Is successful treatment of depression in dialysis patients an achievable goal?

Joseph Chilcot & Joanna L. Hudson

Health Psychology Section, Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King’s College London

Corresponding author: Dr Joseph Chilcot, Health Psychology Section, Psychology Department, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, 5th floor Bermondsey Wing, Guy's Campus, London Bridge, London SE1 9RT (joseph.chilcot@kcl.ac.uk)

Key words: Depression; End-Stage Kidney Failure; Dialysis; Cognitive Behavioural Therapy; CBT; antidepressants; Sertraline.

Conflict of interest: None to declare

Funding: This work received no funding
Abstract

Depression is undisputedly common among individuals with End-Stage Kidney Failure and associated with adverse outcomes. It is well recognized that effective treatments for depression are needed within routine dialysis care. But, are we any closer to successfully treating depression in dialysis patients? We consider this question here with respect to two common treatments, anti-depressant medication and Cognitive Behavioural Therapy (CBT). Currently, there are limited data from randomized placebo-controlled trials regarding the acceptability and efficacy of anti-depressants. CBT trials appear to show more consistent treatment effects, albeit the feasibility of routine delivery remains unknown. No studies in dialysis patients have evaluated the combined effects of CBT with anti-depressants. There is a need to consider pragmatic depression treatment trials in dialysis patients in order to increase study recruitment in order to have more reliable data from which to evaluate the evidence base. Furthermore, we need to understand why treatments work, and for whom do they work? Lastly, addressing issues surrounding treatment acceptability and implementation as part of regular care remain key challenges that require attention if we are to improve the mental health of individuals on dialysis.
Introduction

There is a growing body of evidence demonstrating the association between depression and mortality among individuals with End-Stage Kidney Failure (ESKF). It is estimated that the presence of depressive symptoms is associated with a 50% increase in the risk of mortality\(^1,2\). This is particularly concerning given the high prevalence of depression, which is estimated to be approximately between 23-39%, depending on whether diagnostic or screening tools are used for evaluation\(^3\). Similar estimates of depression prevalence are also reported among individuals with a kidney transplant\(^4\). Furthermore, depression is also associated with other adverse outcomes, including increased hospitalization\(^5\), treatment non-adherence\(^6\) and increased inflammation and malnutrition\(^7\). Such factors may serve as candidate mechanisms underpinning the depression-mortality relationship.

Given the large body of evidence detailing the impact of depression among those on dialysis, developing a robust evidence base for treatment effectiveness is imperative if we are to improve mental health and patient outcomes. Here, we address the question; “Are we any closer to successfully treating depression in dialysis patients?” by considering the current evidence base with a focus on the two most common treatments modalities, anti-depressants and Cognitive Behavioural Therapy (CBT). Before this however, we begin by discussing the importance of treatment acceptability.

Do dialysis patients want yet another set of treatment(s)?

Individuals receiving dialysis are prescribed a complex and demanding treatment regimen, including multiple medications and significant dietary and fluid restrictions. Given this complexity, non-adherence remains common to aspects of treatment, often for a variety of reasons including depression\(^8\) and unhelpful treatment beliefs\(^9,10\). In light of high levels of polypharmacy\(^11\) and significant treatment burden, it is understandable that undertaking additional treatment(s) for depression might be intolerable for some.

A recent study investigated the acceptance of antidepressant treatment by haemodialysis (HD) patients and their renal team\(^12\), by evaluating patients randomized to the management arm of the Symptom Management Involving End-Stage Renal Disease (SMILE) trial\(^13\). As part of this trial, depression symptoms were evaluated monthly for a year using the Patient Health Questionnaire-9 (PHQ-9); PHQ-9 screening score \(\geq 10\) was employed to indicate possible depression. Of the 101 patients evaluated, 39 had depression on at least one or more of the monthly assessments. These 39 patients undertook 373 depression screening assessments during the study. In 147 or these 373 assessments depression was detectable. In approximately 70\% of these cases anti-depressants had been previously prescribed. In cases where health professions recommended intensified anti-depressant treatment, 70\% of patients...
did not accept the recommendation. At 44 assessments points, patients with a PHQ-9 score ≥10 were not receiving anti-depressants; in 91% of those cases patients refused treatment. The primary reason for refusal was the attribution of their depression to an acute event, chronic illness, or dialysis. Interestingly, in 18 instances in which patients accepted the recommendation for treatment, 61% (n=11) of renal services were unwilling to provide treatment. No reasons for rejecting the treatment recommendation were given in 8 of the 11 instances.

Notwithstanding the complexity of this study and the identified limitations, which includes the reliance on the PHQ-9 to indicate depressive cases, these data provide some striking insight into the acceptability of anti-depressant treatment. It suggests that both patients and renal staff are reluctant to initiate or modify anti-depressant treatments. This is also reflected indirectly by the low consent rates observed in clinical trials of anti-depressant in kidney disease patients (discussed below). Efforts to provide better psychoeducation to patients and health care professionals might be one strategy to better support treatment decisions and overcome such barriers.

Given that some patients refuse treatment on the basis of their illness and symptom attributions, specifically eliciting their illness and treatment beliefs and trying to alter them, might be of benefit. Indeed, Taylor et al. argue that offering treatment interventions that are congruent with patient’s illness beliefs and coping styles may promote uptake. Moreover, Taylor et al. identified that treatment interventions that were explicitly linked with the illness label depression were deemed to be less acceptable to ESKF patients. Consideration of how a person’s emotional response to ESKF is identified and subsequently managed in a way that is acceptable to both patients and health care staff is therefore needed. This exploratory work is underway aiming to identify the needs and preferences of ESKF patients and likewise to identify the barriers and facilitators to the detection and management of depression by renal staff. Considering these factors will help to embed evidence-based treatments for depression as part of routine care.

**What is the evidence for anti-depressants in dialysis patients?**

According to the UK National Institute of Health and Care Excellence (NICE) depression guidelines, pharmacotherapy should only be used to treat patients who meet diagnostic criteria for moderate to severe symptoms of depression. When prescribing drug treatments to manage depression in people with physical long-term conditions (LTC) the following factors need to be considered: (i) the potential for drug-drug interactions, (ii) the likely side effects of the medication, (iii) the patient’s previous history of pharmacotherapy treatments, (iv) patient preference, and (v) the toxicity of the drug and the risk of overdose among patients with suicidal ideation.
Despite the ever-growing literature on depression in dialysis patients, there remains a remarkable lack of treatment studies. Most antidepressant trials in dialysis patients have focused on Selective Serotine Reuptake Inhibitions (SSRIs). Unfortunately, most studies examining the effectiveness of antidepressants have been small non-randomized studies\textsuperscript{18–26}, albeit suggesting some potential efficacy. A recent non-placebo-controlled study compared paroxetine and agomelatine (an atypical anti-depressant) in a sample of chronic kidney disease (CKD) patients, reported a similar treatment response by 4 weeks\textsuperscript{27}. By 8 and 12 weeks however, depression scores were significantly lower in those treated with agomelatine. There were no serious adverse events and side effect profiles for each drug were reportedly similar\textsuperscript{27}.

To date, there have only been three randomized placebo-controlled trials of an antidepressant agent in individuals with kidney disease\textsuperscript{28–30}, of which two studies were in dialysis patients. The first, in 14 HD patients found no significant improvement in depression symptoms after an 8 week treatment with fluoxetine compared with placebo\textsuperscript{28}. The most recent study in HD patients was a feasibility randomized placebo-controlled trial of sertraline by Friedli et al\textsuperscript{29}. Of 1353 patients approached for depression screening, 243 were excluded due to inability to read English. 64% consented to be screened (n=709) with 32% (n=231) screening positive using a Beck Depression Inventory of ≥16. 68 (29%) were ineligible for the trial phase because of current treatment for depression. 63 patients gave further consent to be assessed by the study psychiatrist who diagnosed major depressive disorder in 37 (58.7%) of patients. 30 patients were randomized (n=15 in each), half the recruitment target specified in the study protocol\textsuperscript{31}. There were no significant nor clinically meaningful differences in the change of depression symptoms between the two-arms, albeit the study was drastically underpowered. Drop-outs due to adverse events were considerably higher in the Sertraline arm compared to the placebo arm (7 in the sertraline arm, 2 in the placebo arm). Overall, the study clearly demonstrated the problems with conducting a trial of this particular design\textsuperscript{31} since a relatively high proportion of patients were already taking anti-depressants. Modification of trial design to allow inclusion of patients already receiving treatment is one recommendation to improve trial feasibility through getter eligibility.

RCTs on drug therapy of depression in dialysis patients are thus greatly limited. Expanding the target patient population to CKD in general does not add much to our knowledge of this area. Similar issues of scale and feasibility were apparent in a much larger randomized placebo-controlled trial of sertraline in CKD patients\textsuperscript{30}. 977 of 14,658 CKD patients screened positive for depression. 201 were consented and randomized to either sertraline (n=102) or placebo (n=99) arms. Over a 12-week follow-up there were no significant differences between the treatment arm and placebo with regards to depression scores. Remission rates were also similar at 15%, as was end of follow-up health related
quality of life and function scores. Those in the sertraline arm reported significantly more side effects compared with the placebo arm. Thus, the study offered no support for the use of sertraline for major depression in CKD and parallels can be drawn with Friedli et al.\textsuperscript{29} since both studies required a very large screening samples.

