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Chapter 7

General discussion



GENERAL DISCUSSION

The topic of this doctoral dissertation is depressive and anxiety symptoms in Dutch chronic kidney disease (CKD) patients. This dissertation is divided in two parts with two separate aims. The first aim was to investigate the use of self-report questionnaires in dialysis patients. The second aim was to investigate the relevance of depressive and anxiety symptoms in Dutch CKD patients. Special attention has been given to the prevalence of depressive and anxiety symptoms in immigrant in comparison with native dialysis patients, the interplay of depressive and anxiety symptoms with type D personality, and the effect of depressive and anxiety symptoms on adverse events such as mortality.

PART 1 The use of self-report questionnaires

Main findings

Chapter 2

In dialysis patients complaints of uraemia may overlap with somatic complaints of depression, thereby hampering screening for depression. The Hospital Anxiety and Depression Scale (HADS) and the Beck Depression Inventory (BDI) are both self-report screening questionnaires for depression. Both questionnaires were compared with the Mini International Neuropsychiatric Interview (semi-structured interview). Results showed that the BDI, which does include somatic items, proved to be a valid screening tool to assess depressive symptoms in dialysis patients, and performs equally well as the HADS, a self-report rating scale which does not include somatic items.

Chapter 3

Short Form 36 (SF-36) is a self-report questionnaire used to assess Health Related Quality of Life (HRQOL). In order to reduce patient burden Short Form-12 (SF-12) was developed. The aim of this study was to investigate if SF-12 can be used to assess HRQOL in dialysis patients instead of SF-36. Results showed that SF-12 scores can be used to replicate SF-36 scores in cross-sectional studies, and can also be used to detect HRQOL changes over time in cohort studies in dialysis patients. SF-12 and SF-36 were similarly associated with short-term and long-term mortality. However, for individual patients considerable differences were observed between SF-12 and SF-36 measurements. In addition, specific items and detailed information is lost in SF-12. Therefore, if in clinical practice detailed information in individual patients is important, SF-36 is preferred.

Depressive and anxiety symptoms

In CKD patients somatic complaints of depression may overlap with complaints of uraemia, such as tiredness, appetite problems and sleeplessness.^{1,2} These somatic complaints could complicate the assessment of depressive symptoms by using a self-report questionnaire. In chapter 2, however, we demonstrated that two questionnaires each using a different approach, namely including (BDI) and lacking (HADS) questions about somatic complaints, proved to be equally valid screening tools.

Cohen-Cole and Stoudemire³ reported that four approaches have been used to deal with the problem of assessing depression in patients with physical illness. First, in the 'inclusive approach' depressive diagnostic symptoms are included regardless whether they are related to physical illnesses.³ Secondly, in the 'etiologic approach' of Rifkin et al.⁴, a symptom is counted only if the diagnostician feels it is not caused by the physical illness. Thirdly, the 'substitutive approach' of Endicott⁵, in which the psychological symptoms of depression are substituted for the vegetative symptoms, which tend to be nonspecific in a physically ill population. Finally, the 'exclusive approach' of Bukberg et al.⁶, in which symptoms are removed from the diagnostic criteria if they are not found to be more frequent in depressed than in non-depressed patients. The HADS comes close to an exclusive approach, because there are no somatic items in the questionnaire while no specific items were removed either. The BDI can be seen as an inclusive approach.

