25 Depression and Other Psychological Issues in CKD

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Before You Start: Facts you Need to Know

- Depression, anxiety, and other psychological disorders are prevalent in patients with CKD.
- Patients with CKD commonly present with somatic symptoms, such as sleep disturbances, sexual dysfunction, low energy level, easy fatigability, and weight and appetite changes, which may be related to uremia and difficult to differentiate from depressive symptoms.
- Presence of depressive symptoms and major depressive disorder predicts adverse clinical and patient-centered outcomes in patients with CKD.
- Depression is a less commonly recognized problem in patients with CKD and ESKD.
- Often, depression is treated inadequately.
- Clinicians need to know the nuances in recognizing, diagnosing, and treating depression in patients with CKD in order to improve adverse clinical outcomes and quality of life.

Major depressive disorder (MDD) is a constellation of symptoms that a patient experiences for 2 weeks or more, comprised of either depressed mood or anhedonia plus at least 5 of the 9 *Diagnostic and Statistical Manual of Mental Disorders criteria* symptom domains [1] (Box 25.1). Patients with chronic kidney disease (CKD) and end stage kidney disease (ESKD) experience decreased energy, poor appetite, and sleep disturbance commonly that may not necessarily reflect an episode of MDD, but represent symptoms of uremia or burden of other comorbid illnesses, such as congestive heart failure. In addition, other symptom burdens, psychiatric conditions, or cognitive impairment experienced commonly by patients with advanced CKD or ESKD may be present, such as anxiety, chronic pain, erectile dysfunction, dementia, and delirium that need to be differentiated from a depressive disorder [2, 3]. It is even more challenging for clinicians to manage MDD in CKD and ESKD patients, as emerging data has shown pharmacologic treatment with antidepressants does not prove beneficial in abating depressive symptoms consistently and may be associated with increased side effects in these high-risk populations, which leads to only a minority of such patients getting treated appropriately and adequately [3–5]. More recently, CBT was shown to have potential benefit in reducing burden of depressive symptoms in ESKD patients [3, 4, 6]. This chapter discusses management and treatment of MDD in patients with CKD. Pain, sexual dysfunction, and quality of life (QOL) issues in patients with CKD are discussed in other chapters and will not be discussed here.

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Box 25.1 Clinicians Must Know the 9 Criterion Symptom Domains for Major Depressive Disorder Based on the Diagnostic and Statistical Manual of Mental Disorders

1. Depressed mood.
2. Loss of interest or pleasure (anhedonia).
3. Appetite disturbance.
4. Sleep disturbance.
5. Psychomotor agitation or retardation.
6. Fatigue and tiredness.
7. Worthlessness, feeling like a burden, or guilty.
8. Difficulty concentrating.
9. Recurring thoughts of death or suicide.

25.1 Prevalence of Depression in Patients with CKD

There is a high prevalence of depression in patients with chronic illnesses such as cardiovascular diseases (CVD) and ESKD. The point prevalences of depression in the general population and the primary care setting are estimated to be 2–4% and 5–10%, respectively [2]. Conversely, point prevalence of depression in patients with chronic diseases such as post-myocardial infarction (MI), congestive heart failure (CHF), and ESKD on chronic dialysis is much higher at 16%, 14%, and 25%, respectively [2].

A distinction must be made between the presence of depressive affect or depressive symptoms ascertained from patients by the use of self-report scales vs. a depressive disorder diagnosis (such as MDD) made by a physician using an interview. The majority of studies reporting prevalence of depression in patients with CKD and ESKD used self-report questionnaires to assess depressive symptoms instead of reporting a physician or interview-based diagnosis. Unfortunately, the estimates by self-reported rating scales may overestimate the presence of MDD, particularly in patients with advanced CKD or ESKD treated with maintenance dialysis, given the over-emphasis of the somatic symptoms of depression, such as appetite changes, sleep disturbance, and fatigue that are commonly present in such patients [7]. This was illustrated in a meta-analysis [7], where the prevalence of depression in ESKD patients on maintenance dialysis when ascertained by self-report scales was much higher at 39.3%, 95% confidence interval (CI) (36.8–42.0%) vs. by interview at 22.8%, 95% CI (18.6–27.6%). In addition, point prevalence estimates of interview-based depression were also high in CKD stages 1–5 patients not treated with maintenance dialysis at 21.4%, 95% CI (11.1–37.2), as well as in kidney transplant recipients at 25.7%, 95% CI (12.8–44.9), but not as precise as that for patients with ESKD, as reflected in the wide confidence intervals. This could be due to a lesser number of studies evaluating point prevalence of depression in lower stage CKD patients and transplant recipients.

