Mental Health in Chronic and End-Stage Renal Disease

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Abbreviations

AIS	Acceptance of Illness Scale
BDI	Beck Depression Inventory
BFI	Big Five Inventory
CAPD	Continuous automated peritoneal dialysis
CKD	Patients with chronic kidney disease not on HD or PD
COPE	Coping strategies with stress
CS	Cross-sectional study
DSI	Dialysis Symptom Index
DSM V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DT	Distress Thermometer
ESRD	End-stage renal disease
ESS-r	Somatic Symptom Scale revised
FSFI	Female Sexual Function Index
GDS-4	Geriatric Depression Scale
HADS	Hospital Anxiety and Depression Scale
HARS	Hamilton Anxiety Rating Scale
HD	Patients on hemodialysis
HDRS	Hamilton Depression Rating Scale
HPS	Health perceptions questionnaire
IDDM	Insulin-dependent diabetes mellitus
IEFF	Erectile Function International Evaluation Form
KDQoL	Kidney Disease Quality of Life
MHLC	Multidimensional Health Locus of Control scale
MINI	Mini-International Neuropsychiatric Interview
MMSE	Mini Mental Status Examination
MOODS-SR	Self-report questionnaire to assess mood
MOS	Medical Outcomes Study
MR	Medical records
MSAS-SF	Renal Memorial Symptom Assessment Scale
MSPSS	Multidimensional Scale of Perceived Social Support
OL-HDF	Online hemodiafiltration
P	Prospective study
PAS-SR	Self-report questionnaire to assess panic and agoraphobia
PD	Patients on peritoneal dialysis
SCID-D	Structured Clinical Interview for Depression
SCLE 90	Symptom Checklist 90
SF-36	Short Form Health Survey
SOS	Significant Others Scale
TAS	Toronto Alexithymia Scale
TDQ	Taiwan Depression Questionnaire
THS	Trait Hope Scale
WHODAS 2	WHO Disability Assessment Schedule 2.0
WHOQOL-BREF	World Health Organization Quality of Life instrument
3MS	Modified Mini-Mental State Examination

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Introduction

Psychiatrists are often asked to evaluate and treat psychiatric presentations during the course of chronic kidney disease (CKD). Due to a significant overlap between CKD and psychiatric presentations and between renal diseases in general and psychiatry, a new subspecialty has emerged over the past

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Y. Sher, J. R. Maldonado (eds.), *Psychosocial Care of End-Stage Organ Disease and Transplant Patients*,
https://doi.org/10.1007/978-3-319-94914-7_6

decade. *Psychonephrology* is the field of psychosomatic medicine with focus on the psychiatric and psychological problems of patients with CKD, including patients on renal replacement therapy (RRT) [1, 2].

This chapter summarizes current knowledge related to the diagnosis, epidemiology, etiology, and management of psychiatric illness in patients with CKD prior to transplantation, as resulting from systematic reviews, pivotal trials, and pharmacological databases.

Disease Mechanisms in Psychonephrology

The association between CKD and psychiatric presentations can occur in different sequences: patients with chronic psychiatric illness can develop CKD or a patient with CKD may present with new onset psychiatric symptoms.

Patients with chronic psychiatric illnesses are at higher risk of developing CKD; for instance, patients with schizophrenia have a 25% increase in the risk of developing CKD compared to controls [3]. Several factors associated with chronic mental illness may mediate this risk, including direct toxicity of ingested substances (psychiatric medications, substances of abuse, misuse of medications such as Nonsteroidal anti-inflammatory drugs (NSAIDs)), and uncontrolled psychiatric illness leading to nonadherence with medical treatment for diabetes or hypertension and, indirectly, to CKD.

Psychiatric Medications and Nephrotoxicity

Among psychotropic medications, lithium is the most known agent linked to significant risk of developing kidney damage. A recent systematic review and meta-analysis of the lithium toxicity profile suggests that the risk of lithium-induced renal failure is small (0.5% of patients received RRT) [4]. A recent report of 630 patients who received lithium for more than 10 years showed that 32% of the patients had an estimated glomerular filtration rate (eGFR) below 60 mL/min per 1.73 m^2 and 5% of the patients developed stage 4 or 5 CKD [5]. Serum lithium level is routinely monitored in psychiatric treatment due to the medication narrow therapeutic index; however, some studies have questioned the importance of the serum lithium level in developing CKD [6]. Nephrogenic diabetes insipidus is present in 12% of lithium-treated patients [7]. Discontinuing lithium can lead to normalization of GFR, but kidney damage is irreversible in some patients.

Association Between Drugs of Abuse and Chronic Kidney Disease

A histological kidney analysis from 153 cases of deaths due to drug toxicology showed that glomerular pathology was associated with a history of alcohol abuse, while use of benzodiazepines was associated with vascular changes in the kidneys. Acetaminophen and cannabis use were associated with tubular damage, raising concerns for long-term use of these substances for pain [8]. Another postmortem analysis of over 5000 deaths in patients with history of drug use showed that severe intravenous drug use (IVDU) was associated with interstitial inflammation and renal calcification, whereas cocaine abuse was associated with hypertensive and ischemic damage. Cocaine is a well-known offender, contributing to kidney disease via hypertension; its use is detrimental in hepatitis C co-infected patients, leading to rapid onset of chronic renal impairment [9, 10]. Synthetic cannabinoids were also associated with acute kidney injury in case series [11]. Kidney disease can be the direct effect of drug use, such as opioids [12]. An analysis of renal biopsy results of 19 heroin users positive with hepatitis C showed 13 (68.4%) had membranoproliferative glomerulonephritis (MPGN), 2 had chronic interstitial nephritis, 2 had acute glomerulonephritis (GN), 1 had amyloidosis, and 1 had a combination of nephritis with GN [13]. Acute kidney injury has also been described in relation with energy drinks [14].