With both questionnaires performing equally, the question remains which one to use in research or clinical practice. A common barrier for treatment of depressive symptoms in CKD patients is that patients do not feel depressed and/or anxious.⁷ Maybe patients do not regard their depressive and/or anxiety symptoms as signs of mood disturbance, but as a normal phenomenon related to their physical disorder. Therefore, the BDI could be preferred because patients recognize specific complaints such as sleeplessness, fatigue or sexual dysfunction which could make it easier to discuss all complaints (including sadness and anhedonia) with the patient. Additionally, suicidal ideation can be assessed by using the BDI which instantly detects patients with the highest severity of distress (the combination of depressive and anxiety symptoms).⁸ The advantage of HADS, on the other hand, is its feasibility with only seven depression questions compared to the 21 questions of the BDI. Moreover, HADS includes 7 anxiety questions as well whereas BDI only assesses depressive symptoms. Alternatively, Beck Anxiety Inventory (BAI) could be added to the BDI in order to assess anxiety symptoms as well, but this would add another 21 questions to the patients questionnaire. Furthermore, the difficulty of using the BAI is that although it has been used in dialysis patients⁹ validation in dialysis patients or patients with earlier stages of CKD has not been performed. In order to make a

proper comparison with international literature as well as to analyse somatic complaints of depression separately we chose to use BDI in our cohorts (chapter 4, 5, and 6). In clinical practice the advantages of a short list combining depressive and anxiety symptoms (HADS) outweighs the advantages of the BDI, but the use of any questionnaire will depend on intentions of the clinicians using a specific questionnaire.

After choosing which questionnaire to use it is important to emphasize the interpretation of a self-report questionnaire. Self-report questionnaires that assess depressive or anxiety symptoms are often developed to indicate the severity of a depression or anxiety disorder. In clinical practice a cut-off value is used to divide patients into patient groups with or without depressive or anxiety symptoms. Thereafter a cut-off value can be used (1) to screen for depressive symptoms and subsequently confirm the diagnosis by using a structured interview or (2) to indicate a probability of a diagnosis of depression. The chosen cut-off will depend upon the quality of the questionnaire (i.e. the level of sensitivity and specificity), and the reason for which a clinician uses the questionnaire. For screening purposes a cut-off value with a high sensitivity is preferred, and to produce a high probability of a diagnosis of depression (for example after screening) high specificity is preferred. As mentioned before we chose to use the BDI in our cohorts (chapter 4,5 ,and 6). For feasibility we chose not to use a semi-structured interview but a cut-off value with the highest Area Under the Curve (AUC), which minimizes the total of false positive and false negative misdiagnosis (sensitivity 75% and specificity 90.2% (chapter 2)).

Health related quality of life

Depressive and anxiety symptoms have an impact on physical and mental HRQOL in patients with chronic kidney disease.¹⁰ In clinical practice and in a research setting HRQOL is also assessed with a self-report questionnaire. Questionnaires can be used cross-sectionally or sequentially to assess HRQOL changes over time. SF-36 is a frequently used self-report questionnaire to assess HRQOL, which consists of two component scores (physical component score (PCS) and mental component score (MCS)) and eight subdomains (i.e. vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health). SF-12 was developed to reproduce PCS and MCS. In chapter 3 we showed that in a research setting (i.e. the comparison of patient groups) SF-12 can be used instead of SF-36. Therefore, we used SF-12 in the cohorts presented in chapter 4 and chapter 5. We found that individual differences (i.e. in clinical practice) exist between the two questionnaires, which makes it difficult to use the SF-12 score for individual purposes in a clinical setting. Moreover, the loss of the eight subdomains makes it difficult to discuss

specific problems of HRQOL as well as to assess specific effects of treatment (i.e. treatment of depressive and anxiety symptoms). It goes without saying that if researchers want to assess these eight subdomains it would also be preferable to use SF-36 instead of SF-12.

In sum, the choice of a self-report questionnaire to assess depressive and anxiety symptoms and HRQOL in CKD patients is not unequivocal. This choice will depend on the specific reason for which a questionnaire is used by a clinician or researcher.

PART 2 The relevance of depressive and anxiety symptoms in Dutch CKD patients

Main findings

Chapter 4

It is unclear whether the prevalence of depressive and anxiety symptoms differs between native and immigrant patients on chronic dialysis treatment. Therefore, the aim of this study was to determine the prevalence of depressive and anxiety symptoms in immigrant compared to native dialysis patients. Furthermore, we wanted to explore whether differences could be explained by patient characteristics (i.e. sociodemographic and clinical). Results showed that immigrant dialysis patients have a higher prevalence of depressive and anxiety symptoms compared to native dialysis patients. Differences between native and immigrant patients were more pronounced in Asian patients. For both depressive and anxiety symptoms patient characteristics did not explain the differences between native and immigrant patients.

