Exploring The Kidney-Brain Connection:

Anxiety & Depression In Chronic Kidney Disease

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Objectives

- Define anxiety and depression, and discuss prevalence among chronic kidney disease (CKD) patients
- Identify potential risk factors and mechanisms of both anxiety and depression in CKD
- Recognize overlapping symptomatology, and examine the cycle among anxiety, depression, and CKD and associated poor outcomes
- Address challenges in managing anxiety and depression in patients with CKD

Prevalence & Impact Of Depression

- Depression is one of the most common diagnoses among patients seen by psychiatrists in the United States (US)
- An estimated 22.5 million adults in the US had at least one major depressive episode (MDE) 18-25, which represents 8.8% of all US adults[2]
- Prevalence of adults with a MDE was highest among individuals aged 18-25 (20.1%)[2]
- **Prevalence of self-reported or clinician-rated depression in people with CKD, on dialysis or with a kidney transplant, is reported to be 26.5%, 39.3%, and 26.6%, respectively** [3]

US depression rate by adult age group[1]

	18-25	26-49	50+
Depression Rate (%)	18.6%	9.3%	4.5%

Prevalence of MDE was higher for females than for males[1]

10.3% **6.2%**

MDE: Major Depressive Disorder; US: United States

1. National Institute of Mental Health (NIMH). Updated July 2023. Accessed April 23, 2024. https://www.nimh.nih.gov/health/statistics/major-depression
2. Richesson D, et al. SAMHSA. 2023;PEP23-07-01-006(H-58):68.
3. Palmer S, et al. Kidney Int. 2013;84(1):179–191.

Prevalence & Impact Of Anxiety

- Affects 40 million adults (≥18 and older) or 19.1% of the population every year[1,3]
- 31.1% of US adults experience any anxiety disorder at some time in their lives[1]
- Prevalence of anxiety disorders among CKD patients was 19%[2]
- **Prevalence of elevated anxiety symptoms among CKD patients was 43%[2]**

US anxiety rate by adult age group[1]

	18-29	30-44	45-59	60+
Anxiety Rate (%)	22.3%	22.7%	20.6%	9.0%

Prevalence of any anxiety disorder was higher for females than for males[1]

23.4% **14.3%**

- Nearly half of all patients diagnosed with depression also have comorbid anxiety disorder diagnosis[3]
- Presence of comorbid mood and anxiety disorders is associated with increased severity of symptoms, increased suicidal risk, and substance use[4]

1. National Institute of Mental Health (NIMH). Accessed April 15, 2024. https://www.nimh.nih.gov/health/statistics/any-anxiety-disorder
2. Huang CW, et al. *Gen Hosp Psychiatry.* 2021;69:27-40.
3. Anxiety & Depression Association of America. Updated October 28, 2022. Accessed April 15, 2024. https://adaa.org/understanding-anxiety/facts-statistics
4. Saha S, et al. *Depress Anxiety.* 2021;38(3):286-306.

Defining Anxiety & Depression

Anxiety:
DSM-5 Criteria[1,2]

1. Chronic excessive worry for at least 6 months, on more days than not, with at least 3 of the following 6 symptoms;

   - ✓ Restlessness or feeling "keyed up" or "on edge"
   - ✓ Fatigue
   - ✓ Difficulty concentrating
   - ✓ Irritability
   - ✓ Muscle tension
   - ✓ Sleep disturbance

2. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
3. The disturbance is not attributable to the physiological effects of a substance (drugs or medication)
4. The disturbance is not better explained by another medical disorder
5. Common types: Generalized Anxiety Disorder (GAD), Specific Phobia, Social Anxiety Disorder, Panic Disorder, Agoraphobia

Depression:
DSM-5 Criteria[3]

Individual must be experiencing five or more symptoms during the same 2-week period and at least one of the symptoms should be either: (1) depressed mood, or (2) loss of interest or pleasure.

1. Depressed mood most of the day, nearly every day.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.
3. Significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day.
4. A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down).
5. Fatigue or loss of energy nearly every day.
6. Feelings of worthlessness or excessive or inappropriate guilt nearly every day.
7. Diminished ability to think or concentrate, or indecisiveness, nearly every day.
8. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

1. Orlovsky C. HealthCentral. Updated April 29, 2024. Accessed October 10, 2024. https://www.healthcentral.com/condition/anxiety?legacy=psycom
2. Donahue S, et al. Semin Nephrol. 2021;41(6):516-525.
3. Truschel J. HealthCentral. Updated August 26, 2022. Accessed October 10, 2024. https://www.healthcentral.com/condition/depression/dsm-5-depression-criteria

Chronic Kidney Disease Nomenclature[1]

CKD is defined as abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health.