Neuropsychiatric Presentations in Patients with CKD

Causes for new onset neuropsychiatric presentations in patients with CKD include metabolic abnormalities, immune response, and vascular changes. Metabolic changes contributing to psychiatric presentations in CKD include hyponatremia [15], uremia [16], and higher homocysteine levels [17]. A study comparing cerebral glucose metabolism in patients with CKD pre-dialysis with healthy controls (21 each group) showed that pre-dialytic patients with CKD had decreased cerebral glucose metabolism in several areas, including decreased glucose metabolism in the orbitofrontal complex, which correlated with higher depression measured by Hamilton Depression Scale [18]. In vitro studies of asymmetric dimethylarginine (ADMA) and brain-derived neurotropic factor (BDNF) in CKD demonstrated that an increase of ADMA and decrease of BDNF correlated with depressive behavior [19]. Vascular alterations are considered to contribute to posterior reversible encephalopathy [20]. The role of the immune system in mental health presentations in CKD is also being investigated; however, the association between depression and interleukin (IL) levels in CKD is still uncertain [21].

Psychosocial Factors

As many kidney diseases are chronic conditions, patients often have to cope with the associated psychosocial

stressors such as insurance eligibility in the United States [22] or lack of dialysis availability [23]. These factors can lead to significant psychological distress, impaired quality of life (QOL), impaired relationships, and adjustment disorders.

Epidemiology of Mental Health Problems in Chronic Kidney Disease

A significant body of evidence suggests a high prevalence of psychiatric concerns in patients with CKD. Table 6.1 Summarizes the most important studies investigating the prevalence of anxiety, depression, substance abuse, sleep disorders, and sexual dysfunctions. This literature consists mostly of cross-sectional studies without a control group, with most of the subjects belonging to the convenience samples, not always clearly representative of the population studied. The measures used have not always been validated in this population and do not always equal a diagnosis of psychiatric illness. In addition, many of the quality of life studies measure complaints or symptoms as opposed to psychiatric disorders. Studies rarely control for other medical conditions which are themselves associated with an increased risk of psychiatric comorbidities; therefore, it cannot be ascertained if the psychiatric symptoms are driven by the kidney disease or by its frequent medical comorbidities, such as diabetes and coronary artery disease.

Depression

Screening and Evaluation

Over the past 30 years, tens of studies have described and/or measured depression in patients with CKD. The definitions and measurements of depression have significantly varied in this context: from psychological distress measures reported on QOL scales, to qualitative measures of depression without a threshold for clinical significance. Even when structured instruments are used, only a few have been validated in this population (Table 6.2).

Prevalence of Depression in CKD

Depression is the most common psychiatric disorder among patients with CKD [29]. The prevalence of depressive disorders varies between 6.8% [30] and 47.1% [31]. When the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM IV) criteria were applied, 40% of hemodialysis (HD) patients met criteria for a depressive disorder at some point in their life: MDD, 19.6%; dysthymic disorder, 9.8%; and depressive disorder not otherwise specified (NOS), 2.8% [28]. A study of CKD patients that used Structured Clinical Interview for DSM Disorders (SCID) for evaluation showed a prevalence of MDD of 27.9%, similar in men and women [32]. Eighty-five percent of patients who initially screened positive for depression were eventually diagnosed with a depressive disorder after the clinical evaluation [33].

Suicide is significantly elevated in dialysis patients and is discussed in detail in Chap. 7.

Risk Factors for Depression in CKD

Multiple studies have analyzed the risk factors contributing to the emergence of depression in patients with CKD. With very few longitudinal studies available, these risk factors are mostly associations found in cross-sectional studies.

Demographic factors such as female gender or being older are considered to increase the risk to develop depression [34]. Not all studies confirmed the role of these demographic factors; one cross-sectional study of 140 patients with CKD in various stages showed that age, gender, income, employment status, and education were not associated with depression [32]. Early studies showed significant variation in the prevalence of depression in CKD by geographic region, with a 2% prevalence in Japan and 21.7% in the United States [35]. It was considered that these differences were mostly due to a variation in how depression was diagnosed or screened and they have not been yet replicated.

Among the potential biological risk factors, lower albumin and lower indoxyl sulfate [36], lower phosphorus, and high levels of CRP [37] have been associated with increased prevalence of depressive symptoms in this population.

The number of comorbid medical conditions [38] and especially the presence of diabetes mellitus (DM) increase the risk of depression in patients with CKD [37]. Although the risk of depression is not always linked with the general severity of somatic illness in CKD [39], recent findings suggest that patients with CKD stage 3 and above are more likely to develop depression [40].

Several studies have supported the notion that compared with pre-dialysis CKD patients, patients on HD have a higher risk for depression, since their kidney disease is more advanced and they have to face the psychosocial hurdles of their treatments [41–43].

Psychological factors linked to increased risk of depression in CKD include less religiosity [44], lower level of hope [45], and external locus of control [46, 47]. HADS-total score is associated with the use of denial as a psychological defense mechanism, and positively correlated with difficulties in identifying and expressing emotions, and with the intensity of subjective somatic complaints [39]. Additional risk factors for depression in CKD include the presence of pain [48], decreased sexual functioning [49], and lack of aerobic activity [50].

