STUDIES ON DEPRESSION AND FATIGUE IN PEOPLE WITH END-STAGE KIDNEY DISEASE RECEIVING HAEMODIALYSIS

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Thesis

Primary Hypothesis

A randomised controlled trial of sertraline versus placebo, to treat Major Depressive Disorder in patients on haemodialysis, is feasible.

Secondary Objectives

To determine data in relation to the following factors to facilitate the design of a definitive randomised controlled trial of antidepressant medication in patients on haemodialysis with Major Depressive Disorder:

- *The prevalence of depression symptoms and Major Depressive Disorder in patients on haemodialysis*
- *The relationships between depression and fatigue in haemodialysis patients*
- *Current practice patterns in the use of antidepressant medication in haemodialysis patients*

Ayman Guirguis (2017)

Abstract

Depression is common in haemodialysis (HD) patients and is often unrecognised and undertreated, though associated with excess morbidity and mortality. Diagnosis is challenging due to symptom overlap with kidney failure, with fatigue being the most common overlapping symptom. Research on the effectiveness of antidepressant medication in this setting is sparse. A recent systematic review advocated well-designed Randomised Controlled Trials (RCTs) in this setting.

The studies reported in this thesis had a number of aims. The main aim was to undertake a multicentre feasibility randomised, double blind, placebo-controlled trial of sertraline in patients on HD with Major Depressive Disorder (MDD). To identify suitable patients for this, a screening phase was required, which also allowed determination of the prevalence of depression in this setting and of the relative effectiveness of screening tools Patient Health Questionnaire-2 (PHQ-2), Patient Health Questionnaire-9 (PHQ-9), and Beck Depression Inventory-II (BDI-II). It also allowed examination of the relationships of fatigue in this setting (assessed mainly by the Multidimensional Fatigue Inventory (MFI), including those with a diagnosis, and management of depression. The finding, during screening, that a large proportion of the HD cohort was already on antidepressant treatment, presented the opportunity to study 'real-life' practice patterns in the management of antidepressant treatment in this setting.

Recruitment into the RCT was difficult. 1,355 patients in five HD centres were considered for screening, but 243 of these were excluded, mainly because of their inability to read and understand English. Of the remaining 1,110 patients, 709 consented to screening. 231 of these screened positive for high depression symptoms but 130 were not considered for the trial phase, mainly because of concurrent treatment for depression (68 patients), and other contraindicated conditions and medication. In addition, 38 patients declined to take part in the psychiatric interview necessary for diagnosis of MDD.

Of the 63 who underwent the diagnostic interview, 37 (58.7%) were diagnosed with MDD and 30 consented to enter the RCT and were randomised into sertraline or placebo groups. This was half of the anticipated recruitment into the RCT. Twenty-

one patients (70%) completed the six-month study, eight of 15 in the sertraline group and 13 of 15 in the placebo group ($p<0.05$). Drop out was mainly due to adverse or serious adverse events. Depression scores (BDI-II and Montgomery-Åsberg Depression Rating Scale (MADRS)) improved significantly in both the sertraline and placebo groups over six months but there were no significant differences between the treatment groups. There was a slight suggestion of more rapid improvement over the first two months on sertraline, but this was not significant.

Fatigue scores were high in all sub-domains – with only a weak relationship with age and comorbidity. Mental fatigue was the strongest independent predictor of high depressive symptoms (BDI-II $\geq$16, PHQ-9 $\geq$8), while physical fatigue had the strongest relationship with dialysis recovery time, and survival. Distinguishing between these components of fatigue may have a role in refining the diagnosis and management of MDD.

Forty-one of the 76 patients on antidepressant medication at screening were followed up for a mean of 14±5 months. Ten different antidepressant agents were being taken – the most common being Citalopram (39%). Most had been prescribed by GPs. Two-thirds of patients either deteriorated or failed to improve in terms of BDI-II scores during follow-up, many of whom had had no adjustment of medication during this time. Diagnostic evaluation at follow-up showed 37% to be suffering from current or recurrent major depressive episodes (MDE), 48% to have evidence of past MDE, and 15% to have no evidence of ever having been depressed.

