit een perifieer ziekenhuis. Dat ben ik inmiddels wel met diegene eens, en daardoor ben ik des te dankbaarder voor mijn multidisciplinaire en multicenter promotieteam dat dit avontuur met mij aan is gegaan met dit proefschrift als resultaat.

Leden van de leescommissie, prof.dr. Bemelman, prof.dr. Hemmelder, prof.dr. Smit, dr. Meuleman en dr. van Schaik, hartelijk bedankt voor het lezen en beoordelen van mijn proefschrift.

Zonder mijn voorgangers Tessa, Bert, Gerlinde en Robbert was DIVERS nooit geweest waar het nu is. Dank voor jullie voetsporen.

Mijn lieve paranimfen:

Robbert, bedankt voor je oneindige optimisme en energie, de gezellige ritjes naar het LUMC op maandagochtend en onze samenwerking in zowel het onderzoek als het onderwijs. Als jij me niet had overgehaald om te solliciteren bij Adriaan&Carl was dit boekje er nooit geweest. Hoewel ik niet kan zeggen dat ik er nooit een seconde spijt van heb gehad, stond je ook altijd klaar met pragmatische oplossingen en advies. Thanks!

Ingeborg, van samen brak in de collegezaal, via Putten, naar allebei een promotietraject starten. Ik vind het ontzettend fijn dat jij tijdens mijn verdediging naast me staat. Al meer dan tien jaar loyaal lid van Team Els; ik ben blij dat je daar nog nooit op terug gekomen bent. Piramides en zeewier, wijn en kaas; bedankt lieverd!

Een consortium van 19 dialysecentra kan alleen ontstaan met enthousiaste en toegewijde lokale hoofdonderzoekers. Prataap, Louis-Jean, Ellen, Michiel, Marcel, Willem-Jan, Karima, Marijke en Yves; hartelijk bedankt voor de fijne samenwerking vanaf de start van de studie tot aan het indienen van de manuscripten. Ik heb me altijd welkom gevoeld bij jullie op de afdeling.

Alle lieve mensen van de deelnemende dialyse centra van het HMC, HagaZiekenhuis, Franciscus Gasthuis&Vlietland, Jeroen Bosch Ziekenhuis, Maasstad Ziekenhuis, St. Antonius Ziekenhuis, Tergooi Ziekenhuis, Spaarne Gasthuis en OLVG: secretaresses, verpleegkundigen, verpleegkundig specialisten, teamleiders, maatschappelijk werkers, voedingsassistenten, laboranten en nefrologen. Dank voor jullie hulp en inzet bij het uitvoeren van het onderzoek en voor jullie lieve zorg voor de dialyse patiënten, elke dag weer. In het bijzonder mijn collega's van het OLVG West, waar het allemaal is begonnen. Margreet, Anita, Lobbetje, Eline, Regina, Saskia en Kamla, door jullie betrokkenheid bij de uitvoer van DIVERS-II hebben we de studie succesvol uit kunnen rollen in de andere deelnemende centra.

Het succes van DIVERS-II is toe te wijzen aan de toewijding van enthousiaste studenten die stad en land zijn afgereisd om te includeren, vragenlijsten af te nemen en data in te voeren. Joyce, Beritan, Sanne, Essam, Robin, Simon, Noëlle, Dina, Cyjane, Dennis, Serkan, Xander, Nadine en Sonja; dank voor jullie inzet en de hele fijne samenwerking! Ik heb ook ontzettend veel van jullie geleerd en het is een eer om met een aantal van jullie als coauteur in dit proefschrift te staan. Jullie komen er wel! Essam, het is heel fijn om DIVERS-II in jouw ervaren handen achter te laten. Maak er wat moois van!

Zonder de goede begeleiding van de eHealth module vanuit GGZ inGeest had ik dit project niet uit kunnen voeren. Rachel, Lotte en Milou bedankt voor de fijne samenwerking en jullie flexibiliteit. Rosa, het was zo fijn dat jij er was als eHealth/RCT ervaringsdeskundige als ik ergens tegenaan liep. Bedankt dat ik altijd bij je aan mocht kloppen voor advies. Daarnaast

Ingeborg, zo fijn dat je weer terug bent gekomen, dankjewel voor de korte lijntjes en je betrokkenheid.

