

Pharmacological and non-pharmacological treatment options for depression and depressive symptoms in hemodialysis patients

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Abstract

Depression is a mental disorder with a high prevalence among patients with end stage renal disease (ESRD). It is reported that depression afflicts approximately 20-30% of this patient population, being associated, amongst other, with high mortality rate, low adherence to medication and low perceived quality of life. There is a variety of medications known to be effective for the treatment of depression but due to poor adherence to treatment as well as due to the high need for medications addressing other ESRD comorbidities, depression often remains untreated. According to the literature, depression is under-diagnosed and undertreated in the majority of the patients with chronic kidney disease. In the current review the main pharmacological and non-pharmacological approaches and research outcomes for the management of depressive symptoms in hemodialysis patients are discussed.

Introduction

End stage renal disease (ESRD) treated with hemodialysis (HD), is often associated with several comorbidities like hypertension, heart diseases, musculoskeletal problems and diabetes mellitus.¹ Patients receiving HD therapy exhibit low levels of perceived quality of life, usually accompanied by significant emotional distress characteristics such as symptoms of depression and anxiety.² According to the literature, depression is the most common mental disorder in HD patients affecting approximately the 20% of this specific patients group and reported to be the second only to hypertension in frequency as a comorbid diagnosis.³⁻⁵ The last decade, nephrologists have looked systematically for signs of depression since depression is recognized as an important factor which

among others, influences the overall health status and survival of the patient.⁶

The aim of this review is to describe and cover in critical fashion the various treatment options available for the management of depression in patients receiving HD therapy and whether those regimes are effective in improving patients' mental health.

Depression in hemodialysis patients

Definition

According to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DMS-IV), depression is defined by having a loss of pleasure or interest for at least a two week period, accompanied by 5 or more psychological, somatic and behavioral symptoms. It is noteworthy that the World Health Organization ranks depression as the leading cause of disability and the fourth leading contributor to the global burden of disease in 2000 worldwide.⁷ The same organization's projections indicate that depression will be the highest ranked cause of disease burden in developed countries by the year 2020. Sadness, emotional inhibitions, fatigue, sleep disturbances, loss of concentration, intense guilt, and thoughts of suicide or death are some of the symptoms associated with major depression while thoughts of suicide and death are particular symptoms that are of great concern for the general public.^{8,9}

Epidemiology

According to the World Health Organization (WHO) depression is considered to be the second most common condition in the general population with the reported prevalence of lifetime depression to be around 16%.¹⁰ Research findings suggest that the prevalence of depression in the general population is about 12-20%,¹¹ with women reporting higher scores compared to men. In a large WHO study with 245,404 participants from 60 countries from all regions of the world, the prevalence of depression based on ICD-10 criteria was 3.2%, while interestingly, in patients with one or more chronic disease the prevalence of depression climbed between 9.3% and 23.0%.¹² In a very recent cross-national study from 18 countries the average lifetime and 12-month prevalence of depression were 14.6% and 5.5% respectively in the high-income counties and 11.1% and 5.9% respectively in the low- to middle-income countries.¹³ Depression is one of the most common psychiatric abnormalities in patients with ESRD,^{14,15} affecting approximately 20-30% of the patients,¹⁶⁻¹⁸ with some studies reporting even higher percentages.¹⁹

Etiology of depression in hemodialysis patients

Causes of depression are linked also to the

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dialysis treatment *per se*, which requires from a patient to stay attached to the dialysis machine for approximately 4 hours, 3 times a week, a necessity that contributes significantly to a patient's low quality of life and restricts independent living.²⁰ It is noteworthy that health care providers frequently fail to identify and/or treat depression in HD patients (70%) despite the high prevalence of the disease.²¹ In addition, factors such as medication side effects and dietary restrictions may further contribute to the impaired levels of perceived quality of life and the emotional distress experience by the HD population, leading to more severe symptoms.^{22,23} Other factors that could be blamed for the high prevalence of depression in HD patients are social in nature such as work loss, alterations in one's family role, experience of multiple losses, medication adherence,^{14,23-25} low monthly income, years on dialysis and unemployment.^{26,27} Further, there is some evidence suggesting that depression in HD patients could be the result of factors such as a decline in cognitive skills and sexual function,^{28,29} as well as low education levels.³⁰ It's important to recognize that HD patients face many additional challenges which increase the possibility of developing depression or anxiety or other mental conditions. Patients experience major changes in their lifestyle. On the one hand they have very limited, if any, alternative options to the proposed or available treatment of their end-stage renal disease state

