

Depression in Chronic Kidney Disease

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Depression is the most frequent psychiatric problem in patients with chronic renal disease and may predict patient outcome and mortality. Depression is linked to stressful life characterized by many losses and by dependence, which even may lead to suicide. Despite the large number of patients with chronic kidney disease and the economic burden they represent, only a few of these patients receive adequate diagnosis and therapy. Diagnostic and Statistical Manual of Mental Disorders-IV criteria for major depression may help in differentiating symptoms of uremia and depression. Pharmacotherapy is available and antidepressants (tricyclic antidepressants and selective serotonin re-uptake inhibitors) have been used successfully in various studies. Finally, there is a need for further well-designed, longitudinal, survival studies to clarify the relationship better between depression and the different stages of renal dysfunction.

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The term *depression* usually is used to indicate an acute affective experience, a consequence of a physical disease or a medication-induced problem, a primary psychiatric syndrome or a symptom present in other psychiatric disorders. Depression is a pathologic condition that can affect 7% to 15% of men and 13% to 18% of women.¹ In the general population, more than 1 in 8 people request treatment for depression during their lifetime: more than 60% of depressed patients initially consult their general practitioner and a small percentage are referred to a psychiatrist or psychiatric service, and only 30% to 50% of patients are diagnosed with depression.¹ Depressed patients have a low quality of life, a worsening of their physical condition, and loss of role within the family and workplace even greater than patients with other chronic diseases. Moreover, depression may place a significant economic burden on patients, their family, and on the health care system. In the United States, affective disorders comprise 3.3% of national health care resource costs and 54% is related to treatment of the illness or disorder, an 8.1% cost for the impact on productivity and a 28.9% cost because of the increased mortality.¹

Problematic Aspects of Depression

Arieti,² in 1978, already differentiated a physiologic condition, which can be called a *normal sadness*, from what is considered major depression. The boundaries of these 2 conditions are not well defined, they probably are quantitative or qualitative different states of mood. From this respect, the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) defines major depression according to different criteria (Table 1).

Therefore, in contrast with normal sadness, a depressed mood³ may not be associated with real adverse events and if losses are reported, they are grossly exaggerated, anticipated, or imagined. Major depression can be extremely painful, persistent, and pervasive, resisting all attempts to change by encouragement or reasoning. It commonly is associated with worthlessness, low self-esteem, sustained self-deprecation, and feelings of guilt and death wishes. It frequently escalates over time and impacts on interpersonal relations and daily functioning. More frequently than in normal sadness, rhythm disturbances and hormonal dysregulation may be recognized. Besides the symptomatologic criterion, major depression diagnosis, according to the DSM-IV, also is based on chronologic, functional, and exclusion criteria (Table 1). Major depression can be qualified further by the presence of melancholic features³ (Table 2), which corresponds to the classic concept of endogenous depression, whose outcome is

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Table 1 Criteria for Major Depression According to DSM-IV Criteria

Symptomatologic criterion
At least 5 of the following symptoms:
Depressed mood
Markedly diminished interest or pleasure in all, or almost all, activities
Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or a decrease or increase in appetite
Insomnia or hypersomnia
Psychomotor agitation or retardation
Fatigue or loss of energy
Feelings of worthlessness or excessive or inappropriate guilt
Diminished ability to think or concentrate or indecisiveness
Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan or a suicide attempt or a specific plan for committing suicide
Chronologic criterion
Depressive symptoms should last for at least 2 weeks
Functional criterion
Depressive symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
Exclusion criterion
The symptoms are not caused by the direct physiologic effects of a substance (eg, drug abuse or medication) or a general medical condition (eg, hypothyroidism)

Data from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition.³

independent of stressful events, whereas melancholic major depression also can be preceded by such events.

According to DSM-IV, affective, cognitive, somatic, and a psychomotor cluster of symptoms may be recognized in major depression.

The Prevalence and Diagnosis of Depression in Uremia

No large-scale, well-designed, epidemiologic studies in patients with renal diseases have been conducted. In 1993, however, 8.9% of dialyzed patients needed hospitalization because of psychiatric problems.⁴

According to Kimmel laboratory,⁴⁻¹⁴ patients with end-stage renal disease (ESRD) carry the risk for high frequency of moderate depression, which seems to be the most important clinical psychiatric complications in these patients.