25.2 Association of Depression with Adverse Clinical Outcomes

CKD or ESKD patients experiencing either depressive symptoms based on self-report scales or a clinical diagnosis of MDD are at a much higher risk of adverse clinical events as compared to similar patients without such symptoms or diagnosis (Box 25.2). These findings were not only reported in the kidney but also in the cardiovascular literature. Risk of death and hospitalization within a year double in ESKD patients on chronic dialysis with a clinical diagnosis of MDD compared to those without it [8–11]. In addition, a clinical diagnosis of MDD may increase cumulative hospital days and number of admissions to the hospital by 30%, independent

of other comorbidities (Box 25.2) [8–11]. Furthermore, MDD is an independent risk factor for recurrent cardiac events, re-hospitalization, and death in many chronic diseases including CVD and CHF, similar to its independent association with the risk of hospitalization, progression of kidney disease, initiation of dialysis, and death in patients with CKD and ESKD (Box 25.2) [8–11]. Noticeably, the strength of association of depression with adverse outcomes is as high as some of the other comorbidities including diabetes mellitus, peripheral vascular disease, and congestive heart failure. Studies reported greater risk of death within 90 days of dialysis initiation in depressed as compared with non-depressed patients [8–11]. Depression not only predicts adverse clinical outcomes, but also decreases QOL and aggravates sexual and physical dysfunction in patients with CKD and ESRD (Box 25.2) [12, 13]. It is, therefore, important to identify and manage levels of depression and functional impairment without which such problems fail to remit spontaneously in untreated CKD and ESKD patients.

Box 25.2 Clinicians Must Know that Depressive Symptoms and a Clinical Diagnosis of Major Depressive Disorder in CKD and ESKD Patients Are Independent Predictors of Adverse Clinical and Patient-Centered Outcomes

1. Death.
2. Hospitalization (increase cumulative hospital days and number of admissions).
3. Progression of kidney disease.
4. Initiation of dialysis.
5. Poor quality of life.
6. Sexual and physical dysfunction.
7. Fatigue.

25.3 Risk Factors for Depression in Patients with CKD

As depressive symptoms and MDD prognosticate poor clinical outcomes and decreased QOL in patients with CKD and ESKD, clinicians must be able to recognize risk factors for depression (Box 25.3 and Fig. 25.1). Several risk factors for depression in this high-risk population are similar to those in the general population and include younger age, female gender, low household income, lower education, and unemployment (Box 25.3 and Fig. 25.1) [2, 10, 12–14]. Although white race has been reported as a risk factor, a high level of depressive affect has also been reported among African American ESKD patients treated with maintenance hemodialysis [2, 10, 12–14]. Dialysis-related factors such as non-adherence to diet and interdialytic weight gain are associated with depression, but it is not clear whether they are risk factors for or result from the presence of depression [2, 10, 12–14]. Other clinical conditions such as diabetes mellitus, hypoalbuminemia, cerebrovascular and cardiovascular diseases, and comorbid psychiatric disorders, commonly associated with CKD and ESRD, add medical complexities and increase risk for depression (Fig. 25.1) [2, 10, 12–14]. This association between medical comorbidities and depression is similar to that in the general population. Depression makes social interactions and relationships more difficult for patients, leading to estrangement from spouse, family, work, community, and religious organizations (Box 25.3). Post-dialysis fatigue, time spent on dialysis, cognitive impairment, and comorbid illnesses may be further impediments to social interactions and impair ability to build relationships. An attempt should be made by clinicians to identify interrelated risk factors for depression in order to best manage their patients with CKD or ESKD diagnosed with depression.

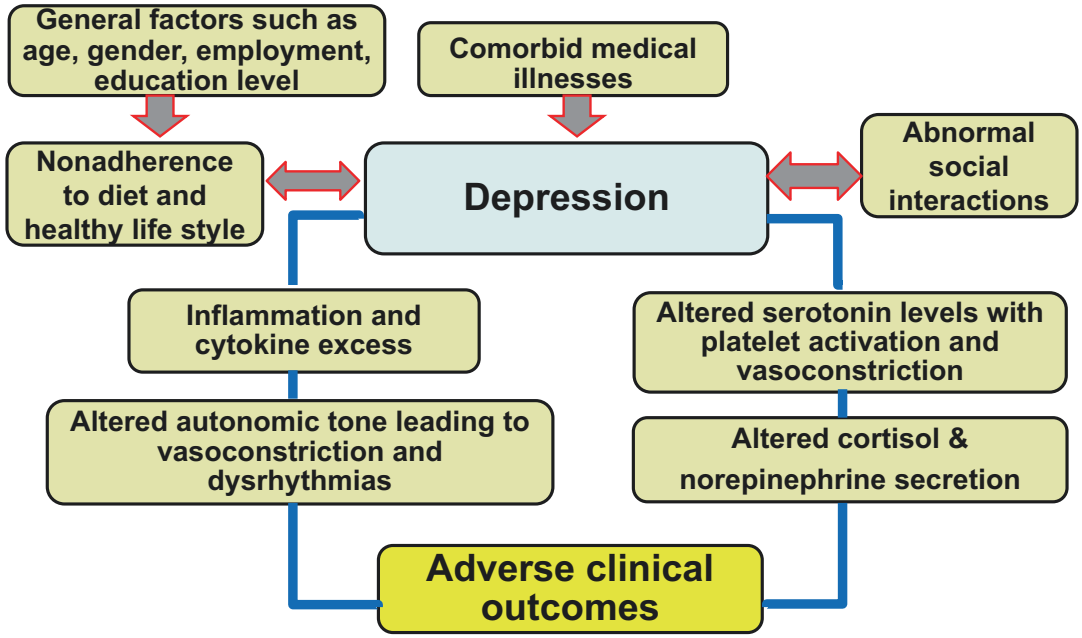

Fig. 25.1 Risk factors for depression and potential mechanisms that associate depression with adverse clinical outcomes

Box 25.3 Clinicians Must Be Able to Recognize Risk Factors for Major Depressive Disorder in CKD and ESKD Patients

1. General factors:
   (a) Younger age.
   (b) White race.
   (c) Female gender.
   (d) Low household income.
   (e) Lower education level.
   (f) Unemployment.
2. Dialysis-related factors:
   (a) Non-adherence to the recommended diet.
   (b) Non-adherence to interdialytic weight gain.
3. Other comorbid illnesses:
   (a) Diabetes mellitus.
   (b) Hypoalbuminemia.
   (c) Cerebrovascular disease.
   (d) Cardiovascular disease.
   (e) Other psychiatric disorders.
4. Psychosocial factors:
   (a) Impaired social interactions.
   (b) Estranged spouse.
   (c) Estranged family members.
   (d) Unemployment.

