

Chapter 36: Recognizing Delirium, Dementia, and Depression

Manjula Kurella Tamura

Division of Nephrology, Stanford University School of Medicine, Palo Alto, California

Neuropsychiatric disorders such as delirium, dementia, and depression are common yet poorly recognized causes of morbidity and mortality among elderly persons with chronic kidney disease (CKD) including end-stage kidney disease (ESKD). Patients with neuropsychiatric disorders are at higher risk for death, hospitalization, and dialysis withdrawal. These disorders are also likely to reduce quality of life and hinder adherence with the complex dietary and medication regimens prescribed to patients with CKD. This chapter will review the evaluation and management of delirium, dementia, and depression among persons with CKD and ESKD.

DELIRIUM

Delirium is an acute confusional state characterized by a recent onset of fluctuating awareness, impairment of memory and attention, and disorganized thinking that can be attributable to a medical condition, intoxication, or medication side effects. A diagnostic algorithm based on Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria, the Confusion Assessment Method, has a sensitivity and specificity for delirium detection >90% (Table 1).¹

Risk Factors

Delirium is typically precipitated by an acute or subacute event such as a neurologic disorder (stroke, subdural hematoma, hypertensive encephalopathy), infection, electrolyte disorder (hypoglycemia, hyponatremia, hypernatremia, hypercalcemia), intoxication (alcohol, drugs, star fruit), or sleep disorder. Elderly patients with cognitive or sensory impairment or those taking multiple medications are thought to be most vulnerable for delirium. Typically, one or more precipitants exist in a vulnerable patient. Elderly patients with multiple chronic diseases, such as elderly patients with ESKD, are thus at especially

high risk. Several ESKD-specific syndromes of delirium deserve special mention:

Uremic Encephalopathy.

Uremic encephalopathy is a syndrome of delirium seen in untreated ESKD. It is characterized by lethargy and confusion in early stages and may progress to seizures and/or coma. It may be accompanied by other neurologic signs, such as tremor, myoclonus, or asterixis. Although rarely used for diagnostic purposes, the EEG shows a characteristic pattern in patients with uremic encephalopathy.² The syndrome is rapidly reversed with dialysis or kidney transplantation.

Dialysis Dysequilibrium.

This syndrome of delirium is seen during or after the first several dialysis treatments. It is most likely to occur in elderly patients with severe azotemia undergoing high efficiency hemodialysis; however, it has also been reported in patients undergoing peritoneal dialysis and long-term hemodialysis.³ The syndrome is characterized by symptoms of headache, visual disturbance, nausea, or agitation, and in severe cases, delirium, lethargy, seizures, and even coma. The incidence and severity of this syndrome are felt to be declining because of earlier initiation of dialysis and institution of preventative measures in high-risk patients (Table 2).

Prevention and Management of Delirium

In hospitalized patients, preventative measures can reduce incidence and costs associated with delirium (Table 3).⁴ Once identified, management of delirium is aimed at identification and treatment of precipitating factors and management of behavioral symptoms. Pharmacologic therapy is indicated only when delir-

Correspondence: Manjula Kurella Tamura, Division of Nephrology, Stanford University School of Medicine, 780 Welch Road, Suite 106, Palo Alto, CA 94304. E-mail: mktamura@stanford.edu

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Table 1. Confusion assessment method

Criteria	Assessment
1. Acute onset and fluctuating course	Is there an acute change in mental status from baseline? Does mental status fluctuate throughout the day?
2. Inattention	Is there difficulty focusing attention?
3. Disorganized thinking	Is thinking disorganized or incoherent?
4. Altered level of consciousness	Is there hyperalertness, lethargy, stupor, or coma?

Diagnosis requires criteria 1, 2, and either 3 or 4.

Adapted from Inouye et al.¹

ium threatens patient safety or interrupts essential therapy. In these cases, haloperidol is the agent of choice, with a usual starting dose of 0.25 to 0.5 mg twice daily. No dosage adjustment is needed in ESKD. Atypical antipsychotic medications, such as risperidone, olanzapine, and quetiapine, have also been used for this purpose. Because of a possible risk of increased mortality when used in patients with dementia, short-term use is recommended.⁵ Benzodiazepines, atypical antipsychotics, and some antidepressants have also been used for treatment of delirium, but these agents have side effects that make them less desirable as first-line agents except in the case of benzodiazepines for alcohol withdrawal. Supportive care to prevent aspiration, deep venous thrombosis, and pressure sores should also be provided in all patients.