In ESRD patients, previous studies have reported a variable prevalence of depression. In fact, a 0% prevalence of depression in the study by Wright et al¹⁵ and Glassman and Siegel¹⁶ was found, whereas Klein et al¹⁷ identified only a 15% rate of depressed patients. In the study by Foster et al¹⁸ and Smith et

al,¹⁹ a 47% prevalence was reported. Moreover, 100% of patients had depression in the study by Reichsman and Levy.²⁰

The reported variability of the prevalence of depression can be a result of different methodologic problems: earlier studies lack information on comorbidities, dialysis delivery/efficacy, undefined behavioral compliance, and psychosocial factors. Kimmel et al⁷ reported a total of 15,701 of 176,368 patients undergoing hemodialysis and peritoneal dialysis (8.9% of the total) who required hospitalization for depression. The rate per 10,000 patient-years was 74 for hemodialysis patients and 64 for peritoneal dialysis patients. The duration of hospitalization averaged 12.7 days for hemodialysis patients and 11.2 for peritoneal dialysis patients. In patients older than 65 years with chronic renal failure, the rate of depression and affective disorders was 90%. In addition, patients dialyzed for 1 year or more were more prone to hospitalization, which might be the end result of "initial denial or because early hopes of reversibility have not been fulfilled."

Psychiatric disorders may be unrecognized⁷ at the beginning of dialysis treatment or may be attributed incorrectly to uremia. In fact, depressed ESRD patients may complain of fatigue, irritability, apathy, anorexia, aches, sleep disorders, bowel disorders, incapacity to concentrate, decrease of appetite, and action tremor, which are usual for uremia but at the same time are similar to symptoms of depression. Only feelings of sadness, helplessness, hopelessness, guilt, presence of a death wish, and loss of libido should be considered as symptoms of depression.

Uremia-Associated Losses and Dependences as Causes of Depression

Several factors for depression can be identified in dialyzed patients. The most important are the feelings of loss^{7,11,21} and dependence (Table 3), a concept advanced in 1986 by Israel.²² Further concerns are about dietary constraints, time restrictions, functional limitations, loss of employment and loss of role in the dyad and workplace, change in sexual function, illness and medications effects, and fear of death.²³ Moreover, dependence on the dialysis machine, the dialysis staff, and physicians also occurs.²²⁻²⁶

Table 2 Criteria for Major Depression With Melancholic Features According to DSM-IV

Lack of pleasure in all or almost all activities, or lack of reactivity to pleasurable stimuli
Presence of at least 3 of the following
A distinct quality of depressed mood
Diurnal variation of mood
Psychomotor retardation or agitation
Loss of weight and appetite
Feelings of excessive or inappropriate guilt

Data from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition.³

Table 3 Uremia-Associated Losses and Dependences**Losses**

- Loss of urinary function
- Loss of the capacity to concentrate
- Loss of work place
- Loss of the freedom to select or to find a job
- Loss of the capability to accept an exacting job
- Loss of the role in the family
- Loss of family dynamics
- Loss of role in social relationships
- Loss of quality of life
- Loss of the sense of femininity
- Loss of menstruation
- Loss of the capability of having orgasm
- Loss of the sense of masculinity
- Loss of erectile function
- Loss of libido
- Loss of capability to set constructive goals
- Loss of good mood
- Loss of life expectancy
- Loss of the capability of practicing a sport
- Loss or limitations in mobility
- Loss of freedom in selecting foods
- Loss of freedom in selecting beverages
- Loss of body weight
- Loss of muscle mass
- Loss of body imaging
- Loss of skin color
- Loss of weight stability
- Loss of sleep hours

Dependences

- On dialysis staff
- On physician
- On medications
- On family
- On a machine
- On dialysis shifts
- On dialysis calendar

Survival and Depression

Several studies^{15-17,19,20,27-36} have assessed the relationship between depression and mortality in hemodialysis patients, but the conclusions have been contradictory. Shulman et al³⁷ followed-up a group of 64 patients for 10 years. At 10 years, patients with Beck Depression Inventory (BDI)³⁸ scores of 14, in comparison with those with a BDI greater than 25, had a survival probability of 26% versus 10%, respectively. For BDI scores in the range of 14 to 24, the probability was nearly 16%. Although somatic items contributed disproportionately to BDI scores, they could not account for abnormally increased scores, and cognitive and emotional subscores paralleled changes in somatic scores. The BDI score correlated with a chronic dysphoric state present for years or months without remission in patients who previously were not depressed before dialysis. The BDI score was the most important predictor of survival. However, 30% of the patients had major depression as measured by interviews and 30% of patients had major depression by BDI scores.