Ook op de afdeling klinische epidemiologie van het LUMC heb ik veel geleerd van het onderwijs en de journal club; Tamara, Yvette, Esmee, Myrthe, Edouard en Chava, bedankt!

Onderzoek in het OLVG wordt fantastisch ondersteund. Joost, die mixed models serveert alsof het cocktails zijn. Chantal, je searches zijn onnavolgbaar. Saskia, door jou werd gemonitord worden een feestje. Diana, een zeer betrokken leidinggevende. Anne en Marianne, altijd bereid om onderzoekers te helpen waar nodig. Team Wetenschap, dankjulliewel voor alle ondersteuning en het meedenken de afgelopen jaren!

Collegae promovendi en Onderzoekers van OLVG (OvO), het was fijn om elkaar te inspireren tijdens lunch besprekingen en borrels en ik ben trots op de output die we leveren vanuit het OLVG.

Mijn collega's en collega-docenten van het Leerhuis: Marga, Saskia, Irene, Miriam, Marjan, Michelle en Sandra. Ik heb ontzettend veel geleerd van jullie passie voor het onderwijs. Bedankt voor de prettige samenwerking en de fijne sfeer op de kamer.

Margot en Noralie, Birit's powerchicks, zonder lockdowns waren er zeker meer onderzoeks- en carrière ideeën uitgewisseld tijdens etentjes. Succes met jullie onderzoek!

Lieve Lotte, jouw warmte uit het zuiden maakt Amsterdam een stukje mooier. Tijdens koffies in Ikaria en ijsjes in Horst gaf jij me altijd het vertrouwen dat het me zou lukken.

Mijn collega's van de PAAZ; bedankt voor de klinische ervaring die ik bij jullie op heb mogen doen en de interesse in mijn onderzoek de afgelopen jaren.

My career as a researcher started in Kampala, Uganda in 2011. Prof. Frank Cobelens, thank you for introducing me to the fun of science and giving me the opportunity for this research elective abroad. Nirupuma Yechoor, thank you for showing me that 'making your own database is what makes life worth living'. Dr. John Mark Bwanika, thank you for showing me around in Kampala and your incredible entrepreneurship. Ruhi Mamuji, you're simply the best and I hope we'll meet again soon.

Lieve vriendinnen&vrienden: Marjan, Meijet, Iris, Rik, Merel, Lucie, Rolf, Maaike, Lisa, Sufia, Yoshi, Myrthe, Aline, Tom, Giulia, Jasper en Thijs. Of het nou verhuizingen, proefschriften, bandoptredens, verbouwingen of zwangerschaps- en geboorte perikelen waren, jullie waren er voor mij. Thanks lieverds!

Lieve schoonfamilie: Lina, René, Alessia, Joost en Luca. Bedankt voor jullie interesse in mijn onderzoek en dat ik deel mag zijn van jullie familie; grazie di cuore!

Marlies & Annemarie, lieve grote zussen, jullie zijn mij altijd een stapje voor in het leven en zijn een voorbeeld als wetenschapper en als moeders van zonen. Dank voor het meedenken, meelezen en meeleven tijdens mijn promotie.

Alle mannen van mijn zussen: Rogier, Ben, Coen, Timme, Jacob & Felix, ik ben ontzettend blij met jullie.

Lieve pap&mam, bedankt voor jullie vertrouwen in mij, ook als ik zelf twijfelde, en de ruimte om mijn eigen keuzes te kunnen maken. Ik denk dat jullie net zo benieuwd zijn als ik wat het gaat worden.

Lieve Marco, we begonnen dit promotietraject met z'n tweeën, en staan hier nu met z'n drietjes. Dankjewel voor je steun, begrip en liefde. Ook tijdens de lockdowns zonder kinderopvang waren we een team. Oscar, wat jij me het afgelopen jaar hebt geleerd is van zo'n ander niveau dan welke academische opleiding dan ook, ik had er geen minuut van willen missen.