Table 6.1 Prevalence of psychiatric disorders in chronic kidney disease

Author	Year	Type of study	Population	N	Control (N)	Instruments	Findings (prevalence)	Findings (risk factors)
Adamczak et al.	2012	CS	CKD HD	697		BDI	Depression 38.6%	Age (older), central catheter, higher serum CPR, coronary artery disease, history of myocardial infarction, stroke, or COPD
Al Zaben et al.	2014	CS	HD	310		SCID-D HDRS	Depressive disorders 6.8%, major depression 3.2%, minor depression 3.6%, significant depressive symptoms 24.2%	Saudi nationality, marital status, stressful life events, poor physical functioning, cognitive impairment, overall severity of medical illness, and history of family psychiatric problems
Al Zaben et al.	2015	P	HD	39		SCID-D HDRS	20/39 patients with major or minor depressive disorder	Eight (40%) fully remitted by 6 weeks and an additional three patients remitted over the next 6 weeks, leaving 45% with significant depressive symptoms persisting beyond 12 weeks
Aribi et al.	2015	CS	HD	50		HADS KDQoL	86.48% sexual dysfunction, 26% sexually inactive, 62% had decrease of sexual activity	Positively correlated with age > 55 years, personal medical history, some nephropathy data, HD period greater than or equal to 1 year, depression, anxiety, and impaired quality of life
Azegbeobor et al.	2015	CS	CKD	160	160 general medical clinic	MINI WHODAS 2	Depression prevalence 17.5% (4.4% in control groups)	Depression was a predictor for disability
Baykan et al.	2012	CS	CAPD and HD	41 CAPD, 42 HD		SCID I HADS SF-36 COPE	Psychiatric disorder: 59.5% in HD group, 53.7% in CAPD group, 26.8% among controls	In all three groups, the most common psychiatric disorder was depressive disorder
Billington et al.	2008	CS	HD	193		THS SOS MHLC HADS	Anxiety 39 (38%), depression 40 (39%)	Hope emerged as an independent significant predictor in five of the multiple regressions: anxiety, depression, effects and symptoms of kidney disease, and mental health quality of life
Cantekin et al.	2014	CS	pre-HD	120		HADS	Depression 35%, anxiety 53.4%	
Chen et al.	2010	CS	HD	200		MINI HADS CFS	Depression 70 (35.0%); 43 (21.5%) had had suicidal ideation in the previous month	Low body mass index (BMI), number of comorbid physical illnesses, greater levels of fatigue and anxiety, more common suicidal ideation, poorer quality of life
Chiang et al.	2013	CS	CKD	270		TDQ	Depression 22.6%	Sleep disturbances, lack of religious beliefs, no regular exercise regimen, CKD stage 3 or above
Cukor et al.	2008	CS	HD	70		HADS SCID I	Any axis I diagnosis 71%, anxiety disorder 45.7%, mood disorder 40%	Anxiety disorder associated with worsened QOL
de Barros et al.	2011	CS	PKD and GN	52 GN, 38 PKD		STAI BDI SF-36	Depression 34.6% of familial GN, depression 60.5% of PKD	
De Vecchi et al.	2000	CS	PD and HD	84 PD, 87 HD		Self-administered questionnaire	Problems sleeping: 49% of PD and 65% of HD	
Donia et al.	2015	CS	HD	76		BDI II, SF-36	Depression 76.3%, 32.9% of total-severe depression	

Table 6.1 (continued)

Author	Year	Type of study	Population	N	Control (N)	Instruments	Findings (prevalence)	Findings (risk factors)
Esen et al.	2015	Cs	Pre-HD	53		FSFI IEFF SF-36 BDI	Sexual dysfunction: Male 46%, Females 51%	No gender differences
Feng et al.	2013	P	CKD 3 and 4	362		GDS SF-12	Depression 13% at baseline	Baseline cognitive impairment, functional disability, and other chronic illnesses were significantly associated with both increasing GDS scores and depressive symptoms
Ferreira et al.	2016	CS	OL-HDF	114		GDS	Depression 28.9%	Depression associated with low social support and decreased muscular mass and creatinine serum levels
Garcia et al.	2010	CS	HD male	47		HADRS	Depression 68.1%	List of symptoms and problems (rs = −0.399; $p = 0.005$), quality of social interaction (rs = −0.433; $p = 0.002$), and quality of sleep (rs = −0.585; $p < 0.001$)
Gonzalez-De-Jesus	2011	CS	CKD	75		HADS SCLE 90	Depressive symptoms 25.3%, anxiety symptoms 30.7%	
Knowles et al.	2014	CS	CKD	80		HADS COPE HPS	Moderate or severe anxiety 16.3%, moderate depression 7.5%	Perception of an illness rather than the actual symptoms themselves best account for adaption to CKD
Kokoszka et al.	2016	CS	HD	107		M.I.N.I. BDI AIS	Depressive disorders 78.5%, MDD 29%, dysthymia 28%, an episode of depression with melancholic features 21.5%. Patients met no criteria for a mental disorder 21.5%	
Lee J. et al.	2013	CS	CKD	280		HADS, WHOQOL-BREF	Depression 47.1%, anxiety 27.6%	Prevalence of depression/anxiety did not differ across CKD stages; depression correlated positively with age, employment, income, education, comorbidity index, hemoglobin level, albumin concentration, and anxiety score and negatively with all WHOQOL-BREF domain scores; Anxiety correlated significantly with QOL, but not with socioeconomic factors
Li et al.	2014	CS	CAPD	42		PSQI Restless legs syndrome criteria HADRS	Sleep disorders 47.6%	Lower albumin, depression
Mauri et al.	2016	CS	ESRD or severe IDDM (awaiting kidney/ pancreas txp)	227	IDDM	SCID I and II MOODS-SR PAS-SR	Current axis I disorders 13.2%, agoraphobia 4.8%, major depressive episode 4.0%	No difference in the distribution of axis I disorders between the two groups (ESRD and IDDM)