Comorbid illnesses were associated with lower survival rates. Age, sex, and serum calcium level were independent significant

associations with mortality after adjustment for BDI. The impact of depression was maximal in the first few years of dialysis. However, the study was performed when quantification of dialysis administration was not available.

Withdrawal From Dialysis/Suicide

Discontinuation of dialysis therapy in the years from 1991 to 1994 was responsible for 17.8% of the deaths occurring in 126,156 patients with ESRD.³⁹ Levy^{40,41} pointed out that the rate of suicide in dialysis patients is 50 times higher than in the general population. Beder⁴² provided a profile of characteristics of patients likely to withdraw from treatment (Table 4) and showed that "hyperindependence and impulsivity carry a poor prognosis, as do denial of illness beyond the initial phase of dialysis and evidence of psychopathology."

In a study with 716 dialysis patients followed-up for 20 years, dialysis withdrawal accounted for 18.5% of all deaths.⁴³ Patients who stopped dialysis were older when starting dialysis, and 65.1% were 61 years of age and older. Cancer, malnutrition, catabolism, and dissatisfaction with life were associated with the decision to withdraw from dialysis. In addition, 50% of the patients had either diabetic nephropathy or atherosclerotic renal vascular disease.

In a study of the Michigan Dialysis Registry (4,753 white and 2,988 black patients), the problem of withdrawal was analyzed carefully and it was shown that it was higher in white patients. Age and diabetic nephropathy had a statistically significant joint effect. In female patients there were slightly lower rates of withdrawal.⁴⁴

McKegney and Lange⁴⁵ have made a case for the communication gap between patients and the dialysis staff. They believed that dialysis patients do not let the staff know that the quality of life provided by the machine is felt to be inadequate to continue to fight, and they also stressed the inadequacy of the dialysis staff in catching this condition. It also has been reported that over-optimism should be avoided by the nephrologist.

In addition to the problem of withdrawal there is the problem of suicide, which is not synonymous with withdrawal. In the

Table 4 Characteristics of Patients Likely to Withdraw From Dialysis

- Patients aged ≥ 60 years
- Depressed patients
- Anxious patients
- Patients with comorbid conditions
- Patients whose self-perception is one of being sick rather than well
- Patients facing imminent surgery
- Patients with dementia
- Patients on dialysis for more than 8 years
- Sophisticated patient who tries to control everything
- Patients of higher economic status
- Patients in denial
- Impulsive hyperindependent patient

Data from Beder.⁴²

United States the rate of suicide among dialysis patients is 0.3 patients per 1,000 patients-years, whereas in the general population the rate is 0.12 per 1,000 person-years. There are many methods of suicide, the most frequent is the ingestion of a high quantity of foods containing potassium.⁴⁶

Suicide in ESRD Patients

Although depression and dialysis withdrawal are relatively common in patients with ESRD, there have been few systematic studies of suicide in this population.

Shulman et al³⁷ reported 7% of deaths by suicide (caused by an overdose of aspirin, bleeding through shunts, and gas from a motor vehicle) and 4.6% of all deaths by dietary non-compliance. In addition, the risk for suicide should be considered even higher than in the general population and comparable with that in patients with other severe chronic illnesses. Their conclusion was that depression has to be monitored in the early stages of chronic renal failure.

In Italy, De Stefano et al⁴⁷ were unable to trace the rate of suicide even in dialyzed patients with depression.

Therapy

Levy et al^{21,48,49} and Kimmel et al⁷ recently have underlined that adequate primary care of patients with renal failure requires a knowledge of the major psychologic stresses, the diet, the procedure, the machine, the medications, and the relationship with the dialysis staff and the physicians. They advised optimization of dialysis therapy on the grounds of evidence-based medicine, which speaks for advanced technology of machine and membranes, the treatment of anemia, and the treatment of a calcium-phosphate imbalance. It also is extremely important for patients to start dialysis therapy on time. Late referral is associated with increased morbidity and mortality⁵⁰⁻⁵² and with worse scores for depression in comparison with patients who receive early referral.⁵³ This must be associated with prevention and psychiatric, psychologic, and psychosocial support. When necessary, pharmacologic treatment should be initiated.

There are many problems with the use of psychotropic drugs^{54,55} in renal failure. This is not only because of changes in pharmacodynamic and pharmacokinetic effects caused by loss of renal function. In fact, absorption is reduced, volume distribution is increased, and protein binding is reduced. The reduction in protein binding causes higher available drug levels.⁴⁸ Finally, deacetylation, acetylation, hydroxylation, O-demethylation, N-demethylation, conjugation, and sulfoxidation may be reduced. In renal disease, the reduction in excretion of drugs is a function of the fraction removed by the kidneys and by the degree of renal function. Therefore, it always is important to know the most simple clinical indicator of renal function, which is the plasma creatinine concentration.²⁹ Finally, the dialysis procedure per se may affect drug concentrations in plasma, but not in tissues, so that a rebound may occur after treatment.

Pharmacologic treatment of depression in renal disease is a topic receiving continuous input by everyday clinical practice.⁵⁶ Antidepressants should be used and should be part of the armamentarium of every nephrologist. For Levy et al,^{21,48,49} the dos-

age should not be more than two thirds of the maximum dose reached in patients with normal renal function. Kimmel et al⁷ suggested that antidepressants should be used for any patients meeting DSM-IV criteria and should be used at a dosage providing the maximum reduction in symptoms with the minimum of side effects.

Patients with ESRD usually respond to pharmacotherapy with few medication side effects. Tricyclic antidepressants (TCAs) and selective serotonin re-uptake inhibitors (SSRIs) have been used successfully in various studies.^{32,48,49,57,58} SSRIs, however, are associated with nausea, headache, insomnia, and nervousness. In the 1990s, TCAs were the drugs of choice, and some of them continue to be used such as nortriptyline. In fact, this drug has an anticholinergic effect, which is the lowest for the category and a favorable therapeutic window in the range of 50 to 150 ng/L. The use of antidepressants should be initiated only on the advice of a specialist, taking into account the possibility of drug interactions. The great majority of TCAs and SSRIs undergo extensive hepatic metabolism by the P-450 enzyme system.⁵⁹ This can lead to active metabolites such as norfluoxetine and nortriptyline, and nonactive metabolites as in the case of fluvoxamine and sertraline. Among SSRIs, several studies pointed out the use of sertraline, bupropion, and nefazodone.^{57,58} In these studies, medication doses were titrated carefully by the psychiatric investigators who took into account the clinical response and the side effects. Their mean BDI scores at the completion of the study were well below baseline values and a dramatic improvement in depressive symptoms was observed. This stresses the importance for treating depression in dialyzed patients.

Conclusions

Depression is a common but underdiagnosed and understudied problem in ESRD patients. In multiple studies in patients with chronic medical illnesses, it has been shown to increase symptom burden, to lead to additive function impairment, to increase medical costs, and to impair self-care and adherence. The available data on chronic renal failure patients with significant medical comorbidities are not sufficient. Therefore, it is important that the assessment of depression should be included in routine patient evaluations. On the other hand, researchers in the field of renal diseases should learn to distinguish major depression from high levels of depressive affect. Finally, there is a need for well-designed, longitudinal, survival analyses to clarify the relationship between depression and different stages of renal dysfunction.

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References

1. Maj M: Demoralizzazione, depressione e il problema della "soglia" per l'uso dei farmaci antidepressivi, in Pancheri P, Cassano GB (eds): *Il Punto Su: Specificità e Aspecificità Terapeutica dei Farmaci Antidepressivi*. Firenze, Scientific Press s.r.l., 1995, pp 101-114
2. Arieti S: I problemi fondamentali e l'orientamento psicologico, in Arieti