25.4 Potential Mechanisms for the Association of Depression with Adverse Outcomes

It is unclear whether depression itself has a direct mechanistic role in the development of cardiac events and other adverse clinical outcomes or whether it is merely a surrogate marker of comorbid illness (Fig. 25.1). However, specific biological factors were proposed and investigated as potential mechanisms by which depression may lead to cardiac events that are compelling. First, both depression and CVD appear heritable in

twin studies. In a study that included 2700 male twin-pairs from the Vietnam era, there was a correlation between genetic influences on depression and CVD, suggesting a common genetic link [2]. Second, depression leads to non-adherence with medications, unhealthy lifestyle, malnutrition, and loss of social network that can precipitate adverse events such as increase in peritonitis events noted in depressed chronic peritoneal dialysis patients compared to those who are not depressed [2]. Third, there are reports of altered autonomic tone, such as lower heart rate variability, in patients with recent MI with depression leading to coronary vasoconstriction and tachyarrhythmia. Therefore, autonomic dysfunction may be a potential pathophysiologic mechanism that can explain how depression leads to adverse clinical outcomes [2]. Fourth, several studies observed enhanced activity of the hypothalamic–pituitary axis, specifically increase in cortisol and norepinephrine secretion, in patients with CVD and MDD. It is hypothesized that increase in the levels of inflammatory cytokines due to depression may result in hyperactive hypothalamic-pituitary-adrenal axis and increase in cortisol and norepinephrine secretion. It is further postulated that increase in cortisol and norepinephrine levels may be important in decreasing the availability of tryptophan, an important precursor for neurocellular function, and, thus, precipitate depressive symptoms by decreasing the availability of neurotransmitters such as dopamine and serotonin [2]. Fifth, inflammation has been implicated, such as an increase in serum C-reactive protein (CRP) and decrease in omega-3-fatty acid serum concentrations. There is an association between inflammation and depression as shown in some patients treated with interferon alpha who show decrease in brain dopamine and serotonin levels that is treatable with paroxetine. To further support the role of inflammation, it was reported that depressed patients with psoriatic arthritis show improvement in their disease activity and depression when treated with etanercept [2]. Another proposed mechanism is the association of altered serotonin levels seen in depression, with resultant increased platelet activation and vasoconstriction that can then lead to coronary events [2]. However, all of the above are potential mechanisms to explain how depression predicts adverse clinical outcomes. Further studies are needed to confirm the mechanistic pathways involved in adverse clinical outcomes, such as higher rates of cardiovascular events, progression to ESKD, hospitalizations, and death, in patients with CKD and depression.

25.5 How to Identify Depression in Patients with CKD

Given one out of four or five patients with CKD or ESKD may be depressed, which puts them at increased risk for adverse clinical outcomes, poor QOL, and functional impairment, it is important for clinicians to screen such patients for depression. It is suggested that screening should be performed at the first outpatient evaluation of a patient in the CKD or dialysis clinic and then repeated annually or semi-annually. Self-report questionnaires [15, 16], that assess depressive symptom severity, perform well as screening tools with high sensitivity and average specificity (Table 25.1). These can be administered easily and consume no significant extra time during a patient visit. The 20-item Center for Epidemiological Studies Depression (CES-D),

Table 25.1 Validated screening tools to screen for and rate depressive symptom severity in patients with CKD and ESRD

Rating scale	Cutoff score in non-CKD patients	Cutoff score in CKD patients	Remarks
21-item BDI-II	≥10	≥11 in CKD	Higher cutoff of ≥14–16 is used in ESRD
16-item QIDS-SR	≥10	≥10 in CKD	Not validated in ESRD
20-item CES-D	≥16	≥18 in ESKD	Not validated in CKD
9-item PHQ-9	≥10	≥10 in ESKD	Not validated in CKD

BDI-II beck depression inventory II, *QIDS-SR* quick inventory for depression symptomatology self-report, *CES-D* Center for Epidemiological Studies Depression, *PHQ-9* patient health questionnaire-9 item, *CKD* chronic kidney disease, *ESKD* end-stage kidney disease

21-item Beck Depression Inventory (BDI-II), and 9-item Patient Health Questionnaire (PHQ-9) scales are screening tools that were validated against the Diagnostic and Statistical Manual of Mental Disorders to diagnose MDD in patients with ESKD (Table 25.1). Similarly, the BDI-II and 16-item Quick Inventory for Depression Symptomatology Self Report (QIDS-SR_{16}) are validated screening tools in patients with CKD (Table 25.1). Of the aforementioned questionnaires, there is no consensus regarding use of one tool over another for this patient population [3].