(continued)

Table 6.1 (continued)

Author	Year	Type of study	Population	N	Control (N)	Instruments	Findings (prevalence)	Findings (risk factors)
McKercher et al.	2013	P	CKD	49		PHQ 9 BAI MSPSS 3MS	MDD 10%, anxiety 9%	
Novick et al.	2016	P	CKD	2286		Interview	15% opioid use, 22% cocaine use	
Peng et al.	2013	CS	CKD	57		SF-36 HARS HADRS	Depression 38.6%, anxiety 54.4%	
Perales et al.	2016	CS	HD	52		SF-36 HADS ESS-r	Anxiety 36.5%, depression 27%	
Saeed et al.	2012	CS	HD	180		BDI	Depression 75%	Married, unemployed
Saglimbene et al.	2016	CS	HD	659		FSFI	Either no sexual activity or high sexual dysfunction in all measured domains (orgasm 75.1%, arousal 64.0%, lubrication 63.3%, pain 60.7%, satisfaction 60.1%, sexual desire 58.0%)	Age, depression, previous cardiac event higher scores; being on transplant-protective
Sanchez-Roman et al.	2011	CS	CKD	120	41	HADS NEUROPSI Attention and Memory	Cognitive impairment 23%	Anemia a risk factor Stage 5 the worse
Silva et al.	2014	CS	CKD on transplant wait-list	50		BAI Lipp Stress Symptoms for Adults Inventory	Anxiety 56%	Stress associated with longer wait time and less education
Simms et al.	2016	CS	PKD not on HD or transplant	349		KDQoL PHQ9 MSPSS	Depression 22%	Female gender was associated with overall poorer psychosocial well-being, whereas increasing age, lower kidney function, larger kidneys, and loss of a first-degree relative from ADPKD were additional risk factors for QOL, depression or psychosocial risk
Spoto et al.	2015	CS	HD and PD	128 HD, 27 PD		BDI, HADS	HD group: depression 22.5% on BDI, 9.3% on HADS; anxiety 25.7% on BDI, 14% on HADS for PD, depression 29.6% BDI, 14.8% HADS; anxiety 11.1% BDI, no anxiety on HADS	No differences in anxiety/ depression between PD and HD
Sumanathissa et al.	2011	CS	CKD	140		SCID	MDD 27.9%: Males 27% (95% CI 17.6–36.3), Females 29.4% (95% CI 16.5–42.4)	Age, gender, income, employment status, and education were not associated with depression. The only significant variable associated with depression was patient's understanding of prognosis
Van Zwieten et al.	2016	CS	HD; median age 70	538		DSM V criteria	Major neurocognitive disorder 52.4%, minor neurocognitive disorder 17.3%	

Table 6.1 (continued)

Author	Year	Type of study	Population	N	Control (N)	Instruments	Findings (prevalence)	Findings (risk factors)
Vazquez-Martinez et al.	2016	CS	HD	40	40	HADS	Depression 27.7%	Risk factors: literate, being a housewife, big family, HD more than 5 years but not statistically significant
Vikhram et al.	2012	CS	HD	130		MINI	40% had a psych disease, moderate depressive episode 13.1%, hx of alcohol use disorder 31.5%	
Zaben et al.	2014	CS	HD	310		SCID-D, HDRS	Depressive disorder 6.8%, MDD 3.2%, minor depression 3.6%, significant depressive symptoms 24.2%	Saudi nationality, marital status, stressful life events, poor physical functioning, cognitive impairment, overall severity of medical illness, and history of family psychiatric problems
Wuerth et al.	2005	CS	PD	380		BDI	Depression 45%	Out of positive screen, 85% were clinically diagnosed with MDD

Table 6.2 Validated measures for depression and anxiety in patients with CKD

Scale	Cutoff	Validity	Author
Beck Depression Inventory (BDI)	11	Sensitivity 89% Specificity 88%	[24]
	16	Sensitivity 91% Specificity 59% Positive predictive value (PPV) 59% Negative predictive value (NPV) 71%	[25]
16-item Quick Inventory of Depressive Symptomatology-Self Report	10	Sensitivity 91% Specificity 88%	[24]
	8	Sensitivity 96% Specificity 79%	[26]
Center for Epidemiologic Studies Depression Scale (CES-D)	18	Sensitivity 69% Specificity 83% PPV 60% NPV 88%	[27]
Patient Health Questionnaire 9 (PHQ 9)	10	Sensitivity 92% Specificity 92% PPV 71% NPV 98%	[25]
Hospital Anxiety and Depression Scale (HADS)	N/A	The anxiety score did not correlate with presence of anxiety disorder on SCID	[28]

Anxiety Disorders

Prevalence of Anxiety Disorders in CKD

The prevalence of anxiety in patients with CKD is reported to range between 16.3% [51] and 54.4% [52], higher than in general population [53] (Table 6.1). As with depression, most of the measures used to assess anxiety have not been validated for CKD population (such as Beck Anxiety Inventory (BAI) or State Trait Anxiety Inventory (STAI)) or have been shown to have poor validity. For instance, compared to SCID, HADS was found to be a poor predictor for an anxiety disorder in HD patients [28], although sensitivity might be better with a lower cutoff of 6 for HADS as compared to 8 or 11 [54]. Most of patients with CKD report some degree of anxiety associated with the illness, starting dialysis, or the dialysis treatments themselves. A recent study of patients with ESRD awaiting kidney transplant that used SCID I and II found that agoraphobia was the most common axis I diagnosis (4.8%) [55].