- S, Bemporad J (eds): *La Depressione Grave e Lieve*. Milano, Feltrinelli, 1981
3. Diagnostic and Statistical Manual of Mental Disorders, 4th edition, DSM-IV™. Washington, DC, American Psychiatry Association, 1994, pp 317-345
 4. Kimmel PL: Psychosocial factors in dialysis patients. *Kidney Int* 59:1599-1613, 2001
 5. Sacks CR, Peterson RA, Kimmel PL: Perception of illness and depression in chronic renal disease. *Am J Kidney Dis* 15:31-39, 1990
 6. Kimmel PL: Depression as mortality risk factors in hemodialysis patients. *Int J Artif Organs* 15:697-700, 1992
 7. Kimmel PL, Weihs K, Peterson RA: Survival in hemodialysis patients: The role of depression. *J Am Soc Nephrol* 4:12-27, 1993
 8. Kimmel PL, Peterson RA, Weihs KL, et al: Aspects of quality of life in hemodialysis patients. *J Am Soc Nephrol* 6:1418-1426, 1995
 9. Kimmel PL, Peterson RA, Weihs KL, et al: Psychologic functioning, quality of life and behavioral compliance in patients beginning hemodialysis. *J Am Soc Nephrol* 7:2152-2159, 1996
 10. Kimmel PL, Peterson RA, Weihs KL, et al: Psychosocial factors, behavioral compliance and survival in urban hemodialysis patients. *Kidney Int* 54:245-254, 1998
 11. Kimmel PL, Peterson RA, Weihs KL, et al: Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients. *Kidney Int* 57:2093-2098, 2000
 12. Kimmel PL, Peterson RA, Weihs KL, et al: Dyadic relationship conflict, gender, and mortality in urban hemodialysis patients. *J Am Soc Nephrol* 11:1518-1525, 2000
 13. Kimmel PL, Phillips TM, Simmens SJ, et al: Immunologic function and survival in hemodialysis patients. *Kidney Int* 54:236-244, 1998
 14. Shidler NR, Peterson RA, Kimmel PL: Quality of life and psychosocial relationships in patients with chronic renal insufficiency. *Am J Kidney Dis* 32:557-566, 1998
 15. Wright RG, Sand P, Livingston G: Psychological stress during hemodialysis for chronic renal failure. *Ann Intern Med* 64:611-621, 1966
 16. Glassman BM, Siegel A: Personality correlates of survival in a long-term hemodialysis program. *Arch Gen Psychiatry* 22:566-574, 1970
 17. Klein HE, Benkert O, Berger S, et al: Psychopathometrie depressiver verstimmungen bei chronischer Haemodialyse. *Arch Psychiatr Nervenkr* 230:339-349, 1981
 18. Foster FG, Cohn GL, McKegney FP: Psychobiologic factors and individual survival in chronic renal hemodialysis. A two year follow-up. *Psychosom Med* 35:64-82, 1973
 19. Smith MD, Hong BA, Robson AM: Diagnosis of depression in patients with end-stage renal disease. *Am J Med* 79:160-166, 1985
 20. Reichsman F, Levy NB: Problems in adaptation to maintenance hemodialysis. *Arch Intern Med* 130:859-865, 1972
 21. Levy NB: Psychiatric considerations in the primary medical care of the patients with renal failure. *Adv Ren Replace Ther* 7:231-238, 2000
 22. Israel M: Depression in dialysis patients: A review of psychological factors. *Can J Psychiatry* 31:445-451, 1986
 23. Kimmel PL: Depression in patients with chronic renal disease. What we know and what we need to know. *J Psychosom Res* 53:951-956, 2002
 24. Kaplan De-Nour A, Shanan J: Quality of life of dialysis and transplanted patients. A cross sectional study. *Nephron* 25:117-120, 1980
 25. Tews HP, Schreiber WK, Huber W, et al: Vocational rehabilitation in dialyzed patients. *Nephron* 26:130-136, 1980
 26. Kutner NG, Devins GM: A comparison of the quality of life reported by elderly whites and elderly black on dialysis. *Geriatr Nephrol Urol* 8:77-83, 1998
 27. Annen D: *Die Patienten der Baasler Heimdialyse*. Thesis, Basel, 1977
 28. Abram HS, Moore GL, Westervelt FB Jr: Suicidal behavior in chronic dialysis patients. *Am J Psychiatry* 127:1199-1204, 1971
 29. Kasturi LG, Wig NN, Chugh KS, et al: Psychiatric aspects of haemodialysis. *Ir Assoc Phys Ind* 12:399-406, 1976
 30. Strauch-Rahausser G, Schaffhleutle R, Lipke R, et al: Measurement problems in long-term dialysis patients. *J Psychosom Res* 21:49-54, 1977
 31. Pach J, Waniek W, Hartmann HG, et al: Haufigkeit und syndromatische ausgestaltung depressiver zustande unter chronischer hemodialyse. *Med Klin* 73:1691-1696, 1978
 32. Haffke E, Rajendran S, Egan JD: Dialysis, depression and antidepressants. *J Clin Psychiatry* 39:759-760, 1978
 33. Lowry RM: Frequency of depressive disorder in patients entering home hemodialysis. *J Nerv Ment Dis* 167:199-204, 1979
 34. Burke HR: Renal patients and their MMPI profiles. *J Psychol* 101:229-236, 1979
 35. Hong BA, Smith MD, Valerius TJ, et al: Depression pretreatment in end-stage renal disease. *Lancet* 1:104-105, 1982
 36. Cassileth BR, Lusk EJ, Strouse TB, et al: Psychosocial status in chronic illness. *N Engl J Med* 311:506-511, 1984
 37. Shulman R, Price JD, Spinelli J: Biopsychosocial aspects of long-term survival on end-stage renal failure therapy. *Psychol Med* 19:945-954, 1989
 38. Beck AT, Ward CH, Mendelson M, et al: An inventory for measuring depression. *Arch Gen Psychiatry* 4:561-571, 1961
 39. Cummings NB: Physician-assisted suicide: A care option for dying patients? *Nephrol News Issues* 10:40-41, 1996
 40. Levy NB: Psychosocial issues. *Dial Transplant* 25:678-684, 1996
 41. Levy NB: Psychiatric considerations in the primary medical care of the patients with renal failure. *Adv Ren Replace Ther* 7:231-238, 2000
 42. Beder J: Withdrawal from dialysis: Mobilization of the healthcare team. *Dial Transplant* 26:535-538, 1997
 43. Mailloux L, Bellucci AG, Napolitano B, et al: Death by withdrawal from dialysis: A 20-year clinical experience. *J Am Soc Nephrol* 3:1631-1637, 1993
 44. Nelson CB, Port FK, Wolfe RA, et al: The association of diabetic status, age and race to withdrawal from dialysis. *J Am Soc Nephrol* 4:1608-1614, 1994
 45. McKegney FP, Lange P: The decision to no longer live on chronic hemodialysis. *Am J Psychiatry* 128:267-274, 1971
 46. Leggat JE Jr, Bloembergen WE, Levine G, et al: An analysis of risk factors for withdrawal from dialysis before death. *J Am Soc Nephrol* 8:1755-1763, 1997
 47. De Stefano R, Fumagalli A, De Cecco G: Emodialisi e disturbo affettivo. *Riv Sper Fren* XCII:157-169, 1988
 48. Levy NB, Blumenfeld M, Beasley CM Jr, et al: Fluoxetine in depressed patients with renal failure and in depressed patients with normal kidney function. *Gen Hosp Psychiatry* 18:8-13, 1996
 49. Blumenfeld M, Levy NB, Spinowitz B, et al: Fluoxetine in depressed patients on dialysis. *Int J Psychiatry Med* 27:71-80, 1997
 50. Ratcliffe PJ, Phillips RE, Oliver DO: Late referral for maintenance dialysis. *BMJ* 288:441-443, 1984
 51. Junger P, Zingraff J, Albouze G, et al: Late referral to maintenance dialysis: Detrimental consequences. *Nephrol Dial Transplant* 8:1089-1093, 1993
 52. Innes A, Rowe PA, Burden RP, et al: Early deaths on renal replacement therapy: The need for early nephrological referral. *Nephrol Dial Transplant* 7:467-471, 1992
 53. Sesso R, Yoshihiro MM: Time of diagnosis of chronic renal failure and assessment of quality of life in hemodialyzed patients. *Nephrol Dial Transplant* 12:2111-2116, 1997
 54. Jacobson S, Pies RW, Greenblatt DJ (eds): *Handbook of Geriatric Psychopharmacology*. Washington, DC, American Psychiatric Publishing Inc, 2002
 55. Aronoff GRM, Berns JS, Brier M, et al (eds): *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults* (ed 4). Philadelphia, American College of Physicians, 1999
 56. Jacobson S: Psychopharmacology: Prescribing for patients with hepatic or renal dysfunction. *Psychiatric Times* XIX:19, 2002
 57. Wuerth D, Finkelstein SH, Ciarcia J, et al: Identification and treatment of depression in a cohort of patients maintained on chronic peritoneal dialysis. *Am J Kidney Dis* 37:1011-1017, 2001
 58. Finkelstein FO, Finkelstein SH: Depression in chronic dialysis patients: Assessment and treatment. *Nephrol Dial Transplant* 15:1911-1913, 2000
 59. Green AR, Nutt DJ: Antidepressants, in Grahame-Smith DJ, Cowen PJ (eds): *Psychopharmacology 1, Part 1: Preclinical Psychopharmacology*. Amsterdam, Excerpta Medica, 1983, pp 1-37