Curriculum Vitae

Els Nadort (1988) is geboren en getogen in Wormer. In 2006 heeft zij haar VWO diploma behaald aan het St. Michaël College in Zaandam. Ze heeft in 2007 haar propedeuse Biomedische Wetenschappen behaald aan de Vrije Universiteit waarna ze is begonnen aan de studie Geneeskunde aan de Universiteit van Amsterdam. Gedurende haar studie heeft Els zich beziggehouden met het coördineren van seksuele voorlichting op middelbare scholen via de International Federation of Medical Students Association (IFMSA) en het signaleren van kindermishandeling in het Emma Kinderziekenhuis. Tijdens haar studie is ze meerdere keren naar het buitenland geweest, onder andere voor haar wetenschapsstage in Oeganda en haar tropencoschap in Tanzania. Ook heeft zij een minor Culturele en Medische Antropologie gevolgd aan de Universiteit van Amsterdam. Haar semiarts stage heeft ze gelopen op de afdeling psychiatrie van het OLVG West, waar ze na haar afstuderen is gestart met een combinatiefunctie als arts-assistent en arts-onderzoeker.

In 2017 begon Els haar promotietraject onder begeleiding van Adriaan Honig, Carl Siegert, Friedo Dekker en Patricia van Oppen, maar na het pensioen van Adriaan Honig heeft Patricia van Oppen het promotorschap overgenomen en is Birit Broekman het team komen versterken. Dit traject werd uitgevoerd op de afdelingen Psychiatrie en Nefrologie van het OLVG, GGZ inGeest en de afdeling Klinische Epidemiologie van het LUMC. Het promotietraject heeft zij gecombineerd met een baan als arts-docent Heelkunde binnen de master geneeskunde aan het VUmc. Zij heeft hiervoor ook haar Basis Kwalificatie Onderwijs behaald. In de toekomst hoopt zij dan ook klinisch werk te kunnen combineren met het doen van onderzoek en het geven van onderwijs.

Els woont samen met Marco en hun zoon Oscar (2020) in Amsterdam. Zij is zich aan het oriënteren op de volgende stap in haar carrière.

Dissertation series

Department of Psychiatry, Amsterdam University Medical Centers

N.M. (Neeltje) Batelaan (2010). Panic and Public Health: Diagnosis, Prognosis and Consequences. Vrije Universiteit Amsterdam. ISBN: 978-90-8659-411-5.

G.E. (Gideon) Anholt (2010). Obsessive-Compulsive Disorder: Spectrum Theory and Issues in Measurement. Vrije Universiteit Amsterdam.

N. (Nicole) Vogelzangs (2010). Depression & Metabolic Syndrome. Vrije Universiteit Amsterdam. ISBN: 978-90-8659-447-4.

C.M.M. (Carmilla) Licht (2010). Autonomic Nervous System Functioning in Major Depression and Anxiety Disorders. Vrije Universiteit Amsterdam. ISBN: 978-90-8659-487-0.

S.A. (Sophie) Vreeburg (2010). Hypothalamic-Pituitary-Adrenal Axis Activity in Depressive and Anxiety Disorders. Vrije Universiteit Amsterdam. ISBN: 978-90-8659-491-7.

S.N.T.M. (Sigfried) Schouws (2011). Cognitive Impairment in Older Persons with Bipolar Disorder. Vrije Universiteit Amsterdam. ISBN: 978-90-9025-904-8.

P.L. (Peter) Remijnse (2011). Cognitive Flexibility in Obsessive-Compulsive Disorder and Major Depression – Functional Neuroimaging Studies on Reversal Learning and Task Switching. Vrije Universiteit Amsterdam. ISBN: 978-90-6464-449-8.

S.P. (Saskia) Wolfensberger (2011). Functional, Structural, and Molecular Imaging of the Risk for Anxiety and Depression. Vrije Universiteit Amsterdam. ISBN: 978-90-8659-536-5.

J.E. (Jenneke) Wiersma (2011). Psychological Characteristics and Treatment of Chronic Depression. Vrije Universiteit Amsterdam. ISBN: 978-94-9121-150-8.