As compared to patients without kidney disease, those with ESKD requiring maintenance dialysis need to have higher cutoffs on the self-report rating scales to diagnose MDD, perhaps due to the presence of somatic symptoms associated with uremia or chronic disease. For example, the cutoffs on the 21-item BDI-II validated for the diagnosis of MDD in the general population, CKD, and ESRD are ≥10, ≥11, and ≥ 14–16, respectively [15, 16]. The 20-item CES-D cutoffs in the general population and ESKD are ≥16 and ≥ 18, respectively. There is no difference in the PHQ-9 and QIDS-SR_{16} cutoffs between the general population and patients with CKD (Table 25.1).

Given the co-existence of somatic symptoms of depression in CKD patients with uremic symptoms and other comorbid medical conditions, those who screen positive on self-report depressive symptom rating scales need to be further assessed with a structured interview to confirm a clinical diagnosis of depressive disorder, such as MDD. In research, clinician-administered structured interviews such as the *Structured Clinical Interview for Depression* (SCID) or the *Mini International Neuropsychiatric Interview* (MINI) have been used to establish diagnosis [15, 16]. These interviews take a significant amount of time (30–60 minutes) and require a certain level of training to administer. Therefore, in the clinical setting, eliciting the presence of 5 or greater of the depression symptom domains, including the presence of sadness or anhedonia, for a period of at least 2 weeks would confirm the presence of a depressive disorder (Box 25.1).

25.6 Differential Diagnosis of Depression in Patients with CKD

Of the psychiatric illnesses identified among the Unites States Medicare ESKD patients admitted to hospitals, presence of depression, dementia, substance, and alcohol abuse could be found in as high as 26%, 26%, and 15% of such patients, respectively [14, 17]. Therefore, it is important for providers to recognize the differential diagnosis of depression in an attempt to manage patients appropriately (Fig. 25.2).

Importantly, there is a need to simultaneously identify cognitive impairment commonly seen in CKD and ESKD patients. Persistent and/or progressive impairment in memory and other cognitive functions such as attention, language, orientation, reasoning, or executive functioning, and the cognitive skill necessary for planning and sequencing tasks, is defined as dementia [17]. A score of <24 on the Mini Mental State Examination (MMSE) is a commonly used screening tool to diagnose dementia, which has limited sensitivity and specificity in patients with CKD and ESKD. Prevalence of dementia may be as high as 16–38% in such patients. It should be appropriately recognized by clinicians, as it also predicts poor outcomes. In addition, cognitive dysfunction acts as an impediment to decision-making, adhering to complex medication dosing schedules, and self-care. Dementia is more insidious in onset, progressive in course over months to years, usually not reversible, and impairs consciousness in advanced stages. Interestingly, many of the risk factors associated with MDD are similar to those for dementia [17].

Delirium can masquerade dementia and depression and should be part of the differential [17]. Clinicians should recognize the fluctuating course of delirium that develops over a short period of time associated with lack of attention and consciousness. Usually, there is no complaint pertaining to loss of memory, and it occurs as a result of medical conditions (e.g. advanced heart failure, liver disease, hypertensive encephalopathy, infections, hypoglycemia, hyponatremia, and