Risk Factors for Anxiety in CKD

Anxiety is more likely to occur in patients with chronic pain [48, 56]), decreased sexual functioning [49], lower level of hope [45], and higher level of IL-6 production [57].

Cognitive Impairment

The presence of cognitive impairment in patients with CKD has been documented in multiple studies**.** It is worth noting that many of these studies do not address significant confounders such as cardiovascular risk factors or mood disorders [58].

Screening and Assessment

Montreal Cognitive Assessment (MOCA) and Mini-Mental State Examination (MMSE) are widely used screening tests of cognition. In clinical practice, results on these screening tests in association with the clinical evaluation typically lead to the diagnosis of a cognitive disorder. More detailed neuropsychological testing is done when there are discrepancies between the subjective and objective findings, or to plan additional services (e.g., supportive services, surrogate decision maker, or neuropsychological rehabilitation). Some of the most used instruments to assess cognition in CKD include: California Verbal Learning Test–Second Edition (CVLTII), Delis-Kaplan Executive Function System (D-KEFS) [59], Consortium to establish a registry for Altzheimer's Disease Neuropsychological Assessment Battery, lexical fluency, digit span test, 64 card Wisconsin Cared Sorting Test [60], NEUROPSY Attention and Memory [61], Rey Auditory–Verbal Learning Test, and Trail making Test [62].

Prevalence of Cognitive Impairment in CKD

In one study, 23% of CKD patients had cognitive impairment when measured with the NEUROPSI Attention and Memory battery [61]. Women with moderate CKD had worse delayed recall and backward digit span [62]. The INVADE study (Project on Cerbrovascular Diseases and Dementia) showed that 10.8% of patients with CKD had cognitive impairment; in addition, 6.2% developed new onset cognitive impairment in 2 years [63]. The BRINK study (Brain in Kidney disease) showed that patients with CKD had worse cognitive function than controls on MMSE, Hopkins Verbal Learning Test-Revised, Digit Span and Symbol-Digit-Modality Test [64].

Risk factors for cognitive impairment in CKD include high serum creatinine [62], anemia, hypertension, diabetes, somnolence, cardiovascular risk factors [61], HD treatment (versus peritoneal dialysis (PD)), 24-hour urine volume, systolic blood pressure, GFR, weight, time in dialysis [61], winter time [65], moderate to severe CKD [60], frailty [66], albumin and prealbumin levels [67], and comorbid obstructive sleep apnea (OSA) [68].

Sleep Disorders

The sleep architecture is significantly altered in patients with CKD and sleep disorders are common. Stages 1 and 2 non-rapid eye movement (REM) sleep are increased, while REM sleep [69] and sleep efficiency are decreased [70]. Even in early CKD, general sleep disturbance is estimated to be present in 84.6% of patients [71].

Screening and Assessment

Several sleep disorder screening questionnaires have been used in studies of CKD populations (e.g., Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, etc.), while the electroencephalography-based monitoring tests such as actigraphy (ambulatory monitoring) or polysomnography remain the gold standard for certain sleep disorder diagnoses. It is important to notice that sleep disorders have been found in CKD patients with no subjective complaints. A cost-effectiveness study done in Japan argues that even screening with a simple self-administered scale such as Epworth Sleepiness Scale is cost effective for patients with CKD [72].

Prevalence of Sleep Disorders in Patients with CKD

Breathing-related sleep disorder, such as OSA, is estimated to be present in 54% of CKD patients not receiving dialysis [73] and in 20–54% of HD patients [74].

Dyssomnias such as restless legs syndrome (RLS) or periodic limb movement syndrome (PLMS) have long been considered an expected finding in CKD. RLS was present in 3.5% of patients with CKD versus 1.5% of controls [75]. More recent studies demonstrated RLS in 17.5% of patients with CKD [76].

Risk Factors for Sleep Disorders in CKD

There is contradictory information about whether sleep disorders correlate with the stages of CKD or dialysis status. Some authors argue that sleep disorders tend to improve over time [77]. Other authors found that more advanced CKD correlates with more sleep disturbances: stage 4 CKD was associated with higher odds ratio for RLS in older hospital patients [78]. Severity of sleep apnea correlated with a lower GFR [79]. In one study, PLMS prevalence increased with CKD stages, but this relationship was unclear for RLS [76]. Other risk factors for sleep disorders in CKD are low albumin [80], low ferritin [78], depression, anxiety, male gender, and duration of CKD [81].

Other Mental Health Presentations in CKD

Fatigue

Often mistaken for depression, fatigue is a common finding in patients with CKD. A recent systematic review and meta-analysis found the prevalence of fatigue in CKD between 42% and 89% [82]. Several structured measures are available to document fatigue: Functional Assessment of Chronic

Illness Therapy-Fatigue (FACIT-F), Piper Fatigue Scale (PFS), or Fatigue Severity Scale (FSS).