Chapter 5

In dialysis patients little is known about type D personality. Patients with type D (distressed) personality have the tendency to experience negative emotions across time (negative affectivity) and to inhibit emotional expression because of fear for social rejection (social inhibition). The aim of the study is to assess the prevalence type D personality, the association with depressive and anxiety symptoms, and stability of type D personality. Results showed that in dialysis patients the prevalence of type D personality was 21%, and type D personality was associated with higher depressive and anxiety symptoms and lower quality of life. The presence of type D personality varies over time, and stability of type D personality is comparable to the stability of depressive and anxiety symptoms.

Chapter 6

Depressive symptoms have been reported to be associated with adverse clinical outcome in CKD patients not on dialysis. This association has not been examined in Europe. Anxiety and depressive symptoms often co-occur. However, as yet there are no data concerning a possible association of anxiety symptoms with adverse clinical outcome. We examined the association of depressive and anxiety symptoms with adverse clinical outcome in Dutch CKD patients not on dialysis. Results showed that depressive and anxiety symptoms are common in patients with CKD in the Netherlands. Depressive symptoms are associated with an increased risk of poor clinical outcome. Anxiety symptoms show a trend for an increased risk of poor clinical outcome. There seems to be no cumulative effect of anxiety symptoms on top of depressive symptoms.

Prevalence of depressive and anxiety symptoms

In recent years three reviews discussed the prevalence of depressive symptoms in the dialysis population.¹¹⁻¹³ The prevalence varied from 27%¹² to 39%^{11;13}, and was mostly assessed with a self-report questionnaire or a structured interview.¹³ When using a structured interview (a diagnosis of depression) the prevalence was 29%¹¹ and 23%¹³, which is lower compared to a self-report questionnaire (depressive symptoms). Moreover, Palmer et al.¹³ also included earlier stages of CKD and transplantation patients, both with a prevalence of 27%.

The prevalence of depressive symptoms increased when the proportion of participants who were married was higher or with more women in the study population.¹³ The prevalence was not modified by age, race, employment, and diabetic status.¹³ The prevalence of depressive symptoms in our cohort of dialysis patients (chapter 4) was 43% (unpublished data), and in our cohort of pre-dialysis patients (chapter 6) was 34%. In the first cohort (chapter 4) patients with depressive symptoms were more often unemployed, had a lower educational level, and had a more severe comorbidity score (unpublished data). No further differences were found at baseline. In the second cohort (chapter 6) patients with depressive symptoms had more often a history of depression and cardiovascular disease. These results seem to indicate that more vulnerable CKD patients have more depressive symptoms. In general, for all these different type of CKD patients (i.e. CKD patients not on dialysis, dialysis patients, and transplantation patients) it is important to realize that the prevalence of depressive symptoms is higher compared to the general population.

The presence of anxiety symptoms was less often examined in patients with chronic kidney disease and varies between 13-50%.¹⁴⁻¹⁹ In our cohort of dialysis patients (chapter 4) the prevalence of anxiety symptoms was 36% (unpublished data). The differences at baseline between patients with and without anxiety symptoms were the same as patients with and without depressive symptoms. In our cohort of pre-dialysis patients (chapter 6) the prevalence of anxiety symptoms was 31% with primarily female patients affected. These patient characteristics are important in order to define risk groups in a clinical or research setting. The nearly similar characteristics of patients with and without depressive or anxiety symptoms suggest that the same patients are at risk of getting depressive or anxiety symptoms.