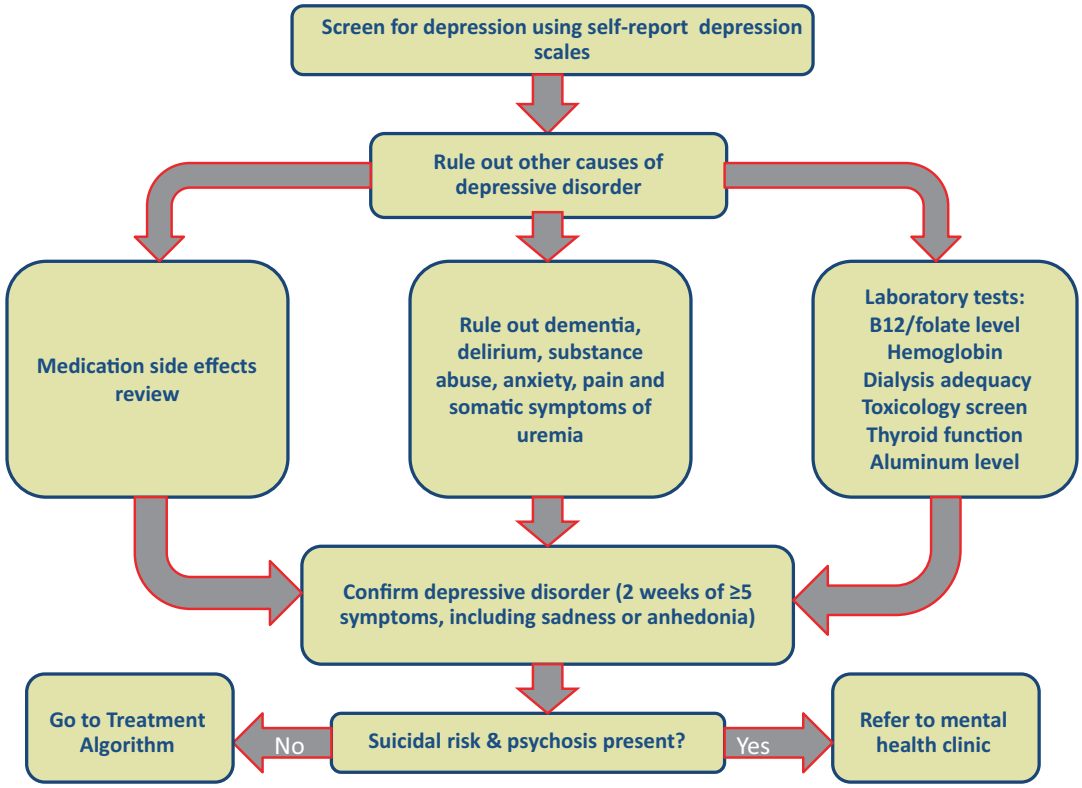

Fig. 25.2 Differential diagnosis of and an algorithm for screening/confirming depression in patients with chronic kidney disease (CKD)

hypercalcemia), side effects of certain medications (e.g. opioids, benzodiazepines, antihistamines, antipsychotics, and anticholinergics), or acute intoxications. Unlike dementia, delirium and depression are usually reversible. In addition, MDD is acute or chronic in onset and associated with intact consciousness, unlike delirium. Therefore, it is very important to differentiate dementia, delirium, and MDD so that management can be tailored accordingly. Box 25.4 shows important differences in dementia, delirium, and depression. Proper work-up for delirium and dementia includes a) medication review; b) obtaining laboratory data to rule out vitamin B12 and folate deficiency, thyroid dysfunction, acquired immunodeficiency syndrome, and substance abuse; c) obtaining brain imaging for presence of significant atherosclerotic cerebrovascular disease; d) assessing sleep disorders (such as restless legs and obstructive sleep apnea) by history and physical examination; and e) assessing dialysis adequacy, anemia, and aluminum toxicity in ESKD patients.

Box 25.4 Clinicians Must Be Able to Differentiate Delirium and Dementia from Depression [17]

1. Delirium:
   (a) Develops over a short period of time.
   (b) Lack of attention and consciousness.
   (c) No complaint pertaining to loss of memory.
   (d) Occurs as a result of.
      - Medical conditions.
      - Side effects of certain medications.
      - Intoxications.
   (e) Reversible.

2. Dementia:
   (a) Develops over months to years insidiously.
   (b) Progressive; altered consciousness in advanced disease.
   (c) Loss of memory common, along with loss of at least one other cognitive function such as:
      • Attention.
      • Language.
      • Orientation.
      • Reasoning.
      • Executive functioning.
      • Cognitive skill necessary for planning and sequencing tasks.
   (d) Usually permanent and irreversible.
3. Depression:
   (a) Develops over months to years.
   (b) Not associated with lack of consciousness.
   (c) No loss of memory.
   (d) Reversible.

Apart from delirium and dementia, generalized anxiety is quite common in patients with kidney disease and should be distinguished from depression by identifying patients who worry excessively on more days than not about a number of topics, that has persisted for more than 6 months, with the presence of self-perception that they are worried and lack control to modify its intensity and frequency [1]. This accompanies 3 of the 6 criterion symptom domains including fatigue, irritability, muscle tension, sleep disturbances, psychomotor agitation, and disturbed concentration [1]. Similarly, somatic symptoms such as sleep disturbances, sexual dysfunction, poor QOL, low energy level, easy fatigability, and weight and appetite changes can be present with uremia and make the diagnosis of MDD difficult. Alcohol and other substance abuse related disorders should be excluded, as these are commonly associated with depression (Fig. 25.2). Finally, fatigue, a common symptom of MDD, can also be present due to coexisting comorbidities in CKD/ESKD patients which should be carefully evaluated [18].

25.7 Treatment of Depression in Patients with CKD

A diligent clinician should recognize MDD, identify its risk factors, triage patients at risk of suicide, and tailor management based on the needs of the specific patient and the resources available. Screening tools enable clinicians to identify patients who are at risk for suicide. It is important to differentiate "thoughts for suicide" from "thinking about death" in patients with end-stage and terminal diseases such as ESKD and cancer in order to triage patients appropriately. Given a majority of patients with kidney disease are elderly, "thoughts of death" may be common without depressive symptoms or thoughts of suicide (Box 25.5). Furthermore, those who screen positive for suicidal thoughts should be queried for presence of active suicidal intent or plan (Fig. 25.2). Those with suicidal intent or plan should be referred to an emergency department or urgent care facility that can provide further urgent psychiatric clinical assessment, triage, and management (Fig. 25.2).

Box 25.5 Clinicians Must Be Able to Recognize those at Risk for Suicide so that Time-Dependent Interventions Can Be Implemented

1. In those with thoughts of suicide or death, ask about suicidal intent or plans:
   (a) How often do you think about suicide?
   (b) Have you made any plans?
   (c) Have you tried taking your life before?
   (d) How do you plan to end your life?
   (e) What will hold you from taking your life?
2. Those patients who have suicidal intent should immediately be referred to an emergency department or urgent care for further evaluation and management. Appropriate steps should be taken to organize support groups from family, friends, community, religious and social organizations based on the availability of resources.