P.D. (Paul David) Meesters (2011). Schizophrenia in Later Life. Studies on Prevalence, Phenomenology and Care Needs (SOUL Study). Vrije Universiteit Amsterdam. ISBN: 978-90-8659-563-1.

R. (Ritsaert) Lieverse (2011). Chronobiopsychosocial Perspectives of Old Age Major Depression: a Randomized Placebo Controlled Trial with Bright Light. Vrije Universiteit Amsterdam. ISBN: 978-90-8570-858-2.

A. (Adrie) Seldenrijk (2011). Depression, Anxiety and Subclinical Cardiovascular Disease. Vrije Universiteit Amsterdam. ISBN: 978-94-6191-052-3.

Y. (Yuri) Milaneschi (2012). Biological Aspects of Late-life Depression. Vrije Universiteit Amsterdam. ISBN: 978-90-8659-608-9.

L. (Lynn) Boschloo (2012). The Co-occurrence of Depression and Anxiety with Alcohol Use Disorders. Vrije Universiteit Amsterdam. ISBN: 978-94-6191-327-2.

D. (Didi) Rhebergen (2012). Insight into the heterogeneity of depressive disorders. Vrije Universiteit Amsterdam. ISBN: 978-94-6191-387-6.

T.M. (Michiel) van den Boogaard (2012). The Negotiated Approach in the Treatment of Depressive Disorders: the impact on patient-treatment compatibility and outcome. Vrije Universiteit Amsterdam. ISBN: 978-90-8891-495-9.

M. (Marjon) Nadort (2012). The implementation of outpatient schema therapy for borderline personality disorder in regular mental healthcare. Vrije Universiteit Amsterdam. ISBN: 978-94-6191-463-7.

U. (Ursula) Klumpers (2013). Neuroreceptor imaging of mood disorder related systems. Vrije Universiteit Amsterdam. ISBN: 978-94-6191-575-7.

E. (Ethy) Dorrepaal (2013). Before and beyond. Stabilizing Group treatment for Complex posttraumatic stress disorder related to child abuse based on psycho-education and cognitive behavioral therapy. Vrije Universiteit Amsterdam. ISBN: 978-94-6191-601-3.

K. (Kathleen) Thomaes (2013). Child abuse and recovery. Brain structure and function in child abuse related complex posttraumatic stress disorder and effects of treatment. Vrije Universiteit Amsterdam. ISBN: 978-94-6191-600-6.

K.M.L.(Klaas) Huijbregts (2013). Effectiveness and cost-effectiveness of the implementation of a collaborative care model for depressive patients in primary care. Vrije Universiteit Amsterdam. ISBN: 978-90-9027404-1.

T.O. (Tessa) van den Beukel (2013). Ethnic differences in survival on dialysis in Europe. The role of demographic, clinical and psychosocial factors. Vrije Universiteit Amsterdam. ISBN: 978-94-6108410-1.

A. (Agnes) Schrier (2013). Depression and anxiety in migrants in the Netherlands. Population studies on diagnosis and risk factors. Vrije Universiteit Amsterdam. ISBN: 978-94-6191-719-5.

B. (Barbara) Stringer (2013). Collaborative Care for patients with severe personality disorders. Challenges for the nursing profession. Vrije Universiteit Amsterdam. ISBN: 978-94-6191-809-3.

C.M. (Caroline) Sonnenberg (2013). Late life depression: sex differences in clinical presentation and medication use. Vrije Universiteit Amsterdam. ISBN: 978-94-6191-866-6.

Z. (Zsuzsika) Sjoerds (2013). Alcohol dependence across the brain: from vulnerability to compulsive drinking. Vrije Universiteit Amsterdam. ISBN: 978-90-8891-695-3.

V.J.A. (Victor) Buwalda (2013). Routine Outcome Monitoring in Dutch Psychiatry: Measurement, Instruments, Implementation and Outcome. Vrije Universiteit Amsterdam. ISBN: 978-94-6191-905-2.