In order to further define patient groups at risk of developing depressive or anxiety symptoms we investigated the prevalence of depressive and anxiety symptoms in immigrant compared to native dialysis patients (chapter 4). Immigrant dialysis patients had a higher prevalence of depressive and anxiety symptoms compared to native dialysis patients. Sociodemographic and clinical characteristics could not explain these differences between immigrant and native patients. There could be several explanations for the difference between native and immigrant patients. First, perceived ethnic discrimination (PED) may be an explanation, because PED contributes considerably to depression in ethnic minority groups in the Netherlands.²⁰ Second, it has been shown that less skills for living in the Dutch society, and more feelings of loss are associated with the presence of both depressive and anxiety symptoms in immigrant chronic dialysis patients.²¹ Finally, religion might play a role in the difference between immigrant and native patients. Ramirez et al.²² showed that in dialysis patients religious struggle was independently associated with greater psychological distress and impaired HRQOL. For clinical research it is important to assess immigrant status besides ethnic origin, and in clinical practice it is important for nephrologists to be aware that immigrant patients are more prone to develop depressive and anxiety symptoms.

In addition to identifying specific patient risk groups, we explored the association of type D personality with depressive and anxiety symptoms (chapter 5). The prevalence of type D personality was comparable to the general population (21%), and type D personality was associated with the presence of depressive and anxiety symptoms. With the cross-sectional nature of this study it is impossible to determine what comes first. In other words: do patients with type D personality have a higher chance to develop depressive and anxiety symptoms or do depressive and anxiety symptoms enhance the expression of certain personality characteristics (i.e type D personality). It has been suggested in cardiac literature that type D personality is not only associated with depression and anxiety, but is also associated with depression in the future.^{23;24} This suggests that type D

personality could predispose for depressive and anxiety symptoms. A prospective study in chronic kidney disease patients might elucidate on these mechanisms.

In chapter 5 we also showed that the prevalence of type D personality varies over time. Only 61% of the patients with type D personality according to the DS-14, express type D personality six months later. This may indicate that type D personality is more a state than a trait phenomenon. In this light, it has been suggested that Type D personality is better presented as an interaction of NA and SI^{25;26}, because many information is lost by dichotomizing NA and SI.^{27;28} Moreover, various cut-off levels²⁹ or a division in low, moderate and high NA and SI subgroups have also been suggested.³⁰ By analysing NA and SI separately (chapter 5) we showed that limits of agreement varied from -10 to 10. Indicating that between two measurements the differences can vary up to 10 points. Therefore, the stability of type D personality does not seem to depend on the statistical method used to analyse NA and SI. This could imply that prospective research on type D personality should be assessed with multiple measurements instead of just one measurement. For example, multiple measurements could be necessary to explore if there is an association of type D personality with morbidity and mortality, and to explore whether this association is independent of depressive and anxiety symptoms.

Effects on clinical outcome

A high prevalence of depressive and anxiety symptoms in CKD patients is associated with a low HRQOL¹⁰, and high morbidity and mortality rates.^{31;32} Recently, a review and meta-analysis described and quantified the association of depressive symptoms with mortality in patients with all stages of CKD.^{31;33} The meta-analysis showed a relative risk of 1.34 (0.92 – 1.97) with mortality for CKD patients not on dialysis. Our study found a comparable (non-significant) association with mortality (chapter 6). However, it is difficult to determine this association, because of the low death rate in CKD patients not on dialysis. This could be a reason why mortality is often combined with starting with dialysis and/or hospitalization, which are also important events in CKD patients not on dialysis. Our results (chapter 6) demonstrate multiple associations between depressive symptoms on several adverse events (i.e. hospitalisation, starting with dialysis, and/or death). Patients with depressive symptoms were around two times more likely to have a combined adverse event within three years. This indicates that it is important to not only assess depressive and anxiety symptoms in dialysis patients, but also in patients with earlier stages of CKD.