These empirical studies confirm that depression is very common in HD patients. Its diagnosis is complicated due to symptom overlap with the uraemic syndrome. Fatigue seems to be a key area of overlap with symptoms of depression with a complex relationship. There was no obvious benefit from antidepressants in this feasibility RCT and there was a high drop-out rate due to adverse events, particularly in the sertraline group. These findings raise concerns about the benefits and risks of antidepressants in patients on HD. Current practice patterns may be subjecting patients to substantial risk for little or no benefit. Identifying whether antidepressant medication is effective in this context is a major clinical need, hence the requirement for a definitive study. There is no doubt that to undertake a definitive study would pose considerable recruitment challenges. The findings presented here emphasise the

importance of finding ways to overcome these challenges that might include efforts to incorporate patients already taking antidepressants.

Abbreviations

5-HT	-	Serotonin
ACE	-	Angiotensin-converting enzyme
ACTH	-	adreno-corticotrophin hormone
ADH	-	Antidiuretic hormone
AKI	-	Acute kidney injury
ALP	-	Alkaline phosphate
ALT	-	Alanine transaminase
ANP	-	Atrial natriuretic peptide
APA	-	American Psychiatric Association
ARF	-	Acute renal failure
ASSertID	-	A Study of Sertraline In Dialysis
AST	-	Aspartate transaminase
ATP	-	Adenosine triphosphate
AUC	-	Area Under Curve
AV	-	Arteriovenous
BDI-II	-	Beck Depression Inventory-II
BFI	-	Brief Fatigue Inventory
BMQ	-	Beliefs about Medicines Questionnaire
CA	-	Cardiac arrhythmia
Ca^{2+}	-	Calcium
CABG	-	Coronary artery bypass grafting
CAPD	-	Continuous ambulatory peritoneal dialysis
CBT	-	Cognitive behavioural therapy
CCPD	-	Continuous cycling peritoneal dialysis

CDC	-	Centres for Disease Control and Prevention
CDI	-	Cognitive Depression Index
CES-D	-	Centre for Epidemiological Studies Depression Scale
CGI	-	Clinical Global Impression
CGI-EI	-	Clinical Global Impression – Efficacy Index
CGI-I	-	Clinical Global Impression – Improvement Scale
CFS	-	Chronic fatigue syndrome
CGI-S	-	Clinical Global Impression – Severity Scale
CHOICE	-	Choices for Healthy Outcomes in Caring for End-Stage Renal Disease
CHOIR	-	Correction of Haemoglobin Outcome in Renal Insufficiency
CI	-	Confidence interval
CI	-	Chief investigator
CIDI	-	Composite International Diagnostic Interview
CKD	-	Chronic kidney disease
Cl^-	-	Chloride
CMHT	-	Community mental health team
CNS	-	Central nervous system
COPD	-	Chronic obstructive pulmonary disease
CREATE	-	Cardiovascular Risk Reduction by Early Anaemia Treatment with Epoetin Beta
CRF	-	Case report form
CRH	-	Corticotropin-releasing hormone
CRP	-	C-reactive protein
CVD	-	Cardiovascular vascular disease
DA	-	Dopamine

DIS	-	Diagnostic Interview Schedule
DNA	-	Deoxyribonucleic acid
DOPPS	-	Dialysis Outcomes and Practice Patterns Study
DSI	-	Diagnostic Structured Interview
DSM	-	Diagnostic and Statistical Manual of Mental Health
ECA	-	Epidemiological Catchment Area
EDTA	-	Ethylenediaminetetraacetic acid
eGFR	-	Estimated glomerular filtration rate
EMA	-	Ecological momentary assessment
EPO	-	Eryhtropoietin
ESA	-	Erythropoietin stimulating agent
ESRD	-	End-stage renal disease
ESRF	-	End-stage renal failure
FACIT-F	-	Functional Assessment of Chronic Illness Therapy – Fatigue
FAS	-	Fatigue Assessment Scale
FHN	-	Frequent Haemodialysis Network
FREEDOM	-	Following Rehabilitation, Economic and Everyday – Dialysis Outcome Measurements
FSS	-	Fatigue Severity Scale
GAD	-	Generalised anxiety disorder
GF	-	General fatigue
GFR	-	Glomerular filtration rate
GI	-	Gastrointestinal
H^+	-	Hydrogen ions
H_2CO_3	-	Carbonic acid