KDIGO: Prognosis of CKD by GFR and albuminuria categories

- low risk (if no other markers of kidney disease, no CKD)
- moderately increased risk
- high risk
- very high risk

GFR Categories (ml/min/1.73m^2) Description and range		Guideline	Persistent albuminuria categories Description and range: A1 Normal to mildly increased <30 mg/g <3 mg/mmol	A2 Moderately increased 30-300 mg/g 3-30 mg/mmol	A3 Severely increased >300 mg/g >30mg/mmol
G1	Normal or High	>=90			
G2	Mildly decreased	60-89			
G3a	Mildly to moderately decreased	45-59			
G3b	Moderately to severely decreased	30-44			
G4	Severely decreased	15-29			
G5	Kidney failure	<15			

1. KDIGO. 2024;105(4S):S117-S314. KDIGO-2024-CKD-Guideline.pdf

Kidney Disease Facts[1]

Affects an estimated 35.5 million people in the US

14% of the adult population

More than 1 in 7 adults

Approximately 90% of those with kidney disease don't know they have it

1 out of 3 adults with severe kidney disease don't know they have it

About 1 in 2 people with very low kidney function (not on dialysis) don't know they have kidney disease

1 in 3 adults in the U.S. is at risk for kidney disease

(~80 million)

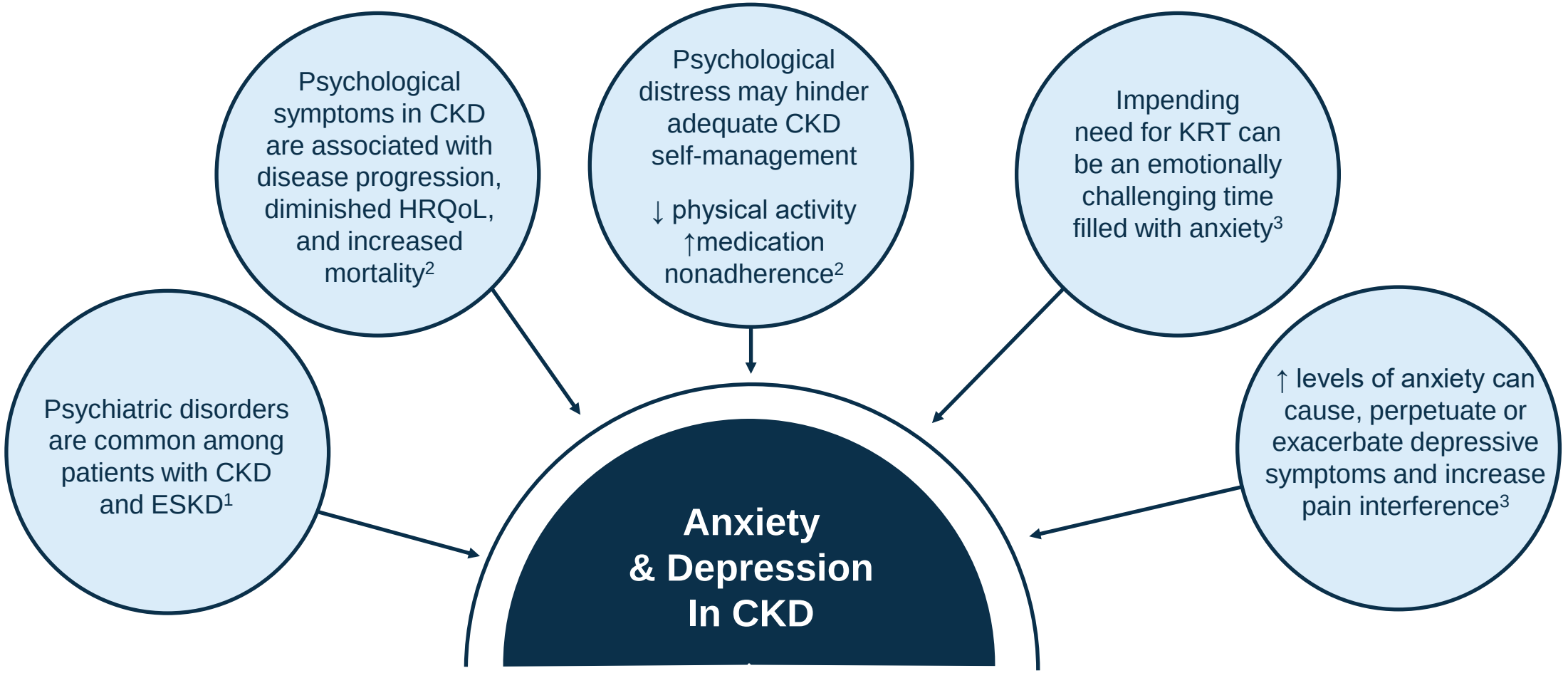
Approximately 1 in 3 adults with diabetes and 1 in 5 adults with high blood pressure may have kidney disease

It is more common in women (14%) than men (12%)

Kidney disease is a leading cause of death in the US

1. National Kidney Foundation. Updated August 6, 2024. Accessed October 10, 2024. https://www.kidney.org/news/newsroom/fsindex#:~:text=Kidney%20disease%2C%20also%20known%20as,than%201%20in%207%20adults