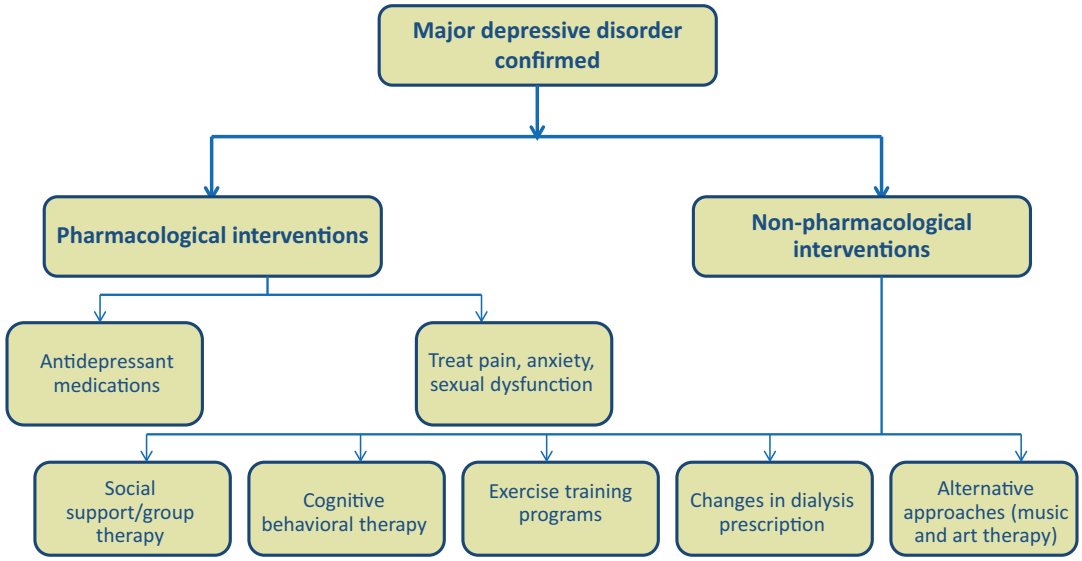

Fig. 25.3 Treatment options for depression in patients with chronic kidney disease (CKD)

Pharmacologic and non-pharmacologic interventions can be implemented to treat MDD in CKD and ESKD patients (Fig. 25.3) [19]. Unfortunately, there is a paucity of data to establish the safety and efficacy of antidepressant medications and other interventions for the treatment of depression in CKD and ESRD patients [19]. Second, high medication discontinuation rate is commonly observed in depressed patients with kidney disease [19]. Third, safety concerns of adverse events drive clinicians to either undertreat MDD or under-dose antidepressants in CKD and ESRD patients (Box 25.6) [19]. Encouraging results of efficacy for the use of antidepressants in treating MDD associated with chronic diseases such as CVD come from a double-blinded placebo controlled randomized trial, the *Sertraline Antidepressant Heart Attack Trial (SADHART)*, that showed sertraline to be safe and efficacious in patients with acute coronary syndrome. Based on these results, sertraline may be considered for treating MDD in CKD and ESKD individuals [19]. The *Chronic Kidney Disease Antidepressant Sertraline Trial (CAST)* evaluated efficacy and safety of sertraline treatment, dose-escalated to a maximum dose of 200 mg daily, compared with placebo in a randomized controlled trial (RCT) in patients with non-dialysis stages 3b-5 CKD and MDD [5]. This RCT demonstrated improvement in depressive symptoms at 12 weeks from baseline in the sertraline and the control arms. However, there was no additional benefit with use of sertraline over placebo in the study participants, and sertraline was associated with increased gastrointestinal side effects as compared with placebo. In ESKD patients receiving hemodialysis, similar improvements in depressive symptoms were observed in the treatment and the placebo arms of recent RCTs. A more recent RCT in ESKD patients with MDD showed a marginal benefit of open-label sertraline as compared with CBT, but there was no control group [4]. There are no RCTs to evaluate safety and efficacy of antidepressants in ESKD patients receiving peritoneal dialysis and kidney transplant recipients [3]. Despite these findings, the European Renal Best Practice guidelines recommend use of antidepressants in patients with CKD stages 3–5 as summarized in Box 25.7 [20].

Box 25.6 Clinicians Face Day-to-Day Challenges in Treating MDD because of Limited Data Regarding Safety and Efficacy of Antidepressant Use in Patients with CKD and ESKD

1. Lack-luster performance of sertraline in recent RCT which demonstrated reduction in depressive symptoms at 12 weeks in the sertraline-treated and the placebo-treated arms, with no added benefit of sertraline over placebo in patients with advanced non-dialysis CKD, e.g. stages 3b-5.
2. Limitations of some studies including small sample sizes and under-dosing of antidepressant medications.
3. High rate of medication discontinuation seen in small studies.
4. Safety concerns related to adverse events from antidepressant medications, thought to be due to:
   (a) Renally excreted active metabolites and risk of accumulation to toxic levels.
   (b) Risk of drug–drug interactions given the presence of other comorbid conditions and high pill burden.
   (c) Cardiac side effects of several classes of antidepressants that may worsen the disproportionate burden of cardiovascular disease seen in CKD and ESKD patients.
   (d) Increased risk of bleeding in the setting of uremic platelet dysfunction.
   (e) Side effects of nausea and vomiting that may exacerbate uremic symptoms.
   (f) CNS depression that may increase risk of cognitive dysfunction or delirium.

Box 25.7 What the Guidelines Recommend for the Use of Antidepressant Medications in Patients with CKD Stages 3–5 [20]

1. KDIGO Controversies Conference on Supportive Care in CKD developed a roadmap to improving quality care. This executive summary concluded that the current evidence is sufficient to support the development of clinical guidelines to help a systematic approach to depression in CKD [22].
2. Active treatment should be started for patients with CKD stages 3–5 who meet criteria for major depressive disorder. Level of evidence and recommendation: 2D.
3. Treatment effect should be re-evaluated after 8–12 weeks of treatment with antidepressant drug therapy. Level of evidence and recommendation: 2D.
4. Selective serotonin reuptake inhibitors should be the first line of therapy if pharmacological intervention is considered for patients with CKD stages 3–5. Level of evidence and recommendation: 2C.

Table 25.2 describes potential side effect profiles of several classes of common antidepressants that can occur at increased frequency in CKD and ESKD patients as compared to those with no kidney disease [19]. Although there is a lack of significant data on the safety and efficacy for the use of antidepressant medications in patients with advanced CKD stages 3–5 and ESKD, this should not discourage clinicians from treating depression appropriately until more data become available because some individuals may still find it beneficial. Management strategies require discussion of risks vs. benefits of antidepressant medications with patients, use of a class of antidepressant with the least possible drug–

Table 25.2 Safety profiles and dose adjustments recommended for different classes of antidepressants in the setting of CKD or ESKD

Medication	Dose in mg/day	Metabolism	Potential side effects	Dose adjustments
Selective serotonin reuptake inhibitors				
Sertraline	50–200	Active metabolite is excreted by kidney and can accumulate	Increased risk of bleeding; GI side effects: Nausea and diarrhea; hyponatremia; sexual dysfunction	Start at lower doses and escalate slowly
Paroxetine	10–40	Prolonged half-life	Same as the class side effects	Lower maximum dose recommended
Fluoxetine	20–80	Prolonged half-life	Same as the class side effects	Use with caution
Citalopram	10–40	Active metabolite can accumulate	Higher doses prolong QTc and increase risk of torsades de pointes	Not recommended for eGFR <20 mL/min
Escitalopram	10–20	Active metabolite can accumulate	Same as the class side effects	Use with caution in severe kidney disease
Dopamine/norepinephrine reuptake inhibitors				
Bupropion	200–450	Active metabolite can accumulate	Cardiac dysrhythmias, wide QRS complex, nausea, insomnia, and dizziness	Reduce frequency or maximum dose
Noradrenergic and serotonergic agonists				
Mirtazapine	15–45		CNS side effects include somnolence and weight gain	Reduce by 30% if CrCl 11–39; by 50% if CrCl <10
Tricyclics (TCAs)				
Amitriptyline	75–150		QTc prolongation, arrhythmias, orthostatic hypotension, CNS, and anticholinergic side effects	None; avoid in CKD and ESKD
Serotonin/norepinephrine reuptake inhibitors				
Venlafaxine	75–225	Accumulation of toxic metabolite	Hypertension, neuroleptic malignant syndrome, serotonin syndrome, sexual dysfunction	Reduce dose by 25–50% in mild-moderate CKD
Serotonin modulators				
Trazodone	150–400		Cardiac dysrhythmias, priapism, liver failure, Stevens-Johnson syndrome	Reduce dose and use with caution in advanced CKD and ESKD

CrCl creatinine clearance, *GI* gastrointestinal, *CNS* central nervous system, *eGFR* estimated glomerular filtration rate, *CKD* chronic kidney disease, *ESKD* end-stage kidney disease

drug interactions, starting antidepressants at a lower dose than that recommended for patients without kidney disease, and close follow-up to monitor treatment response, side effects, and a need for dose adjustment. Providers should pay special attention to drug–drug interactions that are highly likely in chronic hemodialysis patients due to polypharmacy. Typically, antidepressants should be started at low doses and dose escalation should be based on response and tolerability after at least 1–2 weeks of treatment on a particular dose.

Non-pharmacological interventions hold promise for the management of MDD in CKD and ESKD patients without increasing pill burden or raising concerns regarding adverse events and drug–drug interactions (Fig. 25.3) [19]. Such interventions include changes in dialysis prescription, exercise, and CBT (Box 25.8) that were shown to be efficacious in the general population. The *Following Rehabilitation Economics and Everyday-Dialysis Outcome Measurements (FREEDOM)* cohort observational study reported improvements in the depressive symptom severity scores measured by the BDI-II scale and health-related QOL measured by the Short Form-36 (SF-36) scale with six times weekly hemodialysis (Box 25.8) [19]. However, although in the *Frequent Hemodialysis Network (FHN)* trial, frequent hemodialysis (6 times a week as com-

pared with 3 times a week) was associated with significant benefits with respect to both co-primary composite outcomes of death or increase in left ventricular mass and death or a decrease in the physical-health composite score, there were no significant effects of frequent hemodialysis on cognitive performance or self-reported depression [21]. To date, clinical trials suggest that in-person or tele-CBT is not only feasible in patients, but also effective in managing depressive symptoms.