Fatigue was associated with elevated phosphate serum levels, creatinine, advanced age, albumin (nutritional status), post-dialysis serum urea level, anemia [83], higher BMI, poor sleep quality, and mood disturbance [84]. In patients with pronounced fatigue, serum IL-6 levels were significantly higher, while albumin and creatinine levels were significantly lower [85]. Presence of cardiovascular disease, low serum albumin, depression, anxiety, unemployment, poor subjective sleep quality, excessive daytime sleepiness, and RLS were associated with greater fatigue [82, 83, 86, 87].

Chronic Psychotic Disorders

Prevalence of chronic psychotic disorders in CKD population is estimated at 10.2% [28]. For comparison, median lifetime prevalence of schizophrenia in the general population is estimated at 0.4% [88]. This difference in reported prevalence may be due to variation of measurements (some studies measured chronic psychotic disorders, while others focused on schizophrenia only). In addition, patients with chronic psychosis have a high incidence of diabetes [89], which leads to CKD and may contribute to the finding of higher prevalence of psychosis in this group. Patients with schizophrenia and ESRD received suboptimal pre-dialysis care and had a higher risk for mortality than general ESRD patients [90]. Another cohort study showed that patients with serious and persistent mental illness (SPMI) and CKD are more likely to be re-hospitalized than CKD patients without SPMI [91].

Substance Use Disorders

Substance use disorders have an estimated prevalence of 18% in patients with CKD [28]. In an Iranian sample of patients with CKD, 35.9% of patients used tobacco, 14.1% used opium, and 3.1% used alcohol [92]. A cross-sectional study of 2286 US patients with CKD showed a 15% prevalence of opioid use (with "use" defined as > = 5 times lifetime uses) and 22%-cocaine [93]. There is extensive evidence to support the deleterious effects of nicotine upon kidney function [94, 95], although prevalence studies about nicotine dependence in CKD are lacking.

Psychological Adjustments in CKD

Similar to other chronic medical illnesses, living with CKD requires significant adjustments in order to cope with physical limitations, loss of independence, often loss of income and social status, and significant alterations in relationships. In addition, the logistics of dialysis treatments lead to significant life changes. It is not uncommon that the initial diagnosis of CKD or the recommendation for dialysis is met with denial, demoralization, anger, or displacement which, if not resolved, can lead to poor adherence with treatment and significant medical complications.

Emotional defensiveness as a main coping skill tends to negatively affect the mental component of QOL in these patients [96]. Use of denial initially appears to be protective against depression and anxiety, however, may impact the medication adherence [39]. Blame as a defense mechanism was associated with worse adjustment [97], while hope was considered an independent predictor of better QOL [45]. Greater use of reappraisal was associated with lower levels of anxiety, while suppression was associated with greater depression [98]. Hemodialysis systematically affected personality in patients with CKD, with both neuroticism and psychoticism decreasing after initiation of HD [99].

Impact of Mental Health Problems in CKD

There is overwhelming evidence that mental health problems impact QOL of patients with CKD. A systematic review of 38 studies demonstrated a negative impact of depression, anxiety, and perceived stress upon health-related QOL [100]. Levels of depression and anxiety correlated with lower QOL in patients with CKD in multiple studies [28, 31, 52, 101–104]. A meta-analysis of 81 studies including 13,240 patients showed a medium effect size for impact of affect, cognition, and stress level upon QOL in patients with ESRD [105]. In a linear regression analysis, depression and anxiety independently correlated with QOL after adjustments for age, alcohol use, employment, income, education, hemoglobin level, and albumin concentration [31].

Mental health problems have been associated with worse medical outcomes ranging from medical complications to increased health care utilization measures. Major depressive episodes were independent risk factor for negative events (defined as death, hospitalizations, or dialysis initiation) in patients with CKD not on HD [106]. Depression in PD was associated with higher incidence of peritonitis [107]. Periodic limb movement disorder was associated with increased cardiovascular and cerebrovascular risk in CKD patients [108]. Central sleep apnea has been found to be a risk factor for mortality in non-dialyzed CKD patients compared to those without CKD, while mixed sleep apnea was related to rapid decline of renal function in non-dialyzed subjects [109]. Poor sleep quality was shown to be an independent risk factor for cardiovascular damage in CKD [110]. Depression in early CKD was a predictive factor for initiation of HD [40] and was associated with more days spent in the hospital [111, 112].

Studies investigating the impact of depression upon the mortality of patients with CKD have shown contradictory

results. MDD measured by PHQ was associated with 2.95-fold greater risk of death in patients with diabetes mellitus on HD [113]. Depression was associated with increased mortality in geriatric patients with stage 2–3 CKD [114]. A meta-analysis of 22 studies (83,381 participants) comprising 12,063 cases of depression with a follow-up of 3 months to 6.5 years concluded that depression consistently increased the risk of death from any cause but had less certain effects on cardiovascular mortality [115]. In at least two studies, however, depression did not predict mortality in kidney disease [116, 117].

The studies investigating the psychological adaptation to CKD are illustrative of some aspects that can improve the QOL and overall outcomes. Surprisingly, high level of social support had no influence on the adherence of patients with high conscientiousness, while it actually decreased the adherence of patients with low conscientiousness levels [118]. Extraversion and neuroticism were found to be associated with a higher health-related QOL [119]. Acceptance level correlated with higher QOL in patients with CKD [120]. Social adaptability index has been associated with increased survival [121].