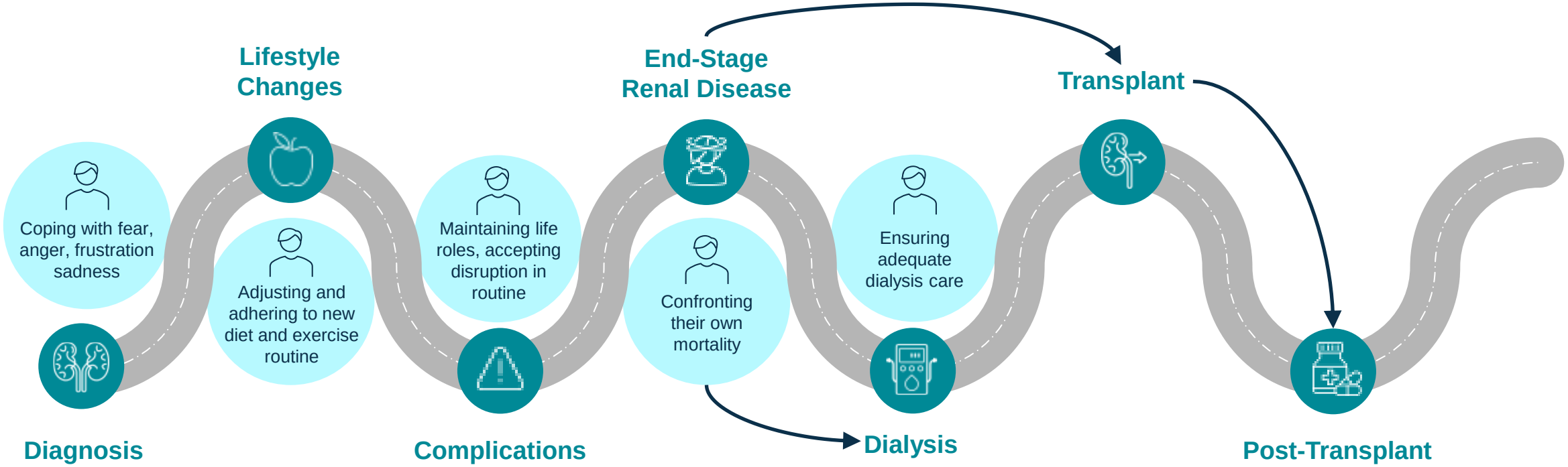
The Impact Of Psychological Distress In CKD



KRT; kidney replacement therapy; CKD; chronic kidney disease; ESKD; end stage kidney disease; HRQoL; health related quality of life

1. Amira O. Niger J Clin Pract. 2011;14(4):460-463.
2. Cardol CK., et al. Kidney Med. 2023;5(10):100712 .
3. Donahue S, et al. Semin Nephrol. 2021;41(6):516-525.

CKD Patient Journey: The Psychological Burden[1]



1. McCarley P. Nephrol Nurs J. 2009;36(4):409-413.

National Estimates Of Mental Health Needs Among Adults With Self-Reported CKD In The United States[1]

Methods	Findings	PAST YEAR: any mental illness	PAST YEAR: serious mental illness	PAST YEAR: mental health treatment	PAST YEAR: unmet mental health care needs
Annual, nationally representative data from US NSDUH 2015 to 2019	Adults reporting no chronic disease N=117,235	17%	4%	12%	5%
22 years and older	Adults reporting HTN/DM but no CKD N=32,290	20%	5%	18%	5%
In-person interviews with computer assistance	Adults reporting CKD N=2,544	27%	7%	21%	6%

NSDUH: National Survey on Drug Use and Health

1. Wilk AS, et al. Kidney Int Rep. 2022;7(7):1630-1642.

Risk Factors Associated With Anxiety & Depression In CKD

Anxiety[1]

- Patient related
  - Demographics
  - Socioeconomic status
  - Dietary habits
  - Activity level
- Medical condition related
  - CKD condition (↑symptoms)
  - Lab abnormalities (↓parathyroid hormone)
  - Psychiatric condition (concomitant depression)
  - Dental related (↑decay)
  - Other (↑comorbidity index, ↑hospitalizations)
- Therapy related
  - Medication
  - Dialysis
  - Diet
- Psychosocial related
  - Poorer perceived QoL
  - Decreased vitality levels

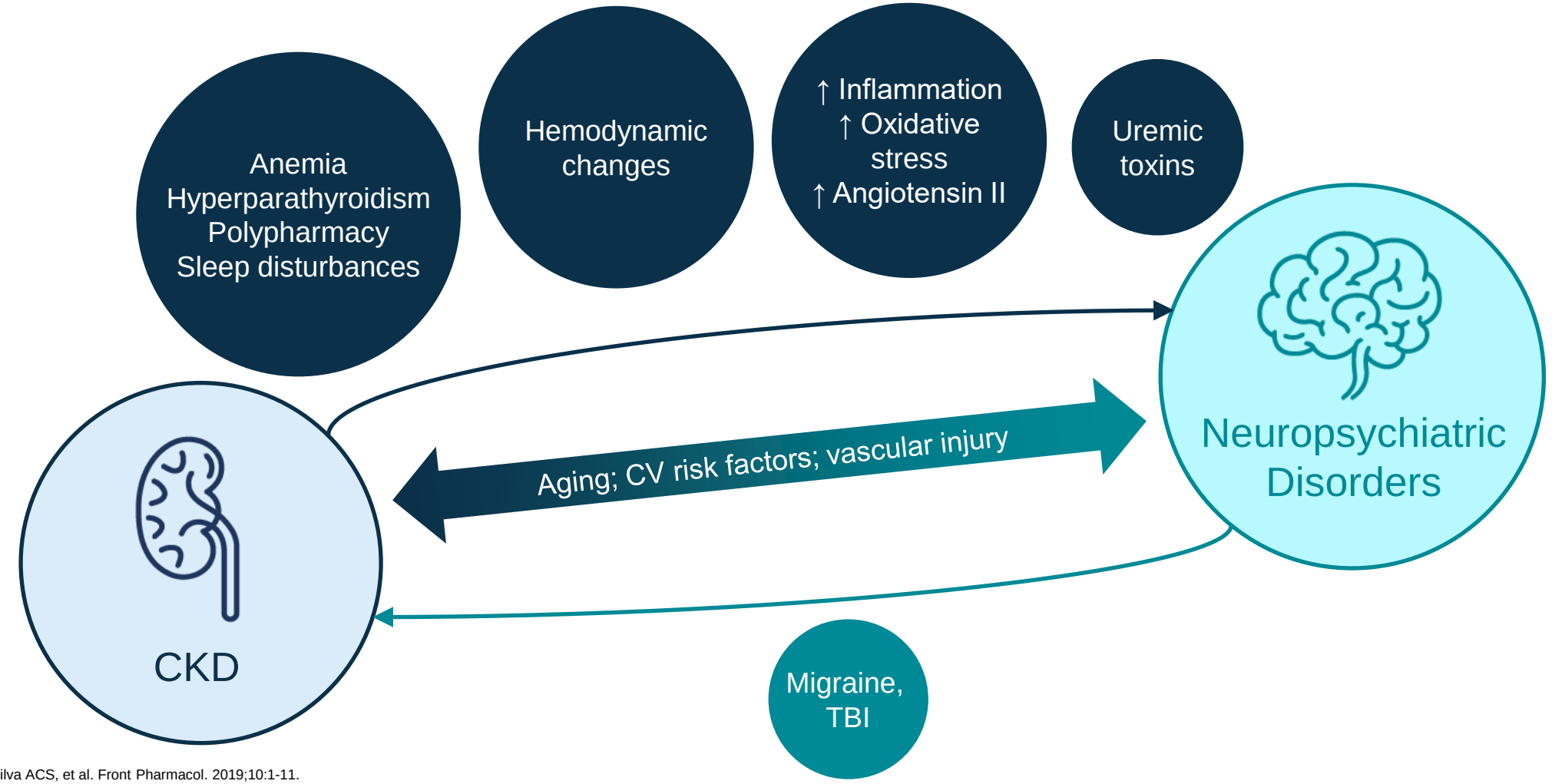
Depression[2,3]