J.G. (Josine) van Mill (2013). Sleep, depression and anxiety: an epidemiological perspective. Vrije Universiteit Amsterdam. ISBN: 978-94-6108-525-2.

S. (Saskia) Woudstra (2013). Framing depression in a SN[a]Pshot: Imaging risk factors of MDD. Vrije Universiteit Amsterdam. ISBN: 978-90-8891-751-6.

N.C.M. (Nicole) Korten (2014). Stress, depression and cognition across the lifespan. Vrije Universiteit Amsterdam. ISBN: 978-94-6108-748-5.

M.K. (Maarten) van Dijk (2014). Applicability and effectiveness of the Dutch Multidisciplinary Guidelines for the treatment of Anxiety Disorders in everyday clinical practice. Vrije Uiversiteit Amsterdam. ISBN: 978-94-92096-00-5.

I.M.J. (Ilse) van Beljouw (2015). Need for Help for Depressive Symptoms from Older Persons Perspectives: The Implementation of an Outreaching Intervention Programme. Vrije Universiteit Amsterdam. ISBN: 978-94-6259-496-8.

A.M.J. (Annemarie) Braamse (2015). Psychological aspects of hematopoietic stem cell transplantation in patients with hematological malignancies. Vrije Universiteit Amsterdam. ISBN: 978-94-6259-594-1.

A. (Annelies) van Loon (2015). The role of ethnicity in access to care and treatment of outpatients with depression and/or anxiety disorders in specialised care in Amsterdam the Netherlands. Vrije Universiteit Amsterdam. ISBN: 978-94-90791-34-6.

C. (Chris) Vriend (2015). (Dis)inhibition: imaging neuropsychiatry in Parkinson's disease. Vrije Universiteit Amsterdam. ISBN: 978-94-6295-115-0.

A.M. (Andrea) Ruissen (2015). Patient competence in obsessive compulsive disorder. An empirical ethical study. Vrije Universiteit Amsterdam. ISBN: 978-90-6464-856-4.

H.M.M. (Henny) Sinnema (2015). Tailored interventions to implement guideline recommendations for patients with anxiety and depression in general practice. Vrije Universiteit Amsterdam. ISBN: 978-94-6169-653-3.

T.Y.G. (Nienke) van der Voort (2015). Collaborative Care for patients with bipolar disorder. Vrije Universiteit Amsterdam. ISBN: 978-94-6259-646-7.

W. (Wim) Houtjes (2015). Needs of elderly people with late-life depression; challenges for care improvement. Vrije Universiteit Amsterdam. ISBN: 978-94-6108-985-4.

M. (Marieke) Michielsen (2015). ADHD in older adults. Prevalence and psychosocial functioning. Vrije Universiteit Amsterdam. ISBN: 978-90-5383-132-8.

S.M. (Sanne) Hendriks (2016). Anxiety disorders. Symptom dimensions, course and disability. Vrije Universiteit Amsterdam. ISBN: 978-94-6259-963-5.

E.J. (Evert) Semeijn (2016). ADHD in older adults; diagnosis, physical health and mental functioning. Vrije Universiteit Amsterdam. ISBN: 978-94-6233-190-7.

N. (Noera) Kieviet (2016). Neonatal symptoms after exposure to antidepressants in utero. Vrije Universiteit Amsterdam. ISBN: 978-94-6169-794-3.

W.L. (Bert) Loosman (2016). Depressive and anxiety symptoms in Dutch chronic kidney disease patients. Vrije Universiteit Amsterdam. ISBN: 987-94-6169-793-6.

E. (Ellen) Generaal (2016). Chronic pain: the role of biological and psychosocial factors. Vrije Universiteit Amsterdam. ISBN: 978-94-028-0032-6.

D. (Dóra) Révész (2016). The interplay between biological stress and cellular aging: An epidemiological perspective. Vrije Universiteit Amsterdam. ISBN: 978-94-028-0109-5.

F.E. (Froukje) de Vries (2016). The obsessive-compulsive and tic-related brain. Vrije Universiteit Amsterdam. ISBN: 978-94-629-5481-6.