Treatment of Mental Health Conditions in Chronic Kidney Disease

Pharmacological Interventions

It is important to remember that renal impairment affects the hepatic metabolism of medications, by inducing or suppressing liver enzymes or by affecting the availability of protein binding [122]. Furthermore, intestinal and hepatic transporters are altered in patients with CKD, on or off dialysis [123]. Authors have suggested that drug development should include information on pharmacokinetics in patients with CKD, on PD and HD, even for nonrenally cleared medications [123]; however, that is not yet the case in the United States. In general, patients with CKD are excluded from psychopharmacological trials due to safety concerns, so information about the safety, tolerability, and efficacy of psychotropics in patients with CKD is limited. For most psychotropics, dose adjustment is recommended once the creatinine clearance decreases, but medications can be continued. Special attention needs to be given to psychotropic agents with nephrotoxic potential (e.g., lithium and topiramate) and to those excreted primarily through the kidney (e.g., gabapentin and baclofen). Detailed information about the dose adjustments necessary in CKD and about possible drug to drug interactions during CKD can be found elsewhere [124]. In addition, Chap. 7 further discusses use of psychotropic medications in patients on dialysis.

Depression

There is poor evidence about the efficacy and safety of antidepressant treatment in patients with CKD [125, 126]. While several open trials suggested the benefit of antidepressants, two randomized controlled trials (RCTs) of antidepressants (fluoxetine and escitalopram) showed no differences in efficacy [126]. In an open randomized study, citalopram was reported to be efficacious in improving symptoms of anxiety and depression in HD patients, but interestingly these improvements were similar to psychological training, consisting of stress management training and education about kidney disease [127]. The Chronic Kidney Disease Antidepressant Sertraline Trial (CAST) study, a double-blind placebo-controlled study examining efficacy and safety of sertraline in patients with CKD and not dialysis-dependent, did not show any difference between sertraline and placebo upon depressive symptoms [128] .

Fatigue

Epoetin is reported to help fatigue in CKD [129]. To our knowledge, there is no information about the efficacy of modafinil or methylphenidate in CKD. Recent in vivo findings suggest a potential for nephrotoxicity for methylphenidate; therefore, it should be used cautiously [130].

Cognitive Impairment

The initiation of HD significantly improved cognitive status in patients with ESRD. There is only anecdotal evidence about the use of acetylcholinesterase inhibitors in patients with dementia and CKD [131]. Interestingly, a population study of 11,943 patients with CKD in Taiwan demonstrated that receiving the flu vaccine was protective against developing dementia, regardless of other risk factors [132].

Sleep Disorders

Dopamine agonists, such as ropinirole and rotigotine, have been found helpful for RLS in patients with CKD [133, 134]. In vitro studies showed that melatonin may have protective effects against oxidative stress and inflammation in renal disorders [135], but clinical trials are lacking at this time. Treatment of sleep apnea with continuous positive airway pressure has been shown to reveal increased symptoms of PLMS [136].

Pharmacokinetics in CKD

CKD can modify the psychopharmacology of psychotropic agents even for medications not primarily excreted by the kidneys. Chronic kidney disease can induce changes in distribution, protein binding, metabolism, and excretion. Obviously when the medication is primarily metabolized and excreted in the kidneys (e.g., gabapentin or topiramate),

the dose will need to be decreased if the patient develops CKD. The use of psychotropic medications in patients with CKD can be limited due to comorbid illness, such as impaired hepatic function, electrolyte disturbances, cardiac arrhythmias, or QTC prolongation. For further detailed information, the reader is referred to additional materials [137].

Other Use of Psychotropics in CKD

An interesting topic is represented by the use of psychotropic medications for nonpsychiatric conditions. Sertraline was shown to be effective for pruritus in ESRD patients [138].

Non-Pharmacological Treatments for Mental Health Symptoms in Patients with Chronic Kidney Disease

Psychotherapeutic Interventions

In nonmedically ill patients, it has been shown that psychological interventions have important advantages in comparison to pharmacological treatment. Psychotherapy allows one to avoid the risk of medication side effects and low adherence with drug therapy. In addition, for many patients, psychotherapy may be easier to accept [139]. Research also indicates that psychotherapy may be more effective in reducing the risk of depression relapse compared to pharmacological therapy [140]. Although there is an increased interest in psychological interventions for patients with CKD, the research, while expanding, is still limited.

A systematic review and meta-analysis of 8 RCTs aimed to evaluate effects of psychological interventions on depression, sleep quality, QOL, and fluid intake restriction adherence, demonstrated that the psychological interventions significantly reduced the Beck Depression Inventory scores and inter-dialysis weight gain [141]. The most widely used psychological intervention was cognitive behavioral therapy (CBT). Another systematic review and meta-analysis concluded that psychosocial interventions were associated with a medium effect size for reduction in depressive symptoms and a small effect size for improved QOL in patients with CKD/ESRD and their caregivers and some evidence suggested also a reduction in anxiety [142].

CBT is an especially helpful modality for depression, anxiety, insomnia, and adherence. It can also teach patients skills to facilitate communication with care providers, problem-solve when necessary, reduce arousal, and correct misconceptions and distortions [143, 144]. A RCT conducted in Brazil compared the effectiveness of 12 weekly sessions of group CBT in chronic hemodialysis patients diagnosed with MDD ($N = 41$) compared to usual care consisting of education and emotional support offered in the dialysis unit ($N = 44$) [144]. The intervention group demonstrated significant improvements compared to the control in average BDI scores, Mini-International Neuropsychiatric Interview (MINI) score, and Kidney Quality of Life dimensions.