DEMENTIA

Dementia is a chronic confusional state characterized by impairment in memory and at least one other cognitive domain, such as language, orientation, reasoning, or executive functioning. The impairment in cognitive function must represent a decline from the patient's baseline level of cognitive function and must be severe enough to interfere with daily activities and independence. The term mild cognitive impairment denotes cognitive impairment (usually memory impairment) beyond that associated with normal aging but without associated functional impairments. Individuals with mild cognitive impairment have a high risk of progression to dementia.

Epidemiology

In the general population, Alzheimer's dementia accounts for

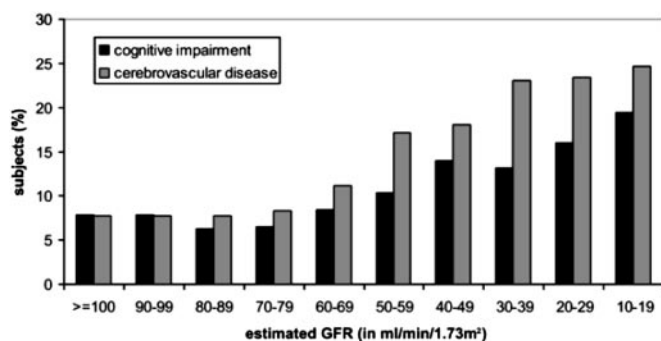


Figure 1. Unadjusted prevalence of cognitive impairment and cerebrovascular disease by estimated GFR among 23,405 US adults. Adapted from reference 11.

60% to 80% of cases of dementia, vascular dementia for 10% to 20%, and other syndromes such as Parkinson's disease-associated dementia and frontotemporal dementia for the remainder. In the ESKD population, some studies suggest that vascular dementia may be much more prominent than in the general population.^{6,7} However, it should be noted that the distinction between vas-

cular dementia and Alzheimer's dementia is not always straightforward, because there is considerable overlap in risk factors and clinical features. Dialysis dementia is a syndrome related to aluminum intoxication first described several decades ago when aluminum contamination of dialysate fluid and the use of aluminum containing binders were more prevalent; however, this disorder is now felt to be rare.

Risk Factors

Older age is a strong risk factor for dementia and mild cognitive impairment. The prevalence of dementia quadruples with each decade of age above the age of 60, reaching 30% over the age of 85.⁸ Stroke and vascular risk factors associated with increased stroke risk, such as hypertension, hyperlipidemia, and diabetes, are linked with an increased risk for dementia in most studies. Anemia, a nontraditional vascular risk factor, has also been linked with dementia and cognitive impairment in both the general elderly population and among hemodialysis patients.^{9,10}

There is growing recognition that CKD is also a strong risk factor for dementia and mild cognitive impairment, independent of age and traditional vascular risk factors. The prevalence of cognitive impairment seems to rise early in the course of CKD, and increases as GFR declines, reaching 20% for persons with a GFR <20 ml/min per 1.73 m² (Figure 1).¹¹ Among hemodialysis patients, the prevalence of cognitive impairment is even higher, estimated at 27% to 37%.^{12,13} An issue that remains unresolved is the extent to which neurodegenerative disease, subclinical cerebrovascular disease, unresolved uremia, or the dialysis process itself contributes to cognitive impairment and dementia.

Evaluation

History taking (ideally from the patient and caregiver) should focus on the duration and severity of cognitive and behavioral deficits, as well as use of medications that might interfere with cognitive function such as antihistamines, antipsychotics, and

Table 2. Prevention of dialysis dysequilibrium

1. Identify high-risk patient: elderly, severe azotemia, initial dialysis treatment
2. Perform reduced efficiency dialysis: reduce blood and dialysate flow rates or perform continuous renal replacement therapy
3. Increase dialysate sodium concentration
4. Administer mannitol