HADS	-	Hospital Anxiety Depression Scale
HAMD	-	Hamilton Rating Scale for Depression
HCO_3	-	Bicarbonate
HD	-	Haemodialysis
HDRS	-	Hamilton Depression Rating Scale
HPA	-	Hypothalamic-pituitary-adrenal
HRQL	-	Health-related Quality of Life
ICD	-	International Classification of Diseases
ICF	-	Informed consent form
IDS	-	Inventory of Depressive Symptomatology
IFN	-	Interferon
IL	-	Interleukin
IMP	-	Investigational medicinal product
IRAS	-	Integrated Research Application System
K^+	-	Potassium
K/DOQI	-	Kidney Disease Outcomes Quality Initiative
KDQoL-SF	-	Kidney Disease Quality of Life Short Form
LVH	-	Left-ventricular hypertrophy
MADRS	-	Montgomery-Åsberg Depression Rating Scale
MAOI	-	Monoamine oxidase inhibitor
MAQ	-	Medication Adherence Questionnaire
MARS	-	Medication Adherence Rating Scale
MDD	-	Major Depressive Disorder
MDE	-	Major depressive episode
MDRD	-	Modification of Diet in Renal Disease

MED	-	Major Depressive Episode
MF	-	Mental fatigue
MFI-20	-	Multi-functional Fatigue Inventory
Mg^{2+}	-	Magnesium
MRHA	-	Medicines and Healthcare Products Regulatory Agency
MI	-	Myocardial infarction
MINI	-	Mini-International Neuropsychiatric Interview
MMSE	-	Mini Mental State Examination
MOS	-	Medical Outcomes Study
Na^{+}	-	Sodium
NE	-	Norepinephrine
NICE	-	National Institute for Health and Clinical Excellence
NIHR	-	National Institute for Health Research
NREM	-	Non-rapid eye movement
OCPD	-	Obsessive Compulsive Personality Disorder
OD	-	Overdose
OSA	-	Obstructive sleep apnoea
OSH	-	Orthostatic hypotension
P	-	Phosphorus
PAL	-	Palliative care
PCA	-	Principal component analysis
PD	-	Peritoneal dialysis
PF	-	Physical fatigue
PFS-R	-	Piper Fatigue Scale- Revised
pH	-	Potential of hydrogen

PHQ-2	-	Patient Health Questionnaire-2
PHQ-9	-	Patient Health Questionnaire-9
PI	-	Principal investigator
PID	-	Patient identification
PIS-2	-	Participant information sheet -2
PRD	-	Primary renal disease
PRIME-MD	-	Primary Care Evaluation of Mental Disorders
PROMIS	-	Patient-reported Outcomes Measurement Information System
PTH	-	Parathyroid hormone
QIDS-SR	-	Quick Inventory of Depression Symptomatology Self-report
QoL	-	Quality of Life
RA	-	Reduced activity
RAS	-	Renin-angiotensin system
RCT	-	Randomised Controlled Trial
REC	-	Research Ethical Committee
REM	-	Rapid eye movement
RFPB	-	Research for Patient Benefit
RFS	-	Rhoten Fatigue Scale
RLS	-	Restless Leg Syndrome
RM	-	Reduced motivation
RNA	-	Ribonucleic acid
ROC	-	Receiver operating characteristics
RRT	-	Renal replacement therapy
SCID	-	Structured Clinical Interview for Depression
SDDS-PC	-	Symptom-driven Diagnostic System for Primary Care

SF-20	-	Short-form Health Survey (20 items)
SF-36	-	Short-form 36
SNRI	-	Serotonin norepinephrine reuptake inhibitor
SPC	-	Summary of product characteristics
SSRI	-	Selective serotonin reuptake inhibitor
SUSAR	-	Suspected unexpected serious adverse reaction
TM	-	Trial manager
TNF	-	Tumour necrosis factor
Tx	-	Transplant patients
UFC	-	Urine free cortisol
URR	-	Urea reduction ratio
VAS-F	-	Visual Analog Scale for Fatigue
VO2 max	-	Volume per time, oxygen, maximum
WHO	-	World Health Organisation
Zung SDS	-	Zung Self-report Depression Scale