- Patient related:
  - Younger age
  - Female
  - Non-white race/ethnicity
  - Lower household income
  - Lower education
  - Smoking status
- Medical condition related:
  - Presence of comorbid conditions (lower eGFR and proteinuria >1 g/g)
  - Hypertension
  - Diabetes

1. Huang CW, et al. Gen Hosp Psychiatry. 2021;69:27-40.
2. Shirazian S. Kidney Int Rep. 2019;4(2):189-190.
3. e Silva ACS, et al. Front Pharmacol. 2019;10:1-11.

QoL=Quality of Life

Factors Linking CKD & Neuropsychiatric Disorders[1]



1. e Silva ACS, et al. Front Pharmacol. 2019;10:1-11.

Anxiety & Depression In CKD: Mechanisms

A rationale for neuropsychiatric disorders secondary to kidney damage, known as the "vascular theory," relies on the hemodynamic similarities between the brain and the kidneys[1]

- Increased susceptibility to anxiety may involve inflammatory processes secondary to uremic toxins, oxidative stress due to increased cytokine production, microvascular damage to the brain, and the involvement of the renin–angiotensin system[2]
- Depression seen in CKD patients can be caused by reaction to the diagnosis and treatment, natural course of the disease, as well as the losses experienced[3]
- Studies suggest that the mechanism of depression in CKD, similarly to other chronic diseases, can be divided into **behavioral** and **biological** mechanisms[4,5]

Behavioral[4]

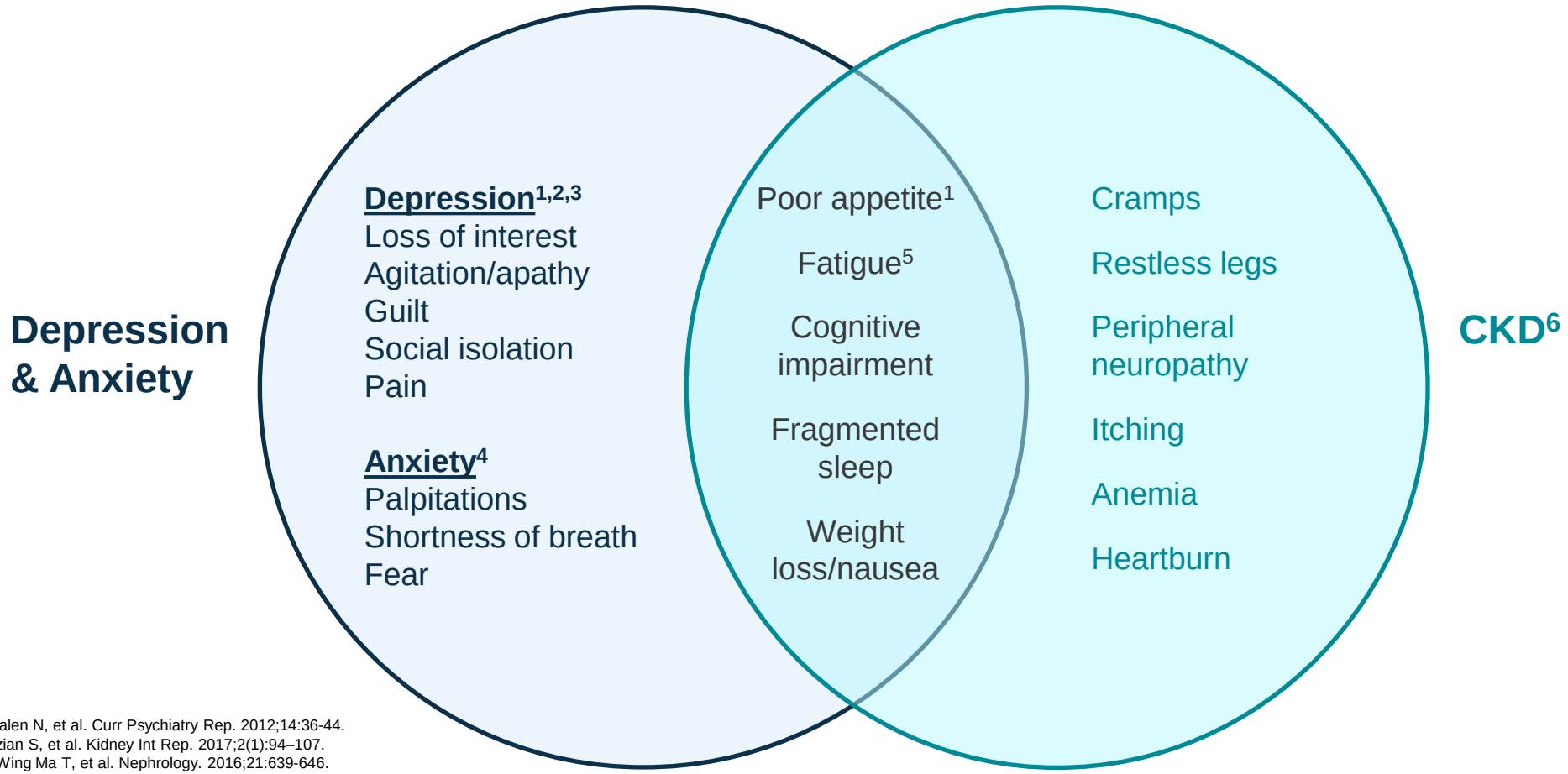
- Burden of disease
- Nonadherence to self-care
- Lack of social support
- Adverse health behaviors
- Poor quality of life