(which requires strict compliance to their dialysis and medicinal regime). This includes having to adjust to a rigorous dietary prescription and a very limited fluid intake. On the other hand, it also becomes a challenge for many HD patients to maintain meaningful life roles regarding employment, family life, and friendships. HD patients have not only to cope with the anger, fear, anxiety, frustration, and sadness of having a serious chronic illness but have also to accept a curtailment of their independence. Finally they have to confront their own mortality and the likelihood of a shortened life span.³¹ Depression in HD patients is characterized by both cognitive and somatic features. The problem is that somatic features of depression such as anorexia, sleep disturbances, fatigue and gastrointestinal disorders, are also common symptoms of uremia.^{32,33} For this reason there is added difficulty in diagnosing depression in HD patients, *i.e.* the identifying a mental illness against the backdrop of the physical illness.^{14,34-36} It is also challenging to distinguish the *non-uremia induced* depressive symptoms from known uremic-induced symptoms such as irritability, cognitive dysfunction, or mild symptoms of encephalopathy or from drug effects or symptoms of inadequate dialysis. It is noteworthy that depression as a mental disorder when it coexists with another psychiatric or medical illness, may render depression relatively to treatment.^{14,35-38}

Research questions and search strategy

The primary questions of this review were: what are the main pharmacological and non-pharmacological approaches and research outcomes for the reduction of symptoms of depression in HD patients? The following databases were searched: MEDLINE, PUBMED, PsycINFO and SCOPUS. The keywords used were: hemodialysis, end stage renal diseases, renal failure, depression, depressive symptoms, pharmacological, non pharmacological, alternative medicine, exercise, medication, drugs, quality of life. We organized our evaluation of the literature in the following sections: measurement of depression, treatment options including pharmacological management, 1st generation antidepressants, 2nd generation antidepressants, non-pharmacological management, including psychotherapeutic approach, alternative therapeutic approaches and exercise. We strived to gather information pertaining to ESRD-HD patients but when not available we report on studies within the chronic renal disease spectrum.

Measurement of depression

The *Beck Depression Inventory* (BDI) is one of the most established instruments used to measure the presence and severity of depression. It is a 21-question inventory developed to measure the degree and severity of the depression's symptoms.³⁹ A score of 14-16 or more has been reported to be an accurate measure for the diagnosis of depression in the HD population and has been successfully used, in its original or revised forms.⁴⁰ Also, one of the most frequently used personality tests is the *Minnesota Multiphasic Personality Inventory* (MMPI).⁴⁰ It's a self-report instrument and contains 566 positive statements dealing with thoughts, feelings, attitudes, physical symptoms and quality of life.^{41,42}

Many times instruments assessing aspects of quality of life (QoL) are also used for assessing mental health. The most common questionnaire found in the literature is the *SF-36 questionnaire* – a self-administered instrument containing 36 items,⁴³ which assesses health related QoL on eight multi-item dimensions, including vitality and mental health.

In clinical practice, the *Nine-Question Patient Health Questionnaire* (PHQ-9),⁴⁴ a self-report instrument, is often used to detect five common mental disorders in primary care: depression, anxiety, alcohol abuse, somatoform disorder, and eating disorder. Another instrument used for measuring depression is the *Hamilton Rating Scale for Depression*.⁴⁵ The questionnaire lists 21-items and rates the severity of symptoms observed in depression such as low mood, insomnia, agitation, anxiety and weight loss.⁴⁶ Moreover, an appropriate tool for assessing depressive symptomatology in the general population is the *Center for Epidemiologic Studies Depression Scale* (CED).⁴⁷ A self-report questionnaire, that contains 20 items and asks caregivers to rate how often over the past week they experienced symptoms associated with depression, such as restless sleep, poor appetite, and feeling lonely. Additionally, the *Zung Self-Rating Depression Scale* contains 20 items,⁴⁸ ten positively worded and ten negatively worded questions, assessing the level of depression or depressive symptoms.^{49,50}

Treatment options

According to the literature, depression is not only under-diagnosed, but it is also undertreated in patients with chronic kidney disease.⁵¹ In the following text, the main pharmacological

and non-pharmacological approaches and research outcomes for the reduction of depression symptoms in HD patients are discussed.

Pharmacological management

Multiple classes of medications are available for treatment of depression in the patient with chronic diseases. Despite the availability of high-tech brain imaging systems, health care providers have to prescribe antidepressants using their clinical judgment and other factors such as effectiveness, toxicity, expense, and ease of administration. Most studies support that low doses of antidepressant medications can have therapeutic results in patients maintained on dialysis (Table 1).⁵²⁻⁶⁷ *There are 2 classes of medication with proven benefits for the depressed patient divided in 1st and 2nd generation.*

First generation antidepressants

Desipramine and tricyclic antidepressants (TCAs) are used orally for treating major depressive disorder. TCAs have been used clinically to treat patients with major depressive illness since the early 1960s. In a small study, the use of TCAs showed a positive effect in HD patients' levels of depression while in a study by Lee and colleagues (2004),⁵⁴ antidepressant treatment decreased the serum level of interleukin-beta1 and increased the serum level of interleukin-6 improving patients' depression symptoms' severity with parallel improvements in various immunological and nutritional indices.⁵⁴ Other pharmacological options for the treatment of depression include monoamine oxidase inhibitors (MAOI) and reverse inhibitors of MAO.^{28,68,69}

Second generation antidepressants

The second generation of antidepressants consists of a category called selective serotonin reuptake inhibitors (SSRIs) including venlafaxine, mirtazapine, bupropion, nefazodone, duloxetine, fluoxetine and fluvoxamine. These act on the central nervous system through their effects on neurotransmitters such as serotonin, norepinephrine, or dopamine. Koo and colleagues (2005) examined the effect of antidepressant treatment in HD patients treated with paroxetine for 8 weeks and found a significant improvement in depressive symptoms.⁵⁵ In one study the safety of fluoxetine in patients with kidney disease was assessed. Specifically nine depressive patients with normal renal failure and seven HD patients were given fluoxetine 20 mg/d in an 8 week study. Depression was assessed by HAMD-17, BDI, Montgomery Asberg Depression Rating Scale, Brief Symptom Inventory, Global Well-being Scale, and the Electronic Visual Analog Scale before, during

and at the conclusion of the 8-week study period. Five of six patients in both the ESRD group and the normal renal function group experienced significant decreases in their overall depression scores with an approximately 25% reduction in the HAMD-17 score.⁵⁷

In another study, the authors found that 8 weeks of SSRIs treatment was enough to improve depression with a concomitant improvement in quality of patients' life.⁵⁶ A year later Kalender *et al.*, (2007) treated HD, peritoneal dialysis and pre-dialysis patients with citalopram, and found very similar results.⁷⁰

Non-pharmacological management

There is a wide spectrum of non-pharmacological and psychotherapeutic techniques for the management of depression in HD patients.⁷¹ In the text below the main non-pharmacological treatment options are discussed exploring in depth their effectiveness and potential for use in this group of patients.

Psychotherapeutic approach

Cognitive Behavioral Therapy (CBT) can be characterized as a comprehensive system of psychotherapy which combines both behavior theory and cognitive learning theory and implements strategies to change chronic patients' way of thinking and attitudes.^{72,73} Current evidence shows that depression is an important target of psychological assessment in HD patients, further supported by evidence showing a significant improvement in the mood of these patients.⁵⁸ Consistent with previous studies, HD patients who had the opportunity to engage in cognitive behavioral therapy and to share their feelings concerning their disease, exhibit lower levels of depression and stress.⁷⁴ Similar improvements were presented in the study by Lii *et al.*, where group therapy successfully reduced patient's depression symptoms.⁵⁹ Furthermore, support from the family and the immediate social circle can decrease depression symptoms by improving

patients' self-esteem.⁷⁵

Recently, a structured psychological intervention was successfully applied in ESRD patients resulting in significant improvements in emotional distress indices such as depression, anxiety and worries thoughts leading to a parallel improvement of patient's QoL score.⁶⁰

Relaxation and imagery techniques have been successfully applied in patients with chronic disease in order to reduce depression symptoms.⁶¹ However, it seems that those techniques may not be as effective in HD patients, despite the fact that the patient's adherence to interventions and their self-satisfaction was significantly improved.⁷⁶ Tsay and Hung (2004) examined the effects of an empowerment intervention program in HD patients indicating a significant improvement both in depression symptoms as well as in self-care and self-efficacy of the participants.⁶² Even though these techniques look very promising for the amelioration or therapy of depres-

Table 1. Overview of depression treatment in hemodialysis patients.

Reference	Intervention	Diagnosis	Period	Methodology	Outcomes
Wuerth <i>et al.</i> ⁵²	7 (patients) sertraline, 2 bupropion, 2 nefazodone	Clinical depression	12 weeks	BDI, HAMD, psychiatric interview	Improvement in depressive symptoms
Kennedy <i>et al.</i> ⁵³	Antidepressant therapy (not stated)	Major depression	7 weeks	BDI, HAMD, MMSE, standardized antidepressant, side effect checklist	Significant recovery in five patients, improvement in one, and discontinuation of therapy in the remaining two
Lee <i>et al.</i> ⁵⁴	20 mg of fluoxetine	Depressed mood	8 weeks	HAMD	>50% reduction in the score of the HAND
Koo <i>et al.</i> ⁵⁵	Paroxetine 10 mg/day	Not specified	8 weeks	BDI	Changes in depression and nutritional status
Turk <i>et al.</i> ⁵⁶	Sertraline HCl, 50 mg/day	Patients who had BDI score ≥ 15 were diagnosed as depressed	8 weeks	BDI	Improvement in QoL
Levy <i>et al.</i> ⁵⁷	Fluoxetine 20 mg/day	Depression	8 weeks	DSM-III-R, HAMD-17	Improvement in depressive symptoms
Koo <i>et al.</i> ⁵⁵	Paroxetine 10 mg/day	Depressive symptoms	8 weeks	BDI, HAMD	Improvement in depressive symptoms and nutritional status
Turk <i>et al.</i> ⁵⁶	Sertraline HCl, 50 mg/day	Depression	8 weeks	BDI	Improvement in QoL
Duarte <i>et al.</i> ⁵⁸	Cognitive-behavioral therapy	Major depression	3 months	BDI, SF-36	Improvement in depressive symptoms
Lii <i>et al.</i> ⁵⁹	Psychosocial intervention	depression	2-months	BDI, SF-36	Depression symptoms and QoL improved significantly
Rocha <i>et al.</i> ⁶⁰	No regular psychological intervention	Depressive symptoms	No details	HADS	A significant reduction of depression symptoms
Jorm <i>et al.</i> ⁶¹	Relaxation techniques	Depressive symptoms	No details	CCDAN	Effective at reducing self-rated depressive symptoms
Tsay <i>et al.</i> ⁶²	Empowerment program	Depression	6 weeks	BDI	Improvement in depressive symptoms
Cho <i>et al.</i> ⁶³	Acupressure with massage	Depression	4 weeks	BDI	Improvement in depressive symptoms
Kim <i>et al.</i> ⁶⁴	Music therapy	Depression	No details	No details	Improvement in depressive symptoms
Babiyak <i>et al.</i> ⁶⁵	Aerobic exercise (3 times per week) & sertraline therapy	Major depressive disorder	6 months	HRSD	Improvement in depressive symptoms
Kouidi <i>et al.</i> ⁶⁶	Intradialytic exercise	Emotional distress	1 year	BDI, HADS	Exercise training reduced emotional distress
Jung <i>et al.</i> ⁶⁷	Aerobic and resistance exercise	-	8 weeks - 12 months	SF-36	Aerobic and resistance exercise improved depression, and health-related QoL

BDI, Beck depression inventory; MMSE, mini mental state exam; MH (SF36), mental health (short form health survey 36); HADS, hospital anxiety and depression scale; RAND 36, RAND 36-item health survey; CCDAN, the cochrane collaboration depression, anxiety and neurosis review group; HRSD, Hamilton rating scale for depression; QoL, quality of life.

sion, more research is needed on their effectiveness in dialysis and other chronic disease patients.

Alternative therapeutic approaches

Alternative therapeutic approaches have always been attractive to chronically ill mental patients since they satisfy their urge for trying and using new ways for relieving their mental and emotional symptoms and at the same time they allow patients to detach themselves from their current medication and possible invasive methods of therapy. For instance, the effectiveness of acupressure with massage in ameliorating fatigue and depression in HD patients was examined by Cho and Tsay (2004). Interestingly, the acupressure group reported significantly greater improvements on both fatigue and depression symptoms than the respective group of patients who received the regular unit care.⁶³ Melody and rhythm are two special ways to express feelings and emotions and could be considered as an alternative way of depression treatment. Kim and colleagues (2006) showed that patients treated with music therapy reported a lower score in depression levels compared to the control group who received no therapy.⁶⁴ The positive impact of music on emotional distress indices was confirmed in a very recent study by Lin *et al.*, where the authors observed that the patients who listened to music during the dialysis sessions exhibited significant reductions in perceived stressors and adverse reactions, a fact that led the authors to conclude that music could be beneficial for promoting wellbeing in HD patients.⁷⁷

Exercise training

Low levels of physical activity have been associated with depression.⁷⁸ Aerobic and resistance exercise have beneficial effects on dialysis patients' well-being. Specifically aerobic exercises improve not only physical functioning but also improved nutritional status, hematological indices, inflammatory cytokines, depression, and health-related QoL.¹⁵ For example, depressive HD patients who participated in a moderate aerobic exercise program improved their depressive symptoms and had lower relapse rates compared with patients that received sertraline.^{65,79} Kouidi *et al.*, (2010) examining the effect of exercise training on Heart Rate Variability and depression in HD patients, reported a beneficial effect of an intra-dialytic exercise program on both mental and cardiac autonomic disturbances.⁶⁶ Also the same researchers showed a relationship between depression and cardiac autonomic dysfunction.⁶⁶ Moreover, in HD patients with significant motor symptoms (restless legs syndrome) and sleep problems (sleep apneas and periodic leg movements), which also affect mental health, exercise has

been shown to improve symptomatology, reduce depressive symptoms, and improve QoL.^{80,81}

Based on such and other beneficial results of exercise, many research groups suggest that exercise should be a mandatory not an optional intervention in HD patients because of its beneficial effects on the overall health of this population.^{15,67}

Conclusions

Hemodialysis patients suffer from many physical and mental conditions. Depression is the most common psychological disorder encountered in 20-30% of HD patients. While *hemodialysis is indisputably a life-sustaining treatment for end-stage renal patients it also has an adverse impact on the mental status of these patients.*

Depression in HD patients results in poor QoL and higher mortality risk and therefore the need for its successful treatment should receive special attention from nephrologists and other specialists involved in renal patients' care. Many medications have been shown to be effective for the treatment of depression but due to patient's poor adherence in treatment as well as due to the high need for medication related to the other comorbidities, depression often remains untreated. To cope with depressive symptoms and improve overall QoL, it becomes imperative to implement a multidimensional approach that includes different intervention strategies.

Treatment of depression should be administered by a team of professionals (psychologists, nurses, physicians, social workers and others) applying different regimes and strategies to provide a better care for the hemodialysis population. It should be noted that the dialysis environment could be an ideal place to observe mood changes, behavior and mental status, however, dialysis units do not usually provide the appropriate privacy for discreet discussions between the patients and health care providers.

In conclusion, depression is a disease that needs to be treated the earliest possible in the life of a hemodialysis patient since it can affect his or her QoL and overall survival. More research is needed to further explore the effectiveness and safety of trusted or new methods for the treatment of depression and depressive symptoms in HD patients.

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