Thesis Structure and Prelude

In order to defend the thesis offered here the following work are organised into four main sections. First, introductory chapters describe 1- the nature, consequences and treatment of kidney failure. 2- an overview of depression- in the general population; in patients with End Stage Renal Disease, including its prevalence, complications and the challenges involved in the diagnosis of Major Depressive Disorder in this setting due to the overlapping symptoms of depression and the uraemic syndrome. 3- a review of fatigue in particular in End Stage Renal Disease including its measurement and its overlap with depression symptoms. Following this, the second section is presented and concerns the consideration of the applied methodology. This includes the measurement of depression symptoms by the Beck Depression Inventory -II and the Patient Health Questionnaire 9, and fatigue by the Multi-Dimensional Fatigue Inventory and Short Form 36(SF-36) energy/fatigue subscale. The Mini-International Neuropsychiatric Interview (MINI) version 6.0 is also described including the Folstein Mini Mental Status Examination as a means of making a formal Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of major depressive disorder. The Montgomery-Asberg Depression Scale (MADRS) is described as a measure of the severity of depressive episodes in patients with mood disorders and is more sensitive to the changes brought on by antidepressant treatment. The third empirical section concerns a series of studies covering depression and fatigue in haemodialysis patients. These include a screening study to identify patients with high depressive symptoms and fatigue scores, a feasibly randomised controlled trial in patients diagnosed with depression and treated with either sertraline or placebo for 6 months, and a study of practice patterns on the use of antidepressants in haemodialysis patients. At the end of each of these studies there is an independent discussion highlighting the major findings. The fourth and final section presents an overarching discussion and the recommendations of the thesis.

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Chapter 1

The Kidney

The kidneys are the waste filtering and disposal system of the body. Up to one-third of all blood leaving the heart passes into the kidneys to be filtered before flowing to the rest of the body's tissues. A person can live with only one functioning kidney but loss of both kidneys leads to rapid accumulation of wastes and death within a few days. The paired organs lie retro-peritoneally along the posterior muscular wall of the abdominal cavity. Each contains around 1 million individual nephrons, the microscopic functional units that filter blood, to produce urine. Each nephron is made of two main parts: the glomerulus, which filters the blood, and the tubule, which is responsible for modification of the composition of the filtrate according to bodily needs.

1.1 Function of the Kidney

The main functions of the kidney are summarised in Table 1.

Table 1: Main kidney functions

Function of the kidney	
Excretion of waste products	Electrolyte homeostasis
Water homeostasis	Blood pressure homeostasis
Acid/base homeostasis	Hormone production

1.1.2 Excretion of Waste Products

The primary function of the kidneys is the excretion of waste products, including those resulting from metabolic activity, protein metabolism, and bacterial action in the intestine. Many of these products are toxic to the body if they accumulate because of kidney failure. These ‘uraemic toxins’ (Table 2) can be classified into three main groups:

- **Small water-soluble molecules**: often the product of metabolic activity, e.g. urea, creatinine, and uric acid
- **Middle molecules:** often low molecular weight proteins, some with structural functions, e.g. beta-2-microglobulin
- **Protein bound compounds**: some of which are produced in the intestine, e.g. *p*-cresol

Table 2: Uraemic toxins (3)

Small water-soluble solutes	Middle molecules	Protein-bound solutes
Asymmetric dimethylarginine	Degranulation-inhibiting protein I	3-Deoxyglucosone
Benzylalcohol	Atrial natriuretic peptide	CMPF
β-Guanidinopropionic acid	β_2-Microglobulin	Fructoselysine
β-Lipotropin	β-Endorphin	Glyoxal
Creatinine	Cholecystokinin	Hippuric acid
Cytidine	Clara cell protein	Homocysteine
Guanidine	Complement factor D	Hydroquinone
Guanidinoacetic acid	Cystatin C	Indole-3-acetic acid
Guanidinosuccinic acid	Adrenomedullin	Indoxyl sulfate
Hypoxanthine	Delta-sleep-inducing peptide	Kinurenine
Malondialdehyde	Endothelin	Kynurenic acid
Methylguanidine	Hyaluronic acid	Methylglyoxal
Myoinositol	Interleukin 1β	N-carboxymethyllysine
Orotic acid	Interleukin 6	P-cresol
Orotidine	Kappa-Ig light chain	Pentosidine
Oxalate	Lambda-Ig light chain	Phenol
Pseudouridine	Leptin	P-OHhippuric acid
Symmetric dimethylarginine	Methionine-enkepahlin	Quinolinic acid
Urea	Neuropeptide Y	Spermidine
Uric acid	Parathyroid hormone	Spermine
Xanthine	Retinol binding protein	
	Tumournecrosis factor alpha	

The glomerulus filters small and middle molecule solutes, allowing excretion in the urine. The composition of the filtrate is further modified by tubular absorption or secretion. For instance, urea reabsorption by the tubules has a role in the medullary counter-current system, which is important in urinary concentration mechanisms. Low molecular weight proteins in the filtrate, e.g. beta-2-microglobulin, are catabolised by tubular cells and the constituent amino acids are reabsorbed. Protein-bound solutes are poorly filtered and tubular secretion may be an important route of elimination.