Biological[4]

- Comorbidities
- Inflammation
- Altered autonomic activity
- Hormonal abnormalities (cortisol)
- Poor quality of life
- Primary factors (genetics)

1. e Silva ACS, et al. Front Pharmacol. 2019;10:1-11.
2. Kim DS, et al. Korean J Intern Med. 2022;37(3):489–501.
3. Thomas R, et al. IORS-JDMS. 2014;13(9):19-22.
4. Shirazian S. Kidney Int Rep. 2019;4:189–190.
5. Shirazian S, et al. Kidney Int Rep. 2017;2(1):94–107.

Depression, Anxiety, & CKD: Symptom Overlap



1. Ver Halen N, et al. Curr Psychiatry Rep. 2012;14:36-44.
2. Shirazian S, et al. Kidney Int Rep. 2017;2(1):94–107.
3. King-Wing Ma T, et al. Nephrology. 2016;21:639-646.
4. Cohen SD, et al. Clin J Am Soc Nephrol. 2016;11:2250-2255.
5. Meyer TW, Hostetter TH.. N Engl J Med. 2007;357:1316-1325.
6. KDIGO. 2024;105(4S):S117-S314. KDIGO-2024-CKD-Guideline.pdf

Mental Health Screening

Anxiety

- There are no current guidelines[1]
- Integration into routine care has been suggested[2]
- Self-reported screening instruments can be used[2]
- Formal diagnosis is based upon meeting DSM-IV criteria and structured interview[2]
- Given high prevalence and association with adverse outcomes, screening is of utmost importance[3]