Weekly chairside CBT, administered by a trained professional during hemodialysis over 12 weeks, was reported to improve depressive symptom severity on the BDI-II scale, overall QOL on the Kidney Disease QOL Questionnaire-Short form (KDQoL-SF), and interdialytic weight gain in patients with ESKD [6]. A trained psychologist attempts to restructure negative thoughts and encourage logical thinking so as to modify behavior and mood. Those who ineffectively handle problems and/or make poor decisions are able to better cope with adversities and improve their depressive symptom severity [19]. This technique administered by trained social workers to the ESKD patients after Hurricane Katrina showed encouraging results in assuaging depressive symptoms. However, the duration and structure of CBT remains unclear and is an area of great research interest. Other psychotherapies such as mindfulness, cognitive restructuring, and stress management have also been explored as possible non-pharmacologic interventions for this patient population. Furthermore, some elements of CBT such as goal setting and problem solving and social support have also been explored for this patient population [3]. However, psychotherapies and elements of CBT remain to be fully established for their effectiveness in patients with kidney diseases [3]. Combined pharmacological intervention and CBT may be also considered, as the combination works better in the general population (Box 25.8) [3]. However, the combination approach remains to be investigated in patients with kidney disease.

Decreased functional capacity is common in patients with ESKD and is associated with poor QOL measures. Resistance exercise training by ankle weights was reported to improve QOL in patients on chronic maintenance hemodialysis (Box 25.8) [19]. Similarly, aerobic exercise over 10 months was effective in reducing heart rate variability, improving depressive symptom severity and QOL measures in a small group of chronic hemodialysis patients (Box 25.8). Therefore, exercise training can potentially function as a non-pharmacological intervention that clinicians can prescribe to treat MDD in CKD and ESKD patients given little harm and the multifaceted benefit of such an intervention. Other potential approaches to treat MDD in CKD and ESKD patients focus on pain management, improving sexual dysfunction, and management of anxiety (Box 25.8) [19]. Further research is required to evaluate if community and religious organizations may intervene and ameliorate depressive symptoms of CKD and ESKD patients by improving their social interaction skills. This may also help in addressing and overcoming marital and family discord that is commonly found in this patient population. Music and art therapy is an exciting field that remains to be more fully explored in patients on chronic hemodialysis while they remain idle on the dialysis machine for a long period of time. It remains to be investigated whether treatment of depression in patients with CKD can result in improvements in QOL and survival.

Box 25.8 Clinicians Should Be Aware of the Non-pharmacological Interventions that Can Be Used to Treat Major Depressive Disorders in Patients with CKD and ESKD Patients

1. Alterations in dialysis prescription.
   (a) Frequent dialysis, six times vs. three times per week.
2. Cognitive behavioral therapy (CBT).
   (a) Trained psychologist to administer therapy.
   (b) Trained social worker to administer support and therapy.

3. Combination of antidepressants and CBT.
4. Exercise training therapy.
   (a) Resistance training exercises (e.g. ankle weights).
   (b) Aerobic exercises.
5. Treatments for anxiety, pain, sleep disorders, and sexual dysfunction.
6. Alternative approaches.
   (a) Music and art therapy.
   (b) Involving community and religious organizations.
   (c) Social interventions to mend support from family and friends.

25.8 Recommendations and Conclusions

Depression is common in patients with kidney disease but less frequently recognized and inadequately treated. It is well-established that a diagnosis of current MDD or depressive symptoms independently predicts adverse clinical outcomes in patients with kidney disease. Therefore, it becomes imperative for clinicians who are involved in the care of such patients to screen for and diagnose depression accurately. Several quick and easily administered self-report scales are validated to screen for depression in these patients. However, those who screen positive for depression on screening need to be further evaluated so that dementia, delirium, anxiety disorders, medication side effects, and other medical conditions, such as underlying sleep disorders, thyroid dysfunction, or dialysis inadequacy, can be excluded. Finally, appropriate management strategies should be implemented to maximize efficacy and safety of depression treatment using available pharmacological and non-pharmacological interventions that are acceptable to specific patients. The ultimate goal of a clinician should be to assuage depressive symptoms and potentially achieve complete remission of depression.

Before You Finish: Practice Pearls for the Clinician

- Clinicians should understand the differences between depressive symptoms and a clinical diagnosis of major depressive disorder.
- Screening for depression should be performed at the first outpatient evaluation of a patient in chronic kidney disease or dialysis clinic and then repeated annually.
- Validated self-report tools exist that can be easily administered to screen for depression. Subsequently, confirmation of a current major depressive disorder should be done by a clinician interview for those who screen positive.
- Those at risk for suicide should be differentiated from those who often think about death based on religious and cultural beliefs, old age, or terminal illness.
- A broad differential diagnosis should be considered before a diagnosis of major depressive disorder is confirmed, based on appropriate physical examination, mini-mental examination, and laboratory data.
- Clinicians should be able to recognize the risk factors for depression.
- Once a diagnosis of major depressive disorder is confirmed, a thorough review of risks vs. benefits of pharmacological and non-pharmacological interventions should be discussed with patients to tailor individualized management strategies.
- To start an antidepressant medicine, the lowest possible dose should be initially prescribed, followed by frequent monitoring and gradual dose escalation every 1–2 weeks based on patient's response to and tolerability of the medication.
- Any adverse effects of antidepressant medications should be monitored closely.
- Non-pharmacologic treatments such as cognitive behavioral therapy and exercise should also be considered.

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