1.1.3 Fluid Haemostasis

The kidneys are able to control the fluid volume of the body by varying the tubular handling of salt and water according to bodily needs. In healthy individuals, around 180 litres of fluid are filtered daily and all but around 2 litres are reabsorbed, mostly in association with sodium (Na^+) and chloride (Cl^-), passively, in the proximal tubule, and distally, regulated by aldosterone. Atrial natriuretic peptide (ANP) may also have a role in increasing the excretion of Na^+ and Cl^- ions in response to fluid overload.

When the body is relatively water-depleted, plasma osmolality is increased, triggering an increase in antidiuretic hormone (ADH) release from the posterior pituitary gland. ADH stimulates the formation of water channel proteins in the collecting ducts of the nephrons, thus permitting water to pass from urine into the tubule cells and on into the blood. In states of water-excess, ADH secretion is suppressed, allowing excretion of the excess water.

1.1.4 Acid/Base Haemostasis

The kidneys regulate the pH of the blood by controlling the excretion of hydrogen ions (H^+) and bicarbonate ions ($HCO3^-$). Hydrogen ions accumulate when proteins are metabolised in the liver and when carbon dioxide in the blood reacts with water to form carbonic acid (H_2CO_3), a weak acid that partially dissociates in water to form hydrogen ions and bicarbonate ions. Both ions are filtered by the glomerulus but

$HCO3^-$ undergoes tubular reabsorption, unlike H^+, which is excreted. The tubule cells may also actively secrete H^+ during acidosis. Reabsorbed $HCO3^-$ can neutralise H^+ to form carbonic acid, which in the capillaries of the lungs dissociates into carbon dioxide and water, allowing carbon dioxide to be exhaled.

1.1.5 Electrolyte Homeostasis

The kidneys maintain the homeostasis of important electrolytes by controlling their urinary excretion.

- **Sodium (Na^+):** Sodium is vital for the regulation of extracellular volume and pressure and for normal neuromuscular function. Over 99% of filtered Na^+ is reabsorbed. Mechanisms are briefly discussed above in section 1.1.3.
- **Potassium (K^+):** Potassium is the main intracellular cation and is vital for neuromuscular function. Unlike sodium, only about 60% to 80% of filtered K^+ is reabsorbed. Most K^+ reabsorption occurs in the proximal tubule and ascending loop of Henle.
- **Chloride (Cl^-):** Chloride is the most prevalent anion in the body. Chloride is vital for the regulation of factors such as pH and extracellular fluid balance and helps to establish the electrical potential of neurons and muscle cells. The proximal tubule and ascending loop of Henle reabsorb about 90% of filtered Cl^-.
- **Calcium (Ca^{2+}):** Calcium is an important structural element in bones and teeth, and is also essential for the contraction of muscle tissue, the release of neurotransmitters by neurons, and the stimulation of cardiac muscle tissue in the heart. The proximal convoluted tubule and the ascending loop of Henle reabsorb most of the filtered Ca^{2+}. Fine tuning takes place in the distal tubule, where parathyroid hormone (PTH) is an important regulator.
- **Magnesium (Mg^{2+}):** Magnesium is essential for the proper function of enzymes that work with phosphate compounds such as ATP, DNA and RNA. The proximal convoluted tubule and loop of Henle reabsorb most of the filtered Mg^{2+}.

1.1.6 Blood Pressure Homeostasis

The kidneys help to control blood pressure by regulating the volume of the extracellular fluid by the excretion of Na^+ ions and water, as discussed above, and by producing the enzyme renin, part of the renin-angiotensin system (RAS), which has many important roles, including the regulation of vascular tone and control of aldosterone secretion.

1.1.7 Hormone Production

The kidneys maintain a small but important endocrine function by producing the hormones calcitriol and erythropoietin.

- **Calcitriol** is the active form of vitamin D in the body. Proximal tubular cells produce calcitriol from 25 hydroxy vitamin D which is the major circulating form of vitamin D. Calcitriol has many actions, including increasing intestinal calcium absorption and suppressing parathyroid hormone secretion.
- **Erythropoietin (EPO)** is produced by the cells of the peritubular capillaries in response to hypoxia. EPO stimulates the cells in the bone marrow to increase their output of red blood cells.

Several hormones produced elsewhere in the body help to control the function of the kidneys.

- **Antidiuretic hormone (ADH),** also known as vasopressin, is produced by the neuro-secretory cells in the hypothalamus. These cells extend into the posