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Depression on Dialysis

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Depression · End-stage renal disease · Dialysis · Beck depression inventory · Criterion contamination

Abstract
Depression is the most common psychopathological condition among patients with end-stage renal disease (ESRD), yet it is still under-recognized and misdiagnosed. Depression reduces quality of life and has a negative clinical impact upon sufferers with chronic illness, including ESRD. This article discusses the negative effects of depression among the ESRD population treated with dialysis, the prevalence of the condition, the methodological issues involved with screening and treatment, and the possible psychological and somatic causes. There is a need to identify the prevalence of the disorder by effective methods, overcome the current issues surrounding depression assessment and to undertake trials of suitable treatments.

Introduction

End-stage renal disease (ESRD) has a significant impact upon the lives of sufferers. The experience of multiple losses, including kidney function, family role, work role, sexual function, time and mobility, impact significantly on the lives of patients [1, 2]. Further stressors, including medication effects [3], dietary constraints, fear of death and dependency upon treatment [4–7], may affect quality of life and exacerbate feelings of a loss of control. It has been widely claimed that depression is the most common psychopathological condition among patients with ESRD [2, 3, 8, 9]. While prevalent, depression is still often unrecognized [10], reflecting a lack of routine psychological evaluation among this patient population [11]. The consequences of missing depression among dialysis patients may be considerable. Comorbid depressive illnesses amplify the impact of chronic illnesses, and increase functional disability and the use of health care services [12]. This article discusses the prevalence, the issues surrounding screening and treatment, and the possible causes and consequences of depression in the dialysis population.

Assessing Depression among Chronically Ill Populations: The Issue of Criterion Contamination

Major depressive disorder is defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), as having a loss of pleasure or interest for 2 weeks, accompanied by 5 or more psychological, somatic and behavioural symptoms. Sadness, emotional inhibitions, lack of energy, sleep disturbances, loss of concentration, intense guilt, and thoughts of suicide or death are some of the symptoms associated with major depression. Thoughts of suicide and death are particular symptoms that are of obvious concern.

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Depression assessment can involve screening or diagnostic assessment. Diagnosis can be undertaken using a diagnostic criterion such as DSM-IV or the International Classification of Diseases (ICD-10). Trained professionals conduct diagnostic assessments typically via structured or semi-structured interviews. Depression screening tools are usually self-reports, requiring the patient to rate symptom frequency or severity. Screening tools employ cut-offs, which are used to indicate depression or significant depressive symptomatology, typically classifying patients by symptom severity (mild, moderate or severe). While screening tools are easier to administer, with several validated against diagnostic criteria, they cannot be used to diagnose clinical depression (major depressive disorder) or other depressive disorders. Whether employed in research or clinical practice, depression assessments differ technically with regard to their diagnostic potential, and different screening tools have varied sensitivities and specificities across different populations.

When applied to chronically ill populations, both screening tools and diagnostic schemes are sensitive to criterion contamination, in that they include somatic enquiry, which overlaps with the symptomatology of physical illness. With regard to ESRD, the somatic ramifications of uraemia, including fatigue, sleep disorders and reduced appetite, are also somatic indicators of depression [13]. A patient with significant uraemic symptoms will score highly on these elements. Consequently researchers and clinicians are left in a predicament about whether these somatic symptoms are the result of depression, illness or a combination of both. The issue of criterion contamination is not unique to ESRD, and impacts upon a range of conditions [14]. It is probable that criterion contamination interferes with depression screening in most, if not all, medical illnesses to varying degrees. Between 50 and 80% of medical inpatients report somatic complaints, including psychomotor retardation, fatigue, anorexia, weight loss and insomnia [15, 16]. Whether these overlapping symptoms should be removed, substituted or included in the diagnostic scheme remains open to debate [17]. Contamination is also encountered in the evaluation of less severe psychological symptoms. Cavanaugh et al. [18] found that one third of non-depressed medically ill patients reported significantly more irritability, sadness, crying, mild pessimism, indecisiveness and dissatisfaction compared to healthy individuals. These milder symptoms have been attributed to an emotional response to the stress of illness and hospitalization [16]. The severer cognitive symptoms including depressed mood, guilt, loss of interest and concentration difficulties have been associated with major depressive disorder (DSM-III-R) in the ESRD population [19]; thus, they may be suitable discriminators for the disorder in this population.

In an attempt to reduce the influence of somatic factors in the assessment of depression, the Cognitive Depression Index (CDI) [20], a subscale of the Beck Depression Inventory (BDI) with somatic questions excluded, has been employed. Sacks et al. [20] suggest that the CDI might be a better predictor of depression due to the reduction of confounding symptoms. However, there is little evidence that the cognitive and somatic elements of depression can be separated using the CDI [1, 3, 21]. Drayer et al. [22] found that depressed dialysis patients report more somatic symptoms than non-depressed ones, and that physical symptoms relate more closely to depression than medical comorbidity [23]. In our pilot study of haemodialysis (HD) patients, we found that the BDI (including somatic enquiry, using a cut-off $\geq$16) had greater sensitivity (88.9%) and specificity (87.1%) as compared to a diagnostic interview, than the CDI (excluding somatic enquiry, cut-off $\geq$10, sensitivity 77.8% and specificity 80.6%) [24].

In addition to determining the most effective depression screening tool, the procedure for screening also requires attention, which our recent study goes someway to addressing. We found that administering the BDI to dialysis patients while they received their treatment agreed highly with off-dialysis assessments [24]. Interestingly, on-dialysis assessments lead to slightly increased somatic scoring; thus, they may reduce false-negative cases, albeit via increased false-positives. When screening a population, it is certainly more favourable to have a tool that reduces false-negatives as opposed to increasing them. Evidence from our research suggests that on-dialysis BDI assessments are a practical method for screening HD patients, improving the detection and monitoring of depression symptoms.

The Prevalence of Depression among the Dialysis Population

It is estimated that depression is the second most common condition encountered in general practice (World Health Organization), with the lifetime prevalence reported to be 16.2% [25]. Among the medically ill, depression is a common concern accounting for half of the identified psychopathology [26].

Table 1. Prevalence of depression among renal dialysis patients, employing screening or diagnostic schemes

Study	Measure/cut-off	Population	Prevalence %	95% confidence interval, %	n
Lowry and Atcherson [27]	American Psychiatric Association criteria	Initiating home HD	18	11.1–27.8	83
Smith et al. [28]	BDI Multiple Affect Adjective Check List DSM-III	HD, PD	47 17 5	34.7–59.7 9.4–28.7 1.7–13.9	60
Wuerth et al. [29]	BDI ≥11	PD	49	44–54	380
Wilson et al. [30]	BDI ≥14 Nurse Nephrology team	HD	38.7 41.9 24.2	30.5–47.6 33.5–50.8 17.5–32.5	124
Sacks et al. [20]	BDI ≥16	HD, PD	26	16.2–38.9	57
Kimmel [1]	BDI >15 BDI >10	HD	24.7 46.4	20.1–29.9 40.8–52.1	300
Lopes et al. [31]	CES-D ≥10 Physician diagnosed	HD	43.0 13.9	41.8–44.2 13.1–14.7	6,987
Craven et al. [19]	Diagnostic Interview Schedule III	HD, PD	8.1	4.1–15.3	99
Martin et al. [32]	HADS ≥8	HD PD	71.4 25	52.1–85.2 16.3–36.3	28 72
Boulware et al. [33]	MHI-5 ≤52 (baseline) MHI-5 ≤52 (over time)	HD, PD	19 24	16.6–21.7 21.3–26.9	917
Lopes et al. [34]	Physician diagnosed 'Down hearted and blue question'[1] 'So down in the dumps …'[1]	HD	17.7 21.5 19.5	16.5–18.6 20.4–22.7 18.4–20.6	5,256 4,881 4,901
Drayer et al. [22]	Primary Care Evaluation of Mental Disorders	HD	28	18.2–40.5	62
Hinrichsen et al. [35]	Research diagnostic criteria – minor/major depressive disorder	HD	17.7 6.5	11.9–25.4 3.3–12.3	124
Hedayati et al. [36]	Structured Clinical Interview DSM-IV	HD	26.5	18.7–36.1	98
Kalender et al. [37]	Structured Clinical Interview DSM-IV	HD PD	33.8 12.8	23.5–45.9 5.9–25.6	68 47
Watnick et al. [10]	Structured Clinical Interview DSM-IV	HD, PD	19	11.0–30.7	62

MHI-5 = Subscale of Medical Outcomes Study Short Form 36; CES-D = Centre for Epidemiological Studies Depression Screening Index.

[1] Unconventional approach – questions taken from the Kidney Disease and Quality of Life Short Form.

It has been suggested that approximately 20–30% of the ESRD population suffer from depression [1, 8, 22, 38], although research has tended to focus on the HD population and neglected patients receiving peritoneal dialysis (PD). The exact prevalence remains contentious, as evidenced by the wide variations reported in the ESRD literature (table 1). Indeed, there is much variation regarding the prevalence of depression among medically ill patients, ranging from 15 to 61% [39]. A recent investigation reported that 38.8% of HD patients screened using the BDI scored ≥14 [30]. A similar prevalence was reported by Martin et al. [32] after screening dialysis patients with the Hospital Anxiety Depression Rating Scale (HADS). Defining depression as 'a HADS depression score of ≥8' led to 34.4% of patients meeting this criterion. However, when using a more stringent score (HADS depression

score ≥11), the prevalence was reduced to only 6.3% [32].

The variation in reported prevalence changes with the type of assessment undertaken and is dependent upon which depression definition is used. Depression screening tools often reveal a higher prevalence compared with diagnostic interviews. Although self-report screening measures, including the BDI, have been validated against well-established psychiatric methods in dialysis patients [8, 10, 40], the most accurate way of screening for depression (without professional evaluation) remains largely unresolved [1, 2, 28], and is predominantly influenced by the issue of criterion contamination. Watnick et al. [10] used the Structured Clinical Interview for Depression (DSM-IV), and reported that 19% of dialysis patients satisfied the DSM-IV [41] criteria for depression. Whilst the type of diagnostic or screening criteria employed may contribute to the varied level of reported prevalence [28, 42], there are also issues relating to statistical power. In a classic comparative study of dialysis patients, Smith et al. [28], using the BDI, demonstrated that 47% of patients satisfied the cut-off for depression, compared to 17% using the Multiple Affect Adjective Checklist and only 5% via a professional psychiatric evaluation. Contention still remains regarding the preferred depression screening tool/technique for the dialysis population. Using an existing or modified depression tool (BDI for example) for the dialysis population is viable. A more ideal, yet problematic, task would be to develop a specific depression assessment tool for the dialysis population. Currently, this work is unlikely to succeed until we improve our understanding of the issues surrounding depression assessment in patients with a chronic illness.

Mortality and Depression among the Dialysis Population

Mortality related to major depression among the general population has been highlighted empirically in several studies [43], despite some methodological issues. Research has shown that depression increases the risk of mortality, particularly via cardiovascular disease [43]. This association has an obvious severe implication for patients with ESRD, as cardiovascular disease remains the largest cause of death among this patient population [44]. The psychological and somatic effects of depression can complicate chronic illness [1, 2], reduce quality of life [37, 45, 46], reduce the motivation to maintain self-care and increase hospitalization rates [34]. The association between depression and immune function is well recognized [47–49]. In ESRD, significant associations have been reported between depression, immune parameters and mortality [45], although some of the data is limited and conflicting [50]. Immune dysfunction may impact upon infection, which is the second largest cause of death among the ESRD population [51]. Furthermore, research has shown significant associations between depression and nutritional status, which could mediate the relationship between depression and mortality in this population [45, 52].

The association between depression and mortality, in both HD and PD, has been demonstrated in several studies [1, 2, 21, 34, 53–57]. Einwohner et al. [55] administered the Zung Depression Scale to a sample of PD patients, and reported that depression independently predicted patient mortality after controlling for serum albumin and comorbidity. Shulman et al. [58] investigated the 2-year survival of HD patients, and found those who had a BDI score of <14 had an 85% survival rate, whilst for those who scored >25 the survival rate was 25% [58]. In a recent study, depression in HD patients predicted mortality after controlling clinical and sociodemographic variables [22]. The Dialysis Outcomes and Practice Patterns Study, a large international cohort study of dialysis patients, demonstrated that depression was independently related to mortality and hospitalization [34], albeit utilizing an unconventional depression screening tool [42]. Kimmel et al. [21] adopted a more conventional approach, administering the BDI and CDI to HD patients at 6-month intervals (mean number of assessments = 2.9 ± 1.7). Using time-varying covariate analysis, they found that both the BDI and CDI predicted mortality, with relative risks of 1.24 and 1.18, respectively. Other studies support an association between the CDI and mortality among dialysis patients [59]. However, several authors have failed to find an association between depression and mortality in dialysis patients [60–62], suggesting the need for further study. These reported variations may implicate differences in study designs, screening tools employed, populations studied and statistical methods used. In a recent longitudinal study of dialysis patients (HD and PD), Boulware et al. [33] investigated the relationship between depressive symptoms, cardiovascular events and mortality. Time-varying models demonstrated that the symptoms of depression were associated with increased all-cause mortality, cardiovascular disease mortality and cardiovascular events, whereas baseline measures were not. However, the significance of these associations was reduced after deploying a 6-month time lag in the analy-

sis. This implies a role for comorbidity in the genesis of depression, rather than depression leading to increased morbidity. This example of reverse causality may help explain some of the previously reported variation [3].

Suicide contributes to the mortality rate associated with major depression. The lifetime suicide risk associated with major depression is estimated to be around 3.4% [63]. Among the dialysis population suicide accounts for around 0.2 deaths per 1,000 patient-years [42, 64]. A recent study of suicide among the United States ESRD programme revealed the standardized incidence ratio of suicide to be 1.84 (95% CI 1.5–2.27). This equates to an 84% higher suicide risk compared with the general population [64]. Approximately 20% of ESRD patients choose to withdraw from dialysis treatment [1, 65, 66], and this is associated with multiple factors including chronic medical comorbidity [67, 68], age [69], ethnicity and gender [67]. The influence of depression upon the decision to withdraw from dialysis treatment has received little attention. A recent study showed that depression was a significant risk factor for withdrawal from HD, even after controlling for age and other clinical variables [71]. Ganzini et al. [72] proposed that patients with major depression should not be encouraged to make a decision about withdrawal until after a period of antidepressant treatment. Whether withdrawal is independently influenced by depression is a complex and controversial issue. Cohen et al. [73] proposed that other neuropsychiatric disorders such as dementia were more relevant than depression in influencing withdrawal decisions. The association between depression and withdrawal from dialysis requires further study. Around 20% of ESRD patients suffer from depression [1, 8, 29, 74], whilst a similar proportion choose to withdraw from dialysis [1, 65, 66]. Researchers need to define the degree of overlap.

Treatment Modality and Depression

Successful transplantation is associated with reduced levels of anxiety and depression compared with those experienced by dialysis patients [75, 76]. The impact of the dialysis modality on the prevalence of depression has yielded contradictory findings [32, 77, 78] and has not been extensively explored. It has been suggested that the prevalence and severity of depression was significantly lower in patients receiving PD compared with those on HD [37]. Feelings of control (health locus of control) may provide a partial explanation for such differences. Wuerth et al. [79] studied the modality choice of PD patients and reported the main reason for choosing PD was that it offered more autonomy and control. Other significant factors included the preference to undertake dialysis at home and the increased flexibility of dialysis schedule afforded by PD [79]. In another study, 85% of PD patients rated their care as excellent compared to 56% of HD patients [80]. The perceived feelings of control and social support may be influenced by the characteristics of a particular dialysis modality. These differences and their relationship to the prevalence of depression merit further study.

Causes of Depression

The aetiology of depression among general and chronically ill populations is multifactorial relating to social, psychological and biological mechanisms. The high prevalence of depression among the chronically ill reflects significant and prolonged changes to the social environment, psychological state, physical ability and pathology. The multiple stressors associated with ESRD may have profound effects on depressive symptomatology. Hopelessness and distress are prominent features of depression among dialysis patients [81]. The routine of dialysis treatment and varying levels of health may impact upon feelings of hopelessness, which may induce episodes of depression. Applying a psychodynamic model to ESRD links depression with the perception of loss [2, 9, 13]. Patients with ESRD encounter losses on both a somatic and psychological level. The dependency upon treatment, accompanied by numerous losses, may lead to perceived feelings of a lack of control [4–7]. Martin and Thompson [82] showed that locus of control measures were significant predictors of work status, cognitive function and physical function. Others have found that mechanisms of internal control are associated with reduced depression among renal dialysis patients [83]. Cvengros et al. [84] studied health locus of control and depression in patients with chronic kidney disease progressing to ESRD. The results revealed that as the disease progressed to requiring dialysis, changes in internal control predicted depression. Interestingly, the relationship was maintained when the somatic elements of the depression assessment (BDI) were removed, thus avoiding the overlap between somatic depression scoring and disease progression [84]. Such empirical evidence supports cognitive adaptation theory [85] which proposes that when faced with psychological adversity (i.e. reaction to illness) perceptions of personal control are heightened, promoting feelings of mastery. Increased feelings of control may elicit improved coping

responses and in turn better adjustment. Furthermore, the invasive routine of dialysis, and associated stress, may inhibit the use of certain coping strategies [86, 37]. The association between illness control and depression has also been shown to depend upon contextual factors, such as a kidney transplant failure [83]. Christensen et al. [83] revealed that heightened internal control was associated with increased depression in patients who had experienced a failed kidney transplant, whereas in those with no transplant history, increased control was associated with reduced depression.

Alternative explanations view depression as the direct or indirect consequence of the renal failure. For example, there are increased levels of cytokines and acute-phase reactants in patients with ESRD [50], possibly implicating cytokine-induced depression [1, 88–90] in the pathogenesis of depression in dialysis patients. Israel [13] reported that uraemia itself may cause depression and suggested a possible genetic predisposition within the ESRD population [13]. Uraemia may impact upon the central nervous system, affecting the synthesis and metabolism of certain neurotransmitters [91]. Increasing evidence has supported the benefits of daily HD upon uraemic symptomatology [92–95], although there is limited evidence to suggest that daily dialysis is associated with a reduction in depression. Two recent abstracts have reported improvements in patients' BDI scores after converting to frequent HD (short daily, or nocturnal HD) [96, 97]. Although anecdotal, this suggests that more effective control of uraemia impacts upon depression and mood. However, there is a great need to test such assertions in controlled studies.

Treatment

Comorbid depression among the medically ill may be different from that of psychiatric illness [2, 13, 40] and harder to treat [98]. Conventional guidelines (NICE) on depression treatment in primary and secondary care may be complicated when applied to the ESRD population, particularly recognition and pharmacological treatment. For example, a widely used class of antidepressants, selective serotonin reuptake inhibitors (SSRI), block cytochrome P450 and thereby increase significant drug-drug interactions, which may be a problem for dialysis patients on a stringent list of medication [99]. The high protein-binding properties of certain antidepressants may cause renal dialysis patients to be more responsive to psychotropic interventions [8]. For a range of antidepressants, including SSRI and serotonin norepinephrine reuptake inhibitors, a cautious approach to prescription is advised, starting with a low dose increasing over time [56]. A group of antidepressants, including citalopram and paroxetine (SSRI), along with initial and usual dosage guidelines have been suggested [100, 101; for a review, see 102]. Tricyclic antidepressants are often avoided due to an increased risk of cardiac problems [103]. Fluoxetine (20 mg/day), in a double-blind placebo-controlled study of HD patients, was found to be effective in alleviating depression symptoms with no significant side effects [104]. While the effective use of antidepressants among dialysis patients has been demonstrated in a small number of studies [56], further research is required to determine the impact of such treatment upon patient outcome and mortality [2].

Due to the difficulties of using drugs in these situations, psychological interventions may be a suitable alternative [105], though the evidence base is sparse. The evidence available suggests that cognitive behavioural therapy may be effective in relieving depression in the dialysis population [106, 107], as may other novel psychological interventions [108].

Wuerth et al. [29] have raised a more fundamental issue regarding treating depression in this population. Many patients refuse evaluation, and few complete the desired course of antidepressant treatment. This may be due to an underlying stigma of depression, which could perhaps be resolved by increased education. Educating staff and patients may promote earlier detection and treatment [109]. Employing a more holistic approach may be the most effective form of treatment for dialysis patients [110].

More effective dialysis may have a role. Daily HD was shown to improve quality of life [93, 94, 111], although these studies were small and largely uncontrolled. There are also significant potential downsides. While daily dialysis may be more effective in controlling uraemia, for some, the daily impact of dialysis and increased treatment-related stress may amplify the burden of treatment [112].

Conclusions

Depression is a prevalent and costly burden to dialysis patients impacting on a psychological and somatic level. Under-recognition of depression in this population is a major concern, particularly given the evidence of its impact on comorbidity and mortality. Longitudinal re-

search is needed to clarify the causal antecedents of depression among patients, the predictive risk factors, its prevalence, its relation to modality and its influence on the decision to withdraw from treatment. The issues regarding criterion contamination require specific attention, since this has a bearing on depression screening across a range of medical conditions. There is a need to establish the correct tools and procedures for depression screening among dialysis patients. Treating depressed dialysis patients has received little attention, particularly with respect to psychological interventions. However, regardless of the treatment options available, many patients refuse evaluation and treatment. Modifying patient and staff education may help improve this process. This catalogue of needs underlines our current state of ignorance.

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