J.E. (Josine) Verhoeven (2016). Depression, anxiety and cellular aging: does feeling blue make you grey? Vrije Universiteit Amsterdam. ISBN: 978-94-028-0069-2.

A.M. (Marijke) van Haeften-van Dijk (2016). Social participation and quality of life in dementia: Implementation and effects of interventions using social participation as strategy to improve quality of life of people with dementia and their carers. Vrije Universiteit Amsterdam. ISBN: 978-94-6233-341-3.

P.M. (Pierre) Bet (2016). Pharmacoepidemiology of depression and anxiety. Vrije Universiteit Amsterdam. ISBN: 978-94-6299-388-4.

M.L. (Mardien) Oudega (2016). Late life depression, brain characteristics and response to ECT. Vrije Universiteit Amsterdam. ISBN: 978-94-6295-396-3.

H.A.D. (Henny) Visser (2016). Obsessive-Compulsive Disorder; Unresolved Issues, Poor Insight and Psychological Treatment. Vrije Universiteit Amsterdam. ISBN: 978-94-028-0259-7.

E.C. (Eva) Verbeek (2017). Fine mapping candidate genes for major depressive disorder: Connecting the dots. Vrije Universiteit Amsterdam. ISBN: 978-94-028-0439-3.

S. (Stella) de Wit (2017). In de loop: Neuroimaging Cognitive Control in Obsessive-Compulsive Disorder. Vrije Universiteit Amsterdam. ISBN: 978-90-5383-225 7.

W.J. (Wouter) Peyrot (2017). The complex link between genetic effects and environment in depression. Vrije Universiteit Amsterdam. ISBN: 978-94-6182-735-7.

R.E. (Rosa) Boeschoten (2017). Depression in Multiple Sclerosis: Prevalence Profile and Treatment. Vrije Universiteit Amsterdam. ISBN: 978-94-028-0474-4.

G.L.G. (Gerlinde) Haverkamp (2017). Depressive symptoms in an ethnically DIVERSe cohort of chronic dialysis patients: The role of patient characteristics, cultural and inflammatory factors. Vrije Universiteit Amsterdam. ISBN: 978-94-6233-528-8.

T.J. (Tjalling) Holwerda (2017). Burden of loneliness and depression in late life. Vrije Universiteit Amsterdam. ISBN: 978-94-6233-598–1.

J. (Judith) Verduijn (2017). Staging of Major Depressive Disorder. Vrije Universiteit Amsterdam. ISBN: 978-94-6299-597-0.

C.N. (Catherine) Black (2017). Oxidative stress in depression and anxiety disorders. Vrije Universiteit Amsterdam. ISBN: 978-94-6299-672-4.

J.B. (Joost) Sanders (2017). Slowing and Depressive Symptoms in Aging People. Vrije Universiteit Amsterdam. ISBN: 978-94-6233-650-6.

W. (Willemijn) Scholten (2017). Waxing and waning of anxiety disorders: relapse and relapse prevention. Vrije Universiteit Amsterdam. ISBN: 978-94-6299-606-9.

P. (Petra) Boersma (2017). Person-centred communication with people with dementia living in nursing homes; a study into implementation success and influencing factors. Vrije Universiteit Amsterdam. ISBN: 978-94-6233-725-1.

T.I. (Annet) Bron (2017). Lifestyle in adult ADHD from a Picasso point of view. Vrije Universiteit Amsterdam. ISBN: 978-94-6299-685-4.

S.W.N. (Suzan) Vogel (2017). ADHD IN ADULTS: seasons, stress, sleep and societal impact. Vrije Universiteit Amsterdam. ISBN: 978-94-6299-673-1.

R. (Roxanne) Schaakxs (2018). Major depressive disorder across the life span: the role of chronological and biological age. Vrije Universiteit Amsterdam. ISBN: 978-94-6299-819-3.

J.J. (Bart) Hattink (2018). Needs-based enabling- and care technology for people with dementia and their carers. Vrije Universiteit Amsterdam. ISBN: 978-94-6295-880-7.