**Cognitive behavioural therapy (CBT)**

Treatment options for depression in dialysis patients are not restricted to anti-depressants agents. Talking therapies, particularly CBT might well have advantages in terms of acceptability to those are reluctant to take anti-depressants and should be considered for individuals with mild to moderate symptoms of depression\textsuperscript{17}. Two meta-analyses exploring the effectiveness of psychological talking therapies (including CBT) for the management of depression in people with coronary heart disease\textsuperscript{32} and diabetes\textsuperscript{33} showed that these types of interventions improve depressive symptoms. However, the size of improvements in depressive symptoms was relatively small. This likely reflects the need to refine psychological treatments further to manage illness specific beliefs and challenging treatment demands and health consequences that present uniquely for each LTC\textsuperscript{34}.

Three randomized controlled trials have tested the efficacy of CBT for depression in HD patients. The first study compared a 12 week group CBT treatment (n=41) to a control arm (n=43) and reported significant improvements in depressive symptoms and quality of life\textsuperscript{35} over a 9 month follow-up. Although a relatively small study, consent rates were impressive compared to the aforementioned drug trials. A total of 350 patients were screened for eligibility, with 100 identified as depressed with 90 randomized (46 to the intervention arm of which 41 started CBT treatment).

In the second study, individual CBT administered in the dialysis centre (n=26), significantly improved depression symptoms, quality of life and daily fluid adherence compared with a waiting list control group (n=33)\textsuperscript{36}. The third study compared five-weeks of individual CBT with usual care in 60 dialysis patients with mild to moderate depression and anxiety symptoms\textsuperscript{37}. Statistically significant effects of CBT on depression and anxiety outcomes were observed post treatment and after nine-weeks of follow-up.

A secondary analysis of data from a RCT testing the efficacy of a brief self-management intervention showed that compared with usual care, those in the intervention arm had significantly fewer depression symptoms over a 12 month follow-up\textsuperscript{38}. Intriguingly, the intervention was designed to target self-management behaviour, through the use of behaviour change techniques, and did not include components that target emotional regulation. It could be that the intervention achieved its effects via increasing personal resources, resilience and self-efficacy\textsuperscript{38}.
Although CBT has shown promise for improving depressive symptoms, how easily CBT treatment protocols can be administered as part of routine dialysis care remains unknown. Efforts to look at the optimal delivery methods are therefore required. One option might be internet delivered CBT (iCBT). The feasibility of iCBT for use in HD patients was first evaluated in a non-randomized controlled single group design, with 22 patients receiving a 8 week on-line CBT intervention, with therapist support. Consent rates were reassuring, with 22 of 30 patients assessed for study eligibility starting the intervention, 20 followed up post treatment and 17 at 3 months follow-up. Clinically significantly improvements were observed for both depression (34%) and anxiety (31%).

A recent study assessed the feasibility of delivering online CBT, with or without therapist telephone support, for psychological distress (mild to moderate depression and anxiety symptoms) in HD patients. Of the 410 patients approached, 182 (44%) completed screening measures. 26% of patients found screening unacceptable; and a further 30% found it unfeasible. Psychological distress was detected in 101 (55%), with 60 meeting the remaining study inclusion criteria. The primary reason for ineligibility was poor computer literacy (N=17). Twenty-five patients were randomised to the supported (N=18) or unsupported arm (N=7) with 92% retained at follow-up. No differences in psychological distress or cost-effectiveness were apparent between the groups, although the study was concerned with feasibility and hence not powered to detect differences in mood outcomes.

**Future directions and conclusions**

Whilst efforts to evaluate effective treatments for depression have been undertaken in dialysis patients recently, it is clear from the current literature that we need to be able to increase recruitment into trials, with one option being employing more pragmatic or adaptive trial designs. We need to better understand and mitigate the barriers to recruitment particularly considering how to include patients already receiving treatment (for example drug wash out for anti-depressant studies) and likewise consider how depression interventions are implemented in a way that is acceptable to patients and renal staff.

For CBT studies, considering how treatments work (i.e. which cognitions and behaviours change in therapy that mediate treatment effects) and which treatments work from whom (i.e. treatment moderators), is required to improve the tailoring of treatment to individuals. Furthermore, there are no studies in dialysis patients that have evaluated the combined effects of CBT with anti-depressants.

Despite these challenges, it is imperative we invest further into treatments trials for depression in order to develop evidence-based treatment guidelines specific to individuals on dialysis. In order to deliver future treatment guidelines, it remains critical that there is access to renal psychology services that are suitably resourced to manage the sometimes complex psychosocial needs of dialysis.
patients. In doing so it is hoped more patients will receive acceptable and efficacious treatment for depression leading to improved mental health and quality of life.

References