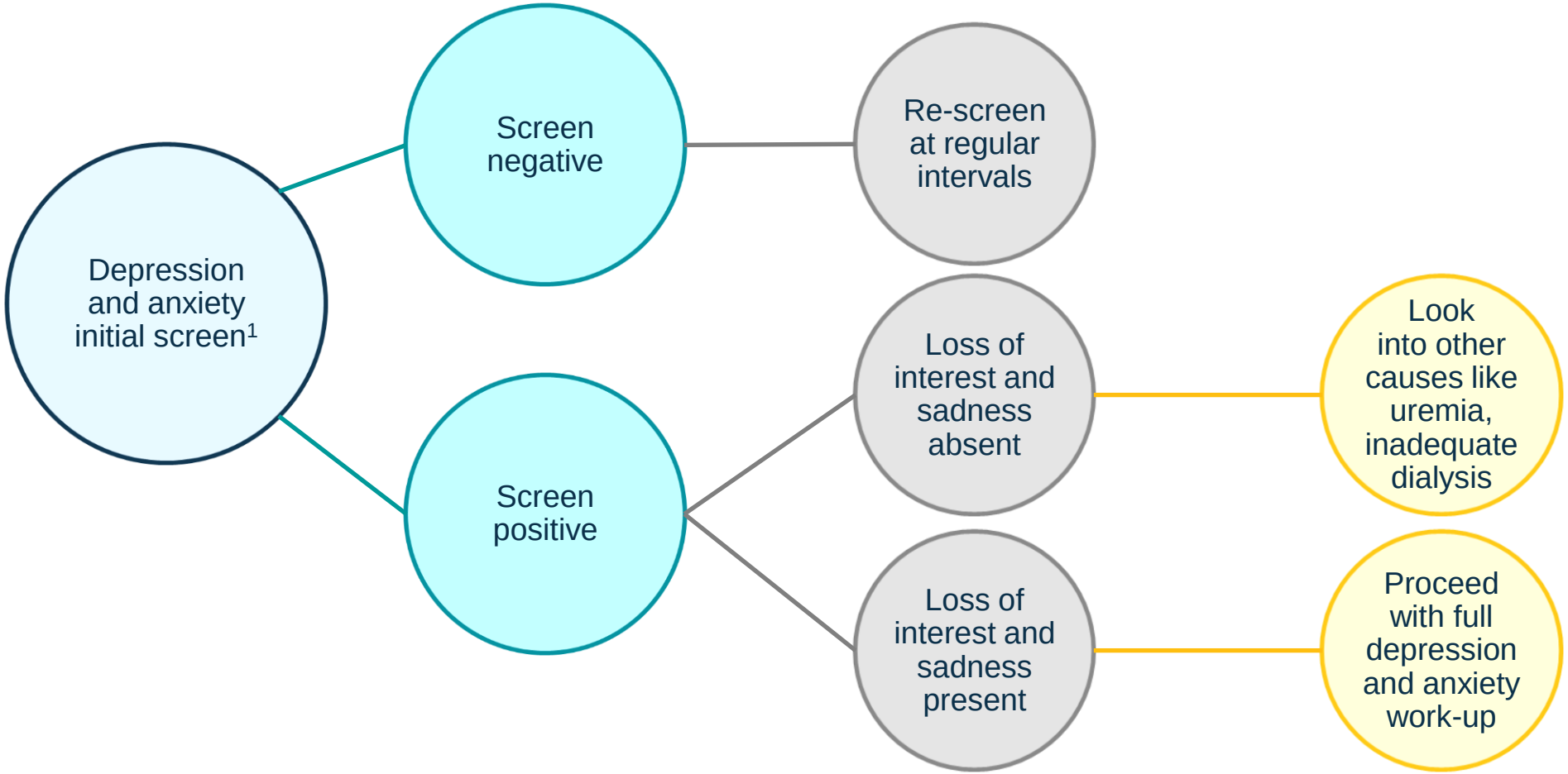
Depression

- Conservative Approach[4]
  - Screen only patients with signs of depression
    - Social isolation, changes in mood or physical functioning, increased physical complaints
- Aggressive Approach[4]
  - Screen all new CKD or ESKD patients with screening questionnaires periodically
    - Initially and every 6 months to 1 year

Addressing mental health is a critical component of the Comprehensive Kidney Care Contracting (CKCC) program

1. Huang CW, et al. Gen Hosp Psychiatry. 2021;69:27-40.
2. Hedayati SS, et al. Kidney Int. 2012;81(3):247-255.
3. McAdams MC, Hedayati SS. Kidney News. 2024;16(5)16.
4. Shirazian S, et al. Kidney Int Rep. 2017;2(1):94–107.

Approach To The Initial Screen



1. Adapted from: Hedayati SS, et al. Kidney Int. 2012;18(3):247-255.

Depression – Validated Screening Tools

Patient Health Questionnaire-9 (PHQ-9)[1]

- 9-item depression module from the full PHQ (3-page questionnaire)
- Major depression is diagnosed if 5 or more of the 9 depressive symptom criteria have been present at least “more than half the days” in the past 2 weeks, and 1 of the symptoms is depressed mood or lack of pleasure

Center For Epidemiologic Studies Depression Scale (CES-D)[2]

- Consists of 20 self-report items rated on a 4-point scale, and its primary aim is to identify and measure the frequency and intensity of these symptoms over one week

Hamilton Rating Scale For Depression (HAM-D)[2]

- Evaluates the severity of depressive symptoms before, during, and after treatment. It scores 17 items on a 5-point or 3-point scale
- Widely utilized in clinical research and trials

Beck Depression Inventory (BDI)[2]

- Evaluates observable behaviors and the severity of depressive symptoms
- Contains 21 multiple-choice questions covering various cognitive, emotional, and physical aspects of depression

- **More studies have validated depression-screening questionnaires in ESKD vs CKD**
- **PHQ-9, BDI, and CES-D are the most validated in CKD and ESKD patients[3]**

1. Kroenke K, et al. J Gen Intern Med. 2001;16:606-613.
2. Cronkleton E. MedicalNewsToday. Published June 20, 2023. Reviewed June 20, 2023. Accessed October 10, 2023. https://www.medicalnewstoday.com/articles/depression-screening-tools
3. Shirazian S, et al. Kidney Int Rep. 2017;2(1):94–107.

Anxiety – Validated Screening Tools

Hospital Anxiety & Depression Scale (HADS)[1]

- 14-item measure to assess anxiety and depression in medical patients, excluding somatic symptoms to reduce the impact of physical illness on the total score
- Items rated on a 4-point severity scale (0-3), scores ≥11 indicate a definitive case
- Validated in CKD patients

General Anxiety Disorder-7 (GAD-7)[3]

- 7-item scale linked to DSM criteria
- Discerns severity of anxiety
- Minimal 0-4; mild 5-9; moderate 10-14; severe 15-21

Beck Anxiety Inventory (BAI)[2]

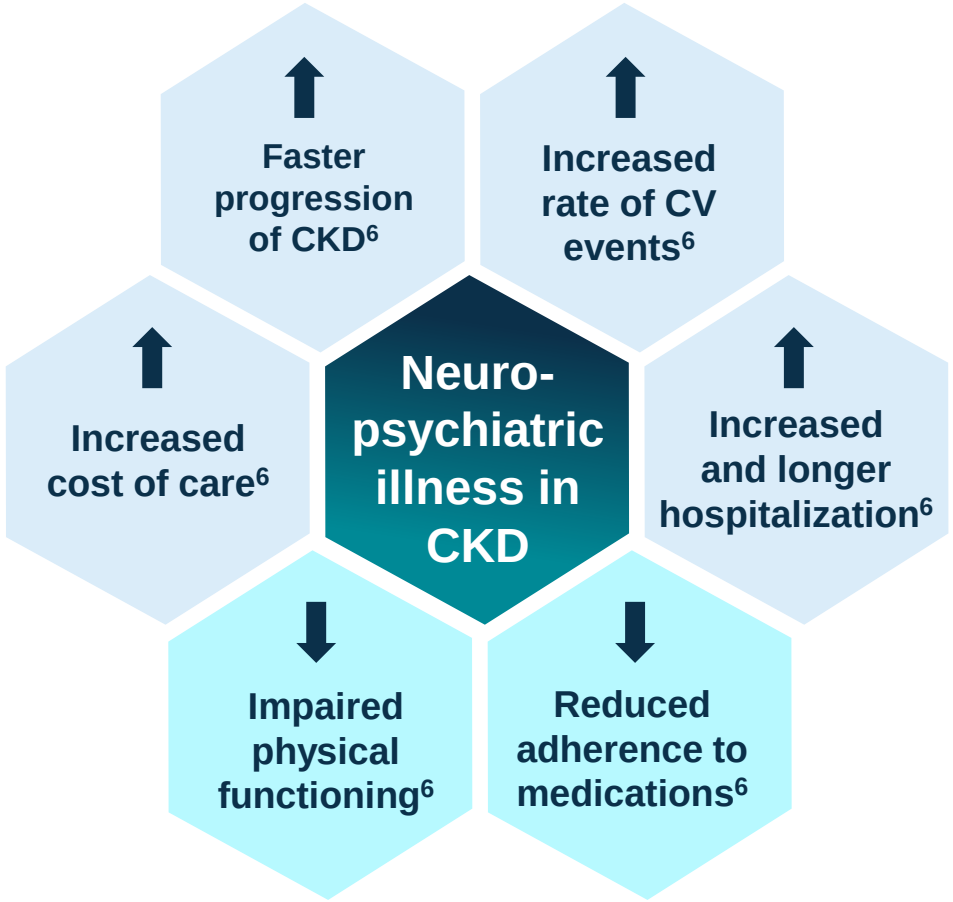
- 21-item self-report assessment tool; items scored from 0-3
- BAI <10: no anxiety; 10≤ BAI <20: mild/moderate anxiety; BAI ≥20: moderate/severe anxiety
- Demonstrates high internal consistency and test–retest reliability over 1 week
- Discriminates anxious diagnostic groups (panic disorder, GAD) from non-anxious diagnostic groups (major depression, dysthymic disorder)

- **No consensus on the gold standard for assessing anxiety in patients with CKD[4]**
- **The HADS, BAI, and GAD-7 have all been used to evaluate symptoms of anxiety in CKD patients[4]**
- **The HADS is validated for use among CKD patients[4]**

1. Zigmond AS, et al. Acta Psychiatr, Scand.1983;67(6):361-370.
2. Beck AT, et al. J Consult Clin Psychol. 1988;56(6):893-897.
3. Spitzer RL, et al. Arch Intern Med. 2006;166(10):1092-1097.
4. Huang CW, et al. Gen Hosp Psych. 2021;69:27-40.

Association With Poor Outcomes

- Depression is associated with an increased risk for adverse clinical outcomes and poor health in patients with CKD[1,2]
- Depressive symptoms, such as low motivation, impaired concentration, and apathy, can significantly affect treatment adherence of patients in ESKD[3]
- Decrease in treatment compliance is one of the potential pathways through which depression may affect mortality and morbidity in patients with late-stage CKD[3]
- Depression, more so than clinical and sociodemographic variables taken together, has been shown to negatively impact health-related quality of life in CKD patients[4]
- Anxiety may drive patients to not welcome the news of decreasing eGFR or increasing need for KRT[5]
- Patients with anxiety may avoid follow-up evaluation[5]
- Anxious avoidance of medical care is challenging to address because it may be difficult to maintain the necessary contact with the patient[5]



1. Finkelstein FO, et al. Kidney Int. 2008;74:843–845.
2. Palmer S, et al. Kidney Int. 2013;84(1):179-191.
3. Asher DR, et al. Hemodial Int. 2012;16(3):387–393.
4. Bautovich A, et al. Aust & New Zeal J Psychiatr. 2014;48(6):530-541.
5. Donahue S, et al. Semin Nephrol. 2021;41:516-525.
6. Parker CP, et al. Adv In Kidney Dis & Health. 2024;31(1):46-51.

Association Between Incident Depression & Clinical Outcomes In Patients With CKD[1]

Depression is highly prevalent and related to increased morbidity and mortality in patients on dialysis, but less is known about patients with earlier stages of CKD

Methods

Observational cohort study in Stockholm, Sweden (SCREAM)

Population:
157,398 adults with CKD stages 3-5 not previously diagnosed with depression

Exposure

Incident diagnosis of depression

Results

Median follow-up 5.1 years

12,712
(8.1%) developed depression

Outcomes	Adjusted RR/HR
Hospitalized days	1.77 (1.71-1.83)
CKD progression	1.38 (1.28-1.48)
MACE	1.22 (1.18-1.27)
Mortality	1.41 (1.37-1.45)

Conclusion: Among patients with non-dialysis–dependent CKD stages 3-5, incident depression is associated with poor prognosis, including hospitalization, CKD progression, MACE, and all-cause mortality.

1. Zhu N, et al. Clin Kid J. 2023;16(11):2243–2253.

MACE=Major Adverse Cardiovascular Events

Challenges In Diagnosis & Treatment[1]

Neuropsychiatric disorders are underdiagnosed and undertreated in patients with CKD due to systemic challenges

- Primary care/nephrology may be uncomfortable with evaluating psychiatric symptoms
- Overlap between psychiatric symptoms, uremia, and other medical/psychiatric conditions
- Conflicting priorities during follow-up appointments
  (i.e., management of lab abnormalities, blood pressure, volume status, dialysis access)
- Lack of clarity on which medical team takes ownership of psychiatric issues
- Stigma associated with mental health diagnosis
- Burden of mental health diagnosis (increasing pills and physician visits)
- Inaccessibility of mental-health–care providers in an overburdened system
- Determining safety and efficacy of pharmacological options for CKD patients

1. Parker CP, et al. Adv In Kidney Dis & Health. 2024;31(1):46-51.

Pharmacologic Treatment Options

Anxiety

First-line treatment:[1]
- Anxiolytic antidepressants
- Antihistamines
- Benzodiazepines

Second-line treatment:
- Antihypertensives
- Anticonvulsants
- Atypical antipsychotics

Depression

First-line treatment:[2,3]
- Selective serotonin reuptake inhibitors (SSRIs)

Alternatives:
- Serotonin/norepinephrine reuptake inhibitors (SNRIs)
- Serotonin modulators
- Dopamine/norepinephrine reuptake inhibitor (DNRI)
- Noradrenergic and serotonergic agonists
- Tricyclic and tetracyclic antidepressants (TCAs)
- Monoamine oxidase inhibitors (MAOIs)

Challenges

- Anxiety disorders require higher doses to achieve response and remission than in depression[1]
- Variable time to onset of action: may take up to 4-6 weeks for therapeutic effect[4]
- Lack of efficacy: a significant proportion of patients fail to remit or only partially remit despite adequate therapy[5,6]
- Nonadherence: both patient factors (eg, concern about side effects, fear of addiction, belief that these medications will not work) and clinician factors (eg, lack of sufficient patient education, poor follow-up)[7]

1. Donahue S, et al. Semin Nephrol. 2021;41:516-525.
2. Hedayati SS, et al. Kidney Int. 2012;81(3):247-255.
3. e Silva ACS, et al. Front Pharmacol. 2019;10:1-11.
4. Uher R, et al. J Clin Psychiatry. 2011;72(11):1478-1484.
5. Olchanski N, et al. Clin Ther. 2013;35(4):512-522.
6. Nierenberg AA, et al. Psychol Med. 2010;40(1):41-50.
7. Sansone RA, Sansone LA. Innov Clin Neurosci. 2012;9(4-5):41-46.

Non-Pharmacologic Treatment Options

Anxiety & Depression	
Psychotherapies[1]	• Cognitive behavioral therapy (CBT) • Interpersonal therapy • Psychodynamic or insight therapy • Brief problem-solving therapy
Mind-Body Therapies[1]	• Meditation • Yoga • Relaxation • Mindfulness • Prayer • Biofeedback and creative therapies (art, music)
Exercise Therapy	• Anaerobic and aerobic (combination most effective)[2]
Web-Based Intervention[3]	• A primarily self-guided intervention program that is executed by means of a prescriptive online program operated through a website

1. BC Renal Agency. Depression and anxiety: the role of kidney care clinics. 2015:1-32.
2. Therapist Aid. Updated 2024. Accessed May 13, 2024. https://www.therapistaid.com/therapy-guide/exercise-and-mental-health-treatments
3. Ashford MT, et al. *JMIR Ment Health*. 2016;3(2):e14,1-23.

Future Directions For Mental Health In CKD

- Develop efficient and validated screening tools for anxiety in patients with CKD[1]
- Initiate early and routine screening intervals for neuropsychiatric disorders[1,2]
- Identify subgroups of patients at high risk for anxiety disorders[1]
- Well-designed epidemiologic studies are needed to understand true incidence, prevalence, and outcomes for anxiety[3]
- Well-designed studies to evaluate interventions for prevention and treatment of depression[4]
- Understand how inflammatory mediators may facilitate the kidney-brain crosstalk[5]
- Focus on patient-centered outcomes for kidney patients[4]
- Consideration for an integrated care model with mental health services readily available to patients[6]

1. Huang CW, et al. Gen Hosp Psychiatry. 2021;69:27-40.
2. Bahall et al. BMC Psychiatry 2023; 23: 733
3. Donahue S, et al. Semin Nephrol. 2021;41(6):516-525.
4. Shirazian S. Kidney Int Rep. 2019;4(2):189-190.
5. e Silva ACS, et al. Front Pharmacol. 2019;10:1-11.
6. Parker CP, et al. Adv In Kidney Dis & Health. 2024;31(1):46-51.

Summary

- There is a high prevalence of both anxiety and depression in patients with CKD
- Overlapping symptomatology between anxiety, depression, and CKD make screening and diagnosis challenging
- Both behavioral and biological mechanisms are linked to the development of anxiety and depression in CKD
- Anxiety and depression are associated with an increased risk for adverse clinical outcomes in patients with CKD
- Systemic factors can pose challenges for management of anxiety and depression in patients with CKD
- There are pharmacological and non-pharmacological approaches for the management of anxiety and depression in CKD
- An integrated care model may provide a novel treatment paradigm for patients with mental health diagnoses and CKD

Questions