Depressive disorders are common and significant among the general population and in individuals with chronic diseases. This article reviews the literature describing the epidemiology and significance of depression in patients with chronic kidney disease (CKD). Although nonpharmacologic treatment is included, the focus of this article is drug therapy. Evidence for efficacy of antidepressants in patients with CKD, drug interactions, and potential adverse effects will be discussed.

**Epidemiology**

Depression occurs in up to one-third of patients with CKD (Lopes et al., 2002; Lopes et al., 2004; Patten, 2001; Tossani, Cassano, & Fava, 2005). Among patients receiving dialysis, depression is the most common psychiatric disorder, and hospitalizations for a primary diagnosis of depression have been found to be higher than cerebrovascular disease or ischemic heart disease (Kimmel & Peterson, 2005). Therefore, it is important for the dialysis care team to have an understanding of this disorder and its treatment in order to provide optimal patient care.

Although methodologies vary widely, most studies estimate the prevalence of depressive symptoms in patients with CKD to range from 20% to 30% (Boulware, Liu, & Fink, 2006; Finkelstein, Watinck, Finkelstein, & Wuerth, 2002; Lopes et al., 2002; Tossani et al., 2005; Wuerth et al., 2003), with the prevalence of a major depressive disorder estimated at 5%-10% (Kimmel & Peterson, 2005). However, comparisons between depression screening tools, such as the Centre for Epidemiological Studies Depression (CES-D) Screening Index and medical records, reveal that fewer patients had a physician diagnosis of major depression than symptoms of depression (13% vs. 43%, respectively), indicating that major depression may be often undiagnosed in patients with CKD (Lopes et al., 2004). Epidemiologic studies have demonstrated depression in patients with CKD to be associated with increased morbidity and mortality; this impact was found to be inde-
Table 1
Symptoms of Major Depressive Episode

- Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
- Significant weight loss when not dieting, weight gain, or decrease or increase in appetite nearly every day
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness, or excessive or inappropriate guilt nearly every day
- Diminished ability to think or concentrate, or indecisiveness, nearly every day
- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide


dependent of such factors as time on dialysis, quality of dialysis, age, race, socioeconomic status, comorbid medical conditions, and country (Boulware et al., 2006; Knight, Ofsthun, Teng, Lazarus, & Curhan, 2003; Lopes et al., 2002, 2004). Depression in patients with CKD has also been described to be a persistent problem, rather than simply associated with dialysis initiation (Boulware et al., 2006; Kimmel & Peterson, 2006). Although it appears that depression is associated with decreased overall survival in patients with CKD, it is unclear if depression is an independent risk factor or if depression influences other variables, such as adherence to medications or treatments, suicidality, or other behaviors that may impact survival (Boulware et al., 2006; Kimmel & Peterson, 2005, 2006; Kurella, Kimmel, Young, & Chertow, 2005; Tossani et al., 2005).

Clinical Features

The diagnosis of a depressive disorder is based upon specific signs and symptoms as described in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (American Psychiatric Association [APA], 2000a). The most common depressive disorder is major depressive disorder (MDD), defined as one or more episodes of major depression. A major depressive episode is characterized by five or more symptoms as listed in Table 1 in a 2-week period, with a change in functioning; at least one of the symptoms must be a depressed mood or loss of interest or pleasure.

Although it is likely common among patients with CKD, depression is difficult to diagnose in this patient population (Finkelstein et al., 2002; Kimmel & Peterson, 2005; Tossani et al., 2005). Signs and symptoms of CKD (such as fatigue), side effects of medications (such as nausea causing weight loss), or comorbid conditions (such as pain) may resemble depressive symptoms. Conversely, treatment of symptoms of CKD may improve patient quality of life, and this may improve mood (Davison, 2007; Kimmel, & Peterson, 2005; Tossani et al., 2005).