Another randomized crossover trial in HD patients with 48.5% meeting criteria for MDD administered chairside CBT during dialysis treatments for 3 months. The study demonstrated that the treatment-first group achieved significantly larger reductions in BDI- II and HAM-D scores, as compared to the wait-list control. Mean scores for the treatment-first group did not change significantly at the 3-month follow-up, indicating persistence of a treatment effect beyond the end of the treatment period [145]. The treatment-first group experienced greater improvements in QOL and inter-dialytic weight gain than the wait-list group, although no effect on adherence was evident.

Another RCT found that group-based CBT was effective in improving adherence to fluid restrictions in patients undergoing hemodialysis [146]. Yet, a more recent RCT of PD patients evaluating the effectiveness of a CBT group approach to improve patient adherence demonstrated a statistically significant difference in edematous status at 6-week follow-up, potentially indicative of fluid restriction adherence [147].

A randomized active-controlled, open-label trial is currently being carried out to test whether a mindfulness-based stress reduction (MBSR) program delivered in a novel workshop-teleconference format would reduce symptoms and improve health-related quality of life (HRQOL) in patients awaiting kidney transplantation. Telephone-adapted MBSR (tMBSR) significantly improved mental HRQOL at follow-up, with over 90% of tMBSR participants reporting practicing mindfulness and finding it helpful for stress management [148].

A group therapy intervention in 48 HD patients significantly reduced depression and improved self-care, self-efficacy, and QOL in this patient population [149].

Case studies and some controlled studies suggest that relaxation and imagery techniques can be successfully used with hemodialysis patients to improve their adjustment. However, a RCT on a specific visual imagery technique in a sample of HD patients did not demonstrate an effect of this intervention on emotional adjustment or QOL, although the rate of patient compliance with the intervention was moderately high and patients reported their satisfaction with the intervention procedures [150].

Tsay and Hung [151] examined the effects of an empowerment intervention program in HD patients in a RCT in Taiwan. The results indicated that scores of the empowerment, self-care, self-efficacy, and depression in the

intervention group had a significantly greater improvement compared to controls [151].

Exercise

Aerobic exercises have been shown to improve not only physical functioning but also nutritional status, hematological indices, inflammatory cytokines, depression, and HRQOL in ESRD patients [152]. There have been a few RCTs examining the effects of exercise on depression in hemodialysis patients. In one such study on the effect of exercise training on heart rate variability and depression in HD patients, BDI scores decreased by 34.5% in HD patients randomized to a 1-year intradialytic exercise training program [153]. In another RCT in patients with reduced aerobic capacity, patients randomized to a 10-month intradialytic exercise training program demonstrated a 21% increase in maximal oxygen uptake (VO_2 max) in the exercise group and a 39% reduction in BDI scores, while control groups had no such changes [154].

Alternative Therapies

Music therapy has been investigated in ESRD. Thirty-six hemodialysis patients in Seoul, Korea, treated with music therapy reported lower scores in both depression and anxiety levels compared to the control group with no therapy [155].

Authors of another study observed that patients who listened to music during the dialysis sessions exhibited significant reductions in perceived stressors and adverse reactions, a fact that led the authors to conclude that music could be beneficial for promoting well-being in hemodialysis patients [156].

Self -Management

Self-management is another approach to target mental health symptoms in patients with kidney disease. Self-management in CKD involves developing knowledge, skills, and behaviors necessary to manage illness and treatments, as well as developing collaborative relationships with healthcare team providers. Self-management in dialysis necessitates that patients and families develop specific skills related to managing the dialysis treatment itself ranging from organizational tasks, such as coordinating transportation, to more active participation in the dialysis treatment, such as preparation for cannulation. Developing strategies to manage the psychosocial consequences of CKD and its treatment is an important part of self-management. Activities such as evaluating one's condition, negotiating treatment plans with care providers, and voicing one's preference for treatment reflect the cognitive dimensions of self-management in this population [157].

Psychoeducation

Pre-dialysis psychoeducational interventions present information about normal function of the kidneys, diseases of the kidneys, nutrition, medications, alternative modes of RRT, and lifestyle.

An important goal of pre-dialysis psychoeducational interventions is to socialize patients into a collaborative role in relating to service providers. Pre-dialysis psychoeducational intervention helps patients learn about CKD and its medical management and supports long-term knowledge retention [158]. Pre-dialysis psychoeducational intervention facilitates vocational rehabilitation and promotes QOL. Devins et al. have shown that pre-dialysis psychoeducational interventions extended time to dialysis therapy [159] and survival [160].

Conclusions

Patients with CKD have a high prevalence of psychiatric symptoms due to biological risk factors and psychosocial burdens of a chronic medical illness requiring significant time and resources for treatment. The most common mental health conditions encountered are depression, anxiety, and cognitive impairments, which in turn worsen adherence with medical treatments. The literature supports screening for depression and cognitive impairment in patients with CKD. Treatment of the psychiatric comorbidities in CKD leads to improvements in QOL and outcomes and increase in survival. The safety and efficacy data on psychopharmacological agents in patients with ESRD are lacking. At the same time, non-pharmacological methods, including psychotherapies, lifestyle and behavioral interventions, as well as complementary therapies, are becoming increasingly utilized in patients with CKD.

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