In chapter 6 we also assessed the association between anxiety symptoms and clinical outcome in CKD patients not on dialysis. There was a trend for the association of anxiety

symptoms and adverse events and there seems to be no additive effect of anxiety symptoms on top of depressive symptoms. This is the first study to explore this association in CKD patients not on dialysis. Moreover, this association has not been assessed in dialysis patients. Further research should elaborate the need to assess anxiety symptoms separately or together with depressive symptoms.

The use of time-varying models (multiple measurements) showed a higher association with mortality compared to one baseline measure as was shown by the two meta-analysis.^{31,32} These consecutive measurements are important because patients who repeatedly score above cut-off have higher mortality rates compared to patients who score above cut-off only once.³⁴⁻³⁶ These results indicate that the short term association between depressive symptoms and mortality is stronger compared to the long term association between depressive symptoms and mortality. In CKD patients not on dialysis the differences between one measurement and consecutive measurements is unknown and could be a topic for future research.

Treatment strategies

In chapter 4 we showed that the prevalence of depressive and anxiety symptoms is high in Dutch dialysis patient (especially in immigrant patients). Furthermore, in chapter 6 we showed that depressive and anxiety symptoms are associated with adverse events (i.e. hospitalisation, starting with dialysis, and/or death) among CKD patients not on dialysis. The next step in clinical research could be to investigate the effect of treatment of depressive and anxiety symptoms. Although we did not investigate this effect we described in chapter 4 and chapter 6 that the use of anti-depressants is very low in pre-dialysis and dialysis patients. Furthermore, only four percent of the dialysis patients described in chapter 4 is already in contact with a psychologist (unpublished data). This suggests that depressive and anxiety symptoms are undertreated in CKD patients.

Several patient and health care related barriers have been suggested as an explanation for the possible undertreatment of depression in dialysis patients. An example of a patient related barrier is that less than 50% of patients identified as clinically depressed agree to undergo treatment.^{37,38} To elucidate this topic Dwyer and Johnson⁷ identified 14 potential patient barriers to mental health treatment in dialysis patients. The three most reported barriers were: the patients do not feel anxious or depressed (41%), the patients do not need treatment for depression and/or anxiety (16%), or the patients are strong enough to handle their own problems (11.7%).⁷ An example of a health care related barrier for treatment was reported by Green et al.³⁹ They reported that renal providers (i.e. nephrologists and nurses) feel that assessment of depressive symptoms is important,

but treatment is the responsibility of the primary health care provider. Another health care related barrier could also be the recognition of symptoms of psychological distress to begin with. Weisbord et al. reported that renal providers are largely unaware of the presence and severity of symptoms (including psychological distress) in patients who are on chronic haemodialysis treatment.⁴⁰ If it would be regarded as an integral part of the clinicians treatment, it may become more acceptable for patients that depressive and anxiety symptoms are assessed.

In recent years, several treatment options were investigated in CKD patients to overcome some of these barriers. For example, cognitive behavioural therapy during the dialysis therapy leads to a significant decrease in depressive symptoms as well as to a significant increase in quality of life and prescription compliance.⁴¹ Moreover, a recent study compared two non-conventional treatment arms.⁴² The first treatment arm was to inform renal providers about symptoms of pain, erectile dysfunction and/or depressive symptoms (after screening). Renal providers subsequently made a treatment decision based on evidence-based treatment algorithms. The second treatment arm was the nurse management arm, in which trained nurses used the same treatment algorithms and discussed the treatment options with treating nephrologists. Changes in symptom scores were thereafter compared with each other and with an observation period before randomisation ('usual care'). Significant improvements (even though small) were found within both treatment arms, but results between the two treatment arms did not differ.

Implementation of these treatment options for depression in chronically ill patients can be difficult.⁴³ Therefore, in patients with diabetes or coronary heart disease collaborative care programs were developed and assessed.⁴³⁻⁴⁶ In such a program, patients work collaboratively with nurses and primary care physicians to establish individualized clinical and self-care goals.⁴³ Collaborative care programs seem to reduce depressive symptoms, reduce symptoms of the chronic illness⁴⁵, and also seem to be cost-effective.⁴⁷ In CKD patients such a collaborative program has not yet been developed. Moreover, recently a study protocol was published for screening and treatment of psychological distress in patients with colorectal cancer.⁴⁸ This protocol compares a stepped care approach with usual care. The stepped care approach uses the following steps in stated order; watchful waiting, self-help program, problem solving therapy by a nurse, and finally psychotherapy, medication or referral to other services. Results of this programme are not available yet, but if this approach is feasible and effective it could also be studied in CKD patients.

Besides these non-pharmacological treatment options there are also pharmacological treatment options in dialysis patients. However, data on the effectiveness of antide-

pressants is scarce because CKD patients are often excluded from randomised control trials.^{49;50} The Chronic Kidney disease Antidepressant Sertraline Trial (CAST) is a double blinded placebo controlled trial which aims to establish safety and efficacy of sertraline.⁵¹ Unfortunately, results from this trial are not available yet.

In conclusion, there are several barriers for treating depressive symptoms in CKD patients. Besides 'conventional' treatment options of depressive symptoms there are other suggested treatment options to overcome treatment barriers. Most of these options show an effect on depressive symptoms. Future research should elucidate on feasible treatment programs for depressive and anxiety symptoms in CKD patients, and the effect of these programs on clinical outcome.

Clinical implications

Clinicians should be aware that the prevalence of depressive and anxiety symptoms is high, and associated with adverse clinical outcome in CKD patients. Moreover, clinicians should be aware that immigrant CKD patients are a high risk group for developing depressive and anxiety symptoms. Also recognising disease specific symptoms of depression and anxiety should be part of training of dialysis nursing staff as well as counselling methods how to cope with especially dialysis related distress. Such counselling could be supervised by the psychiatric liaison service. Assessment of depressive and anxiety symptoms (by using the HADS) should be regarded as an integral part of patient care at the nephrology department. The treating nephrology team could discuss the outcome with the patient. Thereafter, if counselling of disease specific distress has insufficient results, the patients' primary care doctor or the psychiatric liaison service could be consulted, because as yet feasible treatment programs for depressive and anxiety symptoms at the nephrology department are not available. Future research should elucidate on feasible treatment programs for depressive and anxiety symptoms at the nephrology department, and explore the effect of these programs on clinical outcome (i.e. HRQOL, morbidity and mortality).

Recommendations for future research

Throughout the general discussion several recommendations for future research were formulated:

- To investigate the association between anxiety symptoms and clinical outcome of dialysis patients.

- To investigate the short and long term association of depressive and anxiety symptoms with mortality, time to dialysis, and hospitalization in CKD patients not on dialysis.
- To assess the association of type D personality with the course of depressive and anxiety symptoms, and explore the association of type D personality with clinical outcome in CKD patients.
- To explore the higher prevalence of depressive and anxiety symptoms in immigrant compared to native CKD patients. Special attention could be given to the role of religion, acculturation, and discrimination.
- To investigate the effect of treatment of depressive and anxiety symptoms on morbidity and mortality in CKD patients.
- To investigate feasibility and incorporation of screening and treating depressive and anxiety symptoms at the nephrology department.

Main conclusion

Depressive and anxiety symptoms should be an integral part of patient care at the nephrology department. We showed that the prevalence of depressive and anxiety symptoms is high (especially among immigrant patients), and have a negative effect on mortality, starting with dialysis, and hospitalization. There are several self-report questionnaires which could be used in clinical practice or in a research setting. The choice for a specific questionnaire depends on the specific reason for which a clinician or researcher uses it. Additionally, type D personality might be more a state than a trait phenomenon. As a consequence, multiple measurements should be used in order to further examine the effect of type D personality on depressive and anxiety symptoms. Future research should also aim to explore the effect of feasible treatment strategies on morbidity and mortality in Dutch CKD patients.

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