The Kidney Dialysis Outcomes and Quality Initiative (KDOQI) guidelines suggest that depression, anxiety, and hostility should be identified and treated in patients receiving dialysis, and that the patient’s psychological state should be evaluated at dialysis initiation and at least biannually thereafter (National Kidney Foundation [NKF], 2005). The KDOQI guidelines do not offer, however, specific details about how to achieve this goal. The most appropriate screening tools to identify depression among patients with CKD are unknown (Kimmel & Peterson, 2005). Tools to identify depression include the Hamilton Rating Scale for Depression (Hamilton, 1967) and the Beck Depression Inventory (BDI) (Beck, Steer, Ball, & Ranieri, 1996). Shorter screening tools may have similar performance to longer tests (Whooley, Avins, Miranda, & Browner, 1997; Williams, Noel, Cordes, Ramirez, & Pignone, 2002). Most importantly, the majority of patients with depression may be detected by asking about depressed mood and anhedonia (Whooley et al., 1997). Recent studies have used the shorter 10-item Center for Epidemiologic Studies Depression Screen (CES-D) (Lopes et al., 2004) and an even shorter self-reported depression screen from the Kidney Disease Quality of Life (KDQOL) Questionnaire, which asks whether, in the past 4 weeks, the patient has felt “so down in the dumps that nothing could cheer you up” and “downhearted and blue” to successfully screen for depressive symptoms in patients receiving dialysis (Lopes et al., 2002). Patients who answered “all of the time,” “most of the time,” or “a good bit of the time” to these two questions from the KDQOL were considered to be depressed. The authors went on to suggest that these two questions could easily serve as a depression screening tool for patients receiving dialysis (Lopes et al., 2002). Health professionals in close contact with patients receiving dialysis could conduct such relatively simple screening for depression, and then refer on for further psychiatric evaluation as required.

Pathophysiology

The pathophysiology of depressive disorders is complex and poorly
understood. A disruption of brain neurochemistry, including norepinephrine, serotonin, dopamine, and other many other neurotransmitters have been postulated to contribute to depressive disorders (Mann, 2005). Recent theories of the pathophysiology of depressive disorders also involve interactions between psychological stress, genetics, intracellular neuronal regulation, and other neurotrophic factors (Shelton, 2007).

Nonpharmacologic Treatment

Nonpharmacologic approaches play important roles in the treatment of depressive disorders. Psychotherapy may be used in combination with medication management in some cases of depression to enhance symptom control or to increase adherence to medications. Alternatively, management with psychotherapy alone in cases of less severe depression may be effective in reducing depressive symptoms. Psychotherapies that may be effective include interpersonal psychotherapy, cognitive therapy, and behavioral therapy (APA, 2000a).

Electroconvulsive therapy (ECT) may be used effectively in depression and can be considered in patients who are treatment resistant to medication or in patients with psychotic forms of depression. Patients in whom ECT is effective are generally maintained on antidepressant medication to prevent relapse (Kennedy, Lam, Cohen, & Ravindran, 2001).

Pharmacotherapeutic Options For Depression

Current literature suggests that depression is not only underdiagnosed, but it is also undertreated in patients with CKD, with estimates of only 17% to 35% of patients receiving hemodialysis and diagnosed with depression or depressive symptoms being treated with antidepressants (Lopes et al., 2004). Despite the paucity of data evaluating antidepressants in patients with CKD, it is reasonable to assume that treatment using antidepressants in patients with CKD experiencing depressive symptoms will result in improved outcomes (Kimmel & Peterson, 2006).

Approximately half to two thirds of moderate to severe episodes of depression in the general population will improve with antidepressant therapy (Stahl, 2000). First-line agents for the treatment of depression usually include the second generation antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), venlafaxine, mirtazapine, bupropion, nefazodone, and duloxetine, due to their safety profiles compared to older medications, such as tricyclic antidepressants or monoamine oxidase inhibitors (APA, 2000b; Kennedy et al., 2001; Mann, 2005). In particular, for patients receiving dialysis with underlying cardiovascular disease, tricyclic antidepressants should be avoided due to the increased risk of arrhythmias and hypotension with this drug class (APA, 2000b; Mann, 2005). Evaluation of head-to-head comparisons of the second-generation antidepressants for the treatment of MDD reveal that treatment efficacy does not differ substantially among these drugs (Hansen, Gartlehner, Lohr, Gaynes, & Carey, 2005). This review will focus on the use of these second-generation antidepressants in patients with CKD (see Table 2).