Adapted from Owen et al.²⁴

Table 3. Measures for prevention of delirium in hospitalized patients

1. Provide orienting communication
2. Use adaptive equipment such as visual and/or hearing aids
3. Encourage early mobilization
4. Prevent dehydration
5. Provide uninterrupted sleep time
6. Avoid psychoactive drugs
7. Treat pain

anticholinergics. Routine screening for dementia in the general population is controversial. However, given the high prevalence of cognitive impairment in the CKD population and its implications for disease management, screening for cognitive impairment in elderly CKD patients is probably warranted. A large number of screening tests are available with a range of administration times and diagnostic accuracy; thus, there is no single best screening test available. The Mini-Mental State Exam is perhaps the best known cognitive test for dementia screening and requires 7 to 10 min to administer.¹⁴ A score <24 (of a maximum score of 30) has a sensitivity and specificity of >80% for dementia detection in the general population.¹⁵ Other cognitive tests that can be administered in 5 min or less, such as the clock drawing task, the Mini-cog (consisting of the clock drawing task plus uncued recall of three words), or the Short Portable Mental Status Questionnaire, have similar performance characteristics in the general population.¹⁶ Impairments in executive function, which can be assessed by the clock drawing task, may be particularly important to identify, because impairments in this domain are strongly linked with adherence to therapy, functional status, and ability to live independently. Screening tests of cognitive function may also be useful for identifying patients who may lack capacity to provide informed consent for medical procedures.

Delirium and depression frequently coexist with dementia; however, it is important to exclude these conditions as the sole cause of cognitive impairment before establishing a diagnosis of dementia. In practice, this can be difficult in hemodialysis patients, because unresolved uremia and subtle dialysis disequilibrium can lead to temporal fluctuations in cognitive function.¹⁷ As such, the optimal timing of cognitive function testing for patients on hemodialysis is unknown. Neuropsychologic testing on a nondialysis day can be useful if the diagnosis is uncertain.

In addition to cognitive function testing, laboratory testing for B₁₂ deficiency and hypothyroidism is recommended for all patients with suspected dementia. In ESKD patients, inadequate dialysis, severe anemia, and aluminum toxicity should

also be ruled out. The role of testing for genetic markers of dementia risk (e.g., apoE variants) is controversial.

Management

Two classes of medications are now available for treatment of both Alzheimer's and vascular dementia. Cholinesterase inhibitors are approved for treatment of mild to moderate dementia, whereas memantine, an *N*-methyl-D-aspartate receptor antagonist, is approved for treatment of moderate to severe Alzheimer's dementia and may also have some efficacy in treatment of vascular dementia. The clinical benefit of both classes of agents seems to be modest, and the effect of treatment on long-term outcomes such as nursing home placement remains unclear. There is also no data on safety or efficacy of these agents in ESKD patients; thus, therapy decisions should be individualized.

Behavioral symptoms such as agitation or hallucinations should be treated with a stepped approach, beginning with nonpharmacologic approaches such as removal of precipitating factors (e.g., pain, excessive noise), followed by psychosocial interventions (e.g., music therapy, caregiver education), and pharmacologic therapy as a last step. A key aspect of dementia management is the assessment of patient safety and ability to perform self-care functions, comply with medical regimens, and participate in medical decision making. Goals of care should be discussed early in the course of disease when possible.

DEPRESSION

Depression constitutes the most common neuropsychiatric disorder affecting ESKD patients, with up to 45% of incident dialysis patients and up to 20% of prevalent dialysis patients affected.¹⁸ Despite its high prevalence, depression frequently goes undiagnosed in ESKD patients, and as a result, untreated.

Evaluation

Depressive syndromes are categorized as major depression, minor depression, and dysthymia. Using DSM-IV criteria, a diagnosis of depression requires at least five of nine symptoms to be present daily for at least 2 wk (Table 4). Depressed mood or anhedonia must be included, and the symptoms must be severe enough to interfere with functioning.

Screening questionnaires for depression can be difficult to interpret in patients with ESKD or other coexisting conditions because of the overlap between somatic symptoms of depression and ESKD. Of the available screening tools, the Beck Depression Inventory is perhaps the best validated screening tool

Additional Resources

<http://www.hospitalmedicine.org/geriresource/toolbox>
<http://www.americangeriatrics.org/education/depression.shtml>
<http://elderlife.med.yale.edu/public/public-main.php>
http://www.psychiatryonline.com/pracGuide/pracGuideTopic_2.aspx

Assessment tools for delirium, dementia, and depression
Assessment and management tools for depression
Management tools for hospitalized patients with delirium
Delirium practice guidelines

Table 4. DSM-IV diagnostic criteria for depression

1. Depressed mood
2. Anhedonia
3. Change in sleep
4. Change in appetite or weight
5. Change in psychomotor activity
6. Loss of energy
7. Reduced concentration
8. Thoughts of worthlessness or guilt
9. Thoughts of death or suicide

Major depression requires five or more symptoms including depressed mood or anhedonia causing impaired functioning to be present daily for at least 2 wk. Minor depression requires two to four symptoms including depressed mood or anhedonia causing impaired functioning daily for at least 2 wk. Dysthymia requires three to four symptoms including depressed mood causing impaired functioning for at least 2 yr.

to detect depression in ESKD, with sensitivity and specificity rates of >90%. However, because of its length, it is used more commonly in research rather than clinical settings. Other abbreviated tools, such as the Patient Health Questionnaire, which has been validated in ESKD and in elderly populations, and the five-item Geriatric Depression Scale, which has been validated in elderly populations, may be useful when clinical assessment time is limited. Depression may have atypical presentations in elderly patients, including functional decline as the most prominent presenting feature.

In addition to assessment of symptom duration and associated impairment, evaluation should include assessment of coexisting psychiatric disorders and suicide risk. Coexisting cognitive impairment or substance abuse is especially important to identify. If suicidal ideation is endorsed, intent and suicide risk factors (older, white, male, recently hospitalized) should be ascertained, and a plan for immediate psychiatric evaluation arranged.

Management

In the primary care setting, untreated depression is associated with reduced quality of life, poor adherence with treatment, and increased morbidity and mortality. Similar findings have been shown in some, but not all, studies of patients with ESKD.

Several evidence-based treatments for depression are available, including psychotherapy, exercise therapy, pharmacologic therapy, and electroconvulsive therapy.

The initial choice of therapy should be based on treatment history, coexisting medical conditions, and patient preferences. Although not extensively evaluated in patients with ESKD, a recent meta-analysis reported similar efficacy of psychotherapy and pharmacologic therapy in older adults. Thus, psychotherapy should be considered when pharmacologic therapy is not desired or not effective. Many types of therapy are available, including cognitive therapy, behavioral therapy, and family therapy; they differ in the underlying model of illness and focus on the individual *versus* family. Short-term exercise programs (12 wk) also have proven efficacy in reducing depressive symptoms among older adults. Given the other benefits of exercise in patients with ESKD, this form of therapy

should be strongly considered for patients with mild or moderate depression.

Antidepressants are the most commonly used treatment for depression and a mainstay of most guidelines, although recently their efficacy has come into question.¹⁹ Small clinical trials have also reported short-term benefits in patients with ESKD. In clinical trial settings, only 40% to 65% of patients respond to treatment, and thus combination therapy may be needed.¹⁸ Selective serotonin-reuptake inhibitors are perhaps the best-studied antidepressants in patients with ESKD and seem to have similar safety and efficacy profiles as in the general population.^{20,21} Tricyclic antidepressants are generally not considered first-line therapy in patients with ESKD because of their side effect profile and potential for causing cardiac conduction problems and orthostatic hypotension. Several excellent reviews on the treatment of depression have been published.^{22,23} In general, initial treatment should begin with low doses, and clinical response and side effects should be assessed frequently in the first several months. If response has been suboptimal, the dose may be increased after 3 to 4 wk. If symptoms persist despite a full therapeutic trial of antidepressants (e.g., 8 to 10 wk), psychiatric referral is indicated.

TAKE HOME POINTS

- Neuropsychiatric disorders such as delirium, dementia, and depression are common in elderly persons with ESKD and are likely to adversely affect adherence with therapy, quality of life, and other important outcomes
- Brief screening tools are available for each of these conditions to facilitate identification and management
- Elderly patients with ESKD may have two or more coexisting neuropsychiatric disorders; thus, neuropsychiatric evaluation may be useful in cases where the diagnosis is uncertain

DISCLOSURES

None.

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**REVIEW QUESTIONS: RECOGNIZING DELIRIUM,
DEMENTIA, AND DEPRESSION**

1. Which of the following is NOT a required feature of delirium?
 - a. Acute onset
 - b. Fluctuating course
 - c. Inattention
 - d. Language impairment
2. Which of the following is NOT considered a feature of dementia?
 - a. Acute onset
 - b. Interference with activities of daily living
 - c. Memory impairment
3. Which of the following types of therapy may be indicated for patients with ESKD with mild to moderate depression?
 - a. Exercise therapy
 - b. Additional erythropoietin to raise Hb levels to 12 to 13 g/dl
 - c. Selective serotonin reuptake inhibitors
 - d. Psychotherapy