F.T. (Flora) Gossink (2018). Late Onset Behavioral Changes differentiating between bvFTD and psychiatric disorders in clinical practice. Vrije Universiteit Amsterdam. ISBN: 978-94-6295-899-9.

R. (Roxanne) Gaspersz (2018). Heterogeneity of Major Depressive Disorder. The role of anxious distress. Vrije Universiteit Amsterdam. ISBN: 978-94-028-1076-9.

M.M. (Marleen) Wildschut (2018). Survivors of early childhood trauma and emotional neglect: who are they and what's their diagnosis? Vrije Universiteit Amsterdam. ISBN: 978-94-6332-401-4.

J.A.C. (Jolanda) Meeuwissen (2018). The case for stepped care. Exploring the applicability and cost-utility of stepped-care strategies in the management of depression. Vrije Universiteit Amsterdam. ISBN: 978-90-5383-359-9.

D.S. (Dora) Wynchank (2018). The rhythm of adult ADHD. On the relationship between ADHD, sleep and aging. Vrije Universiteit Amsterdam. ISBN: 978-94-6375-034-9.

M.J.(Margot) Metz (2018). Shared Decision Making in mental health care: the added value for patients and clinicians. Vrije Universiteit Amsterdam. ISBN: 978-94-6332-403-8.

I.(Ilse) Wielaard (2018). Childhood abuse and late life depression. Vrije Universiteit Amsterdam. ISBN: 978-94-6380-072-3.

L.S.(Laura) van Velzen (2019). The stressed and depressed brain. Vrije Universiteit Amsterdam. ISBN: 978-94-6380-062-4.

S. (Sonja) Rutten (2019). Shedding light on depressive, anxiety and sleep disorders in Parkinson's disease. Vrije Universiteit Amsterdam. ISBN: 978-94-6380-176-8.

N.P.G. (Nadine) Paans (2019). When you carry the weight of the world not only on your shoulders. Factors associating depression and obesity. Vrije Universiteit Amsterdam. ISBN: 978-94-6380-141-6.

D.J. (Deborah) Gibson-Smith (2019). The Weight of Depression. Epidemiological studies into obesity, dietary intake and mental health. Vrije Universiteit Amsterdam. ISBN: 978-94-6380-144-7.

C.S.E.W. (Claudia) Schuurhuizen (2019). Optimizing psychosocial support and symptom management for patients with advanced cancer. Vrije Universiteit Amsterdam. ISBN: 978-94-6323-468-9.

M.X. (Mandy) Hu (2019). Cardiac autonomic activity in depression and anxiety: heartfelt afflictions of the mind. Vrije Universiteit Amsterdam. ISBN: 978-94-6380-206-2.

J..K.(Jan) Mokkenstorm (2019). On the road to zero suicides: Implementation studies. Vrije Universiteit Amsterdam. ISBN: 978-94-6361-224-1.

S.Y. (Sascha) Struijs (2019). Psychological vulnerability in depressive and anxiety disorders. Vrije Universiteit Amsterdam. ISBN: 978-94-6380-244-4.

H.W. (Hans) Jeuring (2019). Time trends and long-term outcome of late-life depression: an epidemiological perspective. Vrije Universiteit Amsterdam. ISBN: 978-94-6380-228-4.

R. (Ruth) Klaming Miller (2019). Vulnerability of memory function and the hippocampus: Risk and protective factors from neuropsychological and neuroimaging perspectives. Vrije Universiteit Amsterdam. ISBN: 978-94-6182-955-5.

P.S.W. (Premika) Boedhoe (2019) The structure of the obsessive-compulsive brain – a worldwide effort. Vrije Universiteit Amsterdam. ISBN: 978-94-6380-329-8.

C.S. (Carisha) Thesing (2020). Fatty acids in depressive and anxiety disorders: fishing for answers. Vrije Universiteit Amsterdam. ISBN: 978-94-6375-846-8.

R.D. (Richard) Dinga (2020). Evaluation of machine learning models in psychiatry. Vrije Universiteit Amsterdam.

M. (Mayke) Mol (2020). Uptake of internet-based therapy for depression: the role of the therapist. Vrije Universiteit Amsterdam. ISBN: 978-94-6416-150-2.

R.C. (Renske) Bosman (2020). Improving the long-term prognosis of anxiety disorders: Clinical course, chronicity and antidepressant use. Vrije Universiteit Amsterdam. ISBN: 978-94-6375-736-2.

R.W. (Robbert) Schouten (2020). Anxiety, depression and adverse clinical outcomes in dialysis patients. Should we do more? Vrije Universiteit Amsterdam. ISBN: 978-94-6416-179-3.

T.T. (Trees) Juurlink (2021). Occupational functioning in personality disorders: a quantitative, qualitative and semi-experimental approach. Vrije Universiteit Amsterdam. ISBN: 978-94-6421-117-1.

I.P.H. (Ires) Ghielen (2021). Surfing the waves of Parkinson's disease. Understanding and treating anxiety in the context of motor symptoms. Vrije Universiteit Amsterdam. ISBN: 978-94-6416-493-0

L.K.M. (Laura) Han (2021). Biological aging in major depressive disorder. Vrije Universiteit Amsterdam. ISBN: 978-94-93184-91-6

E. (Esther) Krijnen-de Bruin (2021). Relapse prevention in patients with anxiety or depressive disorders. Vrije Universiteit Amsterdam. ISBN: 978-94-6423-298-1

T.D. (Tim) van Balkom (2021). The profiles and practice of cognitive function in Parkinson's disease. Vrije Universiteit van Amsterdam. ISBN: 978-94-6423-391-9

S.M. (Sanne) Swart (2021). The course of survivors of early childhood trauma and emotional neglect: never easy, but worth it? Vrije Universiteit Amsterdam. ISBN: 978-94-6416-650-7

Y.J.F. (Yvonne) Kerkhof (2021). Digital support for self-management and meaningful activities of people with mild dementia. Development, implementation and feasibility of a person-centred touch-screen intervention. Vrije Universiteit Amsterdam. ISBN: 978-90-829978-2-8

I.M.J.(Ilja) Saris (2021). Together alone: Social dysfunction in neuropsychiatric disorders. Vrije Universiteit Amsterdam. ISBN: 978-90-9035-072-1

A. (Angela) Carlier (2021). Biomarkers and electroconvulsive therapy in late-life depression. Vrije Universiteit Amsterdam. ISBN: 978-94-6421-462-8

S. (Sonia) Difrancesco (2021). Sleep, circadian rhythms and physical activity in depression and anxiety. The role of ambulatory assessment tools. Vrije Universiteit Amsterdam. ISBN: 978-94-6416-781-8

B.A. (Bianca) Lever-van Milligen (2021). The interplay between depression, anxiety and objectively measured physical function. Vrije Universiteit Amsterdam. ISBN: 978-94-6423-443-5

J.M. (Joeke) van der Molen-van Santen (2021). Remember to play… and stay active! Evaluation of the effects, cost-effectiveness and implementation of exergaming for people living with dementia and their informal caregivers. Vrije Universiteit Amsterdam. ISBN: 978-94-6332-795-4

W.A. (Wicher) Bokma (2021). Worrying about the future: towards evidence-based prognosis in anxiety disorders. Vrije Universiteit Amsterdam. ISBN: 978-94-93270-17-6

H.M.Heller (Hansje) Heller (2021). Affective dysregulation in pregnancy. Vrije Universiteit Amsterdam. ISBN: 978-94-93270-24-4

A.P.M. (Arnold) van der Lee, (2021). Continuity of care for patients with a severe mental disorder. Vrije Universiteit Amsterdam. ISBN: 978-94-6421-570-0

R.J.W. (Richard) Vijverberg (2022). Care needs of children and adolescents in psychiatry: steps towards personalized mental healthcare. Vrije Universiteit Amsterdam. ISBN: 978-94-6423-521-0

N. (Natasja) Schutter (2022). Loneliness and social isolation in older adults: consequences, vulnerability and the role of depression Vrije Universiteit Amsterdam. ISBN: 978-94-6332-815-9.