Although some pharmacokinetic studies exist, very few studies have evaluated the efficacy of antidepressant drugs in patients with CKD. Several small (fewer than 10 patients) studies have demonstrated the short-term efficacy of desipramine (tricyclic antidepressant), fluoxetine (SSRI), and fluvoxamine (SSRI) in patients receiving hemodialysis (Blumenfield et al., 1997; Kamo et al., 2004; Kennedy, Craven, & Rodin, 1989; Levy et al., 1996). In two studies of patients with depression receiving peritoneal dialysis (n = 22 and n = 44), who were treated with various second-generation antidepressants (including nefazodone, sertraline, citalopram, paroxetine and buproprion), it was observed that 50% and 52%, respectively, demonstrated an improved BDI score at 12 weeks (Wuerth et al., 2001, 2005). One study that evaluated the effect of antidepressant treatment on nutritional status in 34 patients with depression who were receiving hemodialysis (treated with paroxetine [SSRI] 10 mg daily and psychotherapy for 8 weeks) observed a statistically significant improvement in depressive symptoms, as well as a nutritional status (protein catabolic rate, serum albumin, and blood urea nitrogen level) when compared with non-depressed control patients who did not receive treatment (Koo et al., 2005). Two studies have evaluated the impact of antidepressants on quality of life in patients with CKD [Kalender, Ozdemir, Yalug, & Dervisoglu, 2007; Turk et al., 2006]. In one study, 40 patients receiving hemodialysis were prescribed sertraline (SSRI) 50 mg daily for 8 weeks, and demonstrated improved depressive symptoms and quality of life scores (Turk et al., 2006). In the second study, 34 patients receiving hemodialysis, continuous ambulatory peritoneal dialysis, or pre-dialysis CKD, received citalopram (SSRI) 20 mg daily for 8 weeks, and demonstrated improved depressive symptoms and quality-of-life scores (Kalender et al., 2007). To date, no published studies have evaluated the utilization of venlafaxine, mirtazapine or escitalopram, in patients receiving dialysis. Only one small study has evaluated any of the second-generation antidepressants in patients with CKD but not yet receiving dialysis; however, these patients were not the specific focus of the study (Kalender et al., 2007). Because existing studies of antidepressants in patients with CKD are limited by their small size, lack of control groups, and nonrandomized designs, further research is needed to provide evidence of effectiveness of antidepressant treatment in this population.

SSRIs

The selective serotonin reuptake inhibitors (SSRIs) (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) inhibit serotonin reuptake,
with a resultant increase of serotonin concentration in the synapse between serotonergic neurons (Stahl & Grady, 2003). Common side effects of SSRIs include sedation, insomnia, dry mouth, nausea, headache, and sexual dysfunction. An adverse effect associated with SSRIs that is of particular importance in patients with CKD is the association between the use of SSRIs and gastrointestinal bleeding, particularly in patients taking aspirin and warfarin (Looper, 2007; Yuan, Tsoi, & Hunt, 2006). However, no studies to date have evaluated the risk of gastrointestinal bleeding associated with SSRIs in patients with CKD. Of all the available antidepressants, the SSRIs have the most data available for use in patients with CKD (Blumenfield et al., 1997; Cohen, Tessier, Germain, & Levy, 2004; Kalender et al., 2007; Kamo et al., 2004; Koo et al., 2005; Levy et al., 1996; Turk et al., 2006; Wuerth et al., 2003, 2005). With the exception of paroxetine, no renal dose adjustments are required for SSRIs.

### Bupropion

Bupropion is a norepinephrine dopamine reuptake inhibitor (NDRI), that has very little effect on serotonin (Stahl & Grady, 2003). Comparative randomized controlled trials show that bupropion has fewer sexual side effects, however more headaches and insomnia than other second-generation antidepressants (Hansen et al., 2005). Bupropion is associated with a dose-related increase in seizure risk, particularly with doses greater than 450 mg per day. Bupropion-related seizures are believed to be caused by its active metabolites, and these metabolites can accumulate in patients with CKD (Cohen et al., 2004; Ross, & Williams, 2005). Bupropion has also been reported to improve symptoms of restless leg syndrome (Kim et al., 2005). The dose of bupropion must be reduced for use in patients receiving dialysis (Cohen et al., 2004). Bupropion is also used for smoking cessation, and a small pharmacokinetic study of bupropion for smoking cessation in patients on hemodialysis recommended 150 mg every 3 days as an appropriate dose (Worrall, Almond, & Dhillon, 2004).

### Mirtazapine

Mirtazapine has a unique mechanism of action that results in an increase of noradrenergic and serotonergic transmission, without inhibiting the reuptake of serotonin or norepinephrine (Holm & Markham, 1999; Stahl & Grady, 2003). There is some suggestion that mirtazapine may have an earlier onset of antidepressant effect compared with other antidepressants; however, this difference was not found to be statistically significant in a recently published meta-analysis (Hansen et al., 2005).
Mirtazapine has been shown to have more somnolence, dry mouth, weight gain, and sexual dysfunction than its comparators (Hansen et al., 2005; Holm & Markham, 1999). In addition to its antidepressant effect, mirtazapine has also been reported to be useful for the treatment of pruritis in a small number of patients (Hundley & Yosipovitch, 2004). The clearance of mirtazapine is reduced by 30% in patients with creatinine clearance less than 40 mL/min and by 50% for patients receiving dialysis (Organon USA, 2007), and the dosage should be reduced for these populations.

**Venlafaxine**

Venlafaxine inhibits reuptake of serotonin, norepinephrine, and dopamine at low, medium, and high doses, respectively (Stahl, 2000). Comparative trial data suggest that venlafaxine causes more dizziness and nausea than comparator antidepressants (Hansen et al., 2005). Venlafaxine has been reported to elevate blood pressure in a dose-dependent manner; therefore, monitoring is especially important for patients with pre-existing hypertension (Feighner, 1995; Thase, 1998). In addition to treating mood disorders, venlafaxine has also demonstrated efficacy for the treatment of neuropathic pain (Rowbotham, Goli, Kunz, & Lei, 2004). The dose of venlafaxine should be reduced by 25% for patients with creatinine clearance between 10 and 70 mL/min, and by 50% for patients with a creatinine clearance less than 10 mL/min (Wyeth, 2007). Duloxetine is also a serotonin norepinephrine reuptake inhibitor that has been shown to be effective for the treatment of depression and neuropathic pain; however, the use of duloxetine in patients with creatinine clearance less than 30 mL/min or receiving dialysis is not recommended (Lilly, 2007).

**Drug Interactions**

All antidepressants are hepatically metabolized by the cytochrome (CYP) P450 system, resulting in numerous drug-drug interactions with other medications. The SSRIs have variable effects on cytochrome P450 enzymes; fluoxetine, fluvoxamine, and paroxetine are the most potent inhibitors of specific cytochrome isoenzymes. Citalopram, escitalopram, bupropion, mirtazapine, and venlafaxine have fewer drug-drug interactions (Nieuwstraten, Labiris, & Holbrook, 2006). Recent reviews of antidepressant drug interactions provide specific details and clinical significance of interacting medications (DeVane, 2006; Nieuwstraten et al., 2006; Preskorn & Flockhart, 2004; Spina, Scordo, & D’Arrigo, 2003).

**Discontinuation Syndrome**

A discontinuation syndrome has been associated with antidepressants, particularly with the SSRIs and venlafaxine. Symptoms have been termed “FINISH” (flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, hyperarousal) and can begin 24 to 72 hours of discontinuation or reduction in dosage. Strategies to avoid the antidepressant discontinuation syndrome include patient education, gradual tapering (dose reduction every 5 to 7 days), and avoidance of abrupt cessation of therapy (Looper, 2007; Warner, Bobo, Warner, Reid, & Rachal, 2006). Health care providers should maintain a high index of suspicion for antidepressant discontinuation syndrome in patients with such symptoms who may have accidentally or purposefully discontinued medications (Warner et al., 2006).

**Serotonin Syndrome**

Any antidepressant that increases serotonin may precipitate a rare but serious adverse event known as serotonin syndrome, which can be associated with monotherapy or combinations of serotonergic drugs. Symptoms include hyperthermia, changes in mental status, nausea, diarrhea, dizziness, palpitations, unsteady gait, agitation, anxiety, restlessness, shivering, diaphoresis, tremor, hyperreflexia, and autonomic instability (hypertension or hypertension). Patients are at greatest risk of serotonin syndrome shortly after a drug is initiated, the dose is increased, or an interacting drug is initiated. In addition to stopping the offending agent, treatment is largely supportive (Boyer & Shannon, 2005; Looper, 2007).

**Course of Therapy**

Although very few studies of antidepressants in patients with CKD exist, most principles guiding the use of antidepressants in the general population, especially those with comorbid medical conditions, are still important to patients with CKD. For example, it is appropriate to start treatment at the lowest effective doses, monitoring frequently for adverse effects, exacerbation of symptoms, and drug interactions (Mann, 2005; Tossani et al., 2005). Suicide is an important consideration for all patients being treated for depressive disorders, and patients must be evaluated for suicide risk prior to and during treatment with antidepressants (APA, 2000b; Kennedy et al., 2001).

When initiating treatment with antidepressants, it is important to educate patients on when to expect response to treatment, identification of side effects, and the importance of adherence. Patients who discontinue antidepressants early are more likely to experience relapse or recurrence of depression (Melfi et al., 1998). Treatment of the acute phase of a depressive episode is approximately 6 to 10 weeks, and it is recommended that patients be evaluated for symptom improvement every 1 to 2 weeks (Mann, 2005). If patients do not experience a response within 3 to 4 weeks of treatment with an antidepressant at therapeutic doses, it is recommended to alter treatment by increasing the dose or switching to another antidepressant (Kennedy et al., 2001). Patients who do not tolerate one antidepressant, even within the class of SSRIs, will often tolerate another (Brown & Harrison, 1995; Mann, 2005).
Continuation of medication treatment for at least 6 to 9 months once remission of symptoms has been achieved is usually recommended to prevent relapse of symptoms (Kennedy et al., 2001; Mann, 2003; Stahl, 2000). Chronic therapy may be considered for patients with multiple episodes of depression or when remission is incomplete. Once antidepressant therapy is to be discontinued, the dosage should be tapered gradually to prevent discontinuation symptoms.

**Conclusion**

Screening, identifying, participating in treatment plans, and monitoring therapy for depressive disorders are all important roles that nurses play in caring for patients with CKD. An understanding of the prevalence and importance of depressive disorders among patients with CKD is important for staff providing direct patient care to this group of patients. Identification of major depression in patients with CKD is challenging due to multiple contributing factors, overlapping symptomatology, and complex presentation. Useful screening tools include a two-item questionnaire (about feeling blue or down in the dumps). Second-generation antidepressants are considered first-line therapy. Several of the second-generation antidepressants require dose adjustments for kidney dysfunction (including paroxetine, bupropion, mirtazapine, and venlafaxine [see Table 2]); however, adverse effects and drug interactions should guide treatment choices in an individual patient. Monitoring for efficacy and toxicity is an extremely important part of the therapeutic plan, and the health care team can play an important and active role in the management of depression in such complex patients.

**References**


antidepressant treatment on nutritional status in chronic hemodialysis patients. American Journal of the Medical Sciences, 329, 1-5.


ANSWER/EVALUATION FORM
Pharmacotherapeutic Options for the Treatment of Depression in Patients with Chronic Kidney Disease
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   a. Review the epidemiology of depression in patients with CKD. __________ minutes.
   b. Relate the significance of depression in patients with CKD to the effect on nursing care. 1 2 3 4 5
   c. Discuss the pharmacologic therapeutics used in the treatment of depression in patients with CKD. 1 2 3 4 5
3. The content was current and relevant. 1 2 3 4 5
4. This was an effective method to learn this content. 1 2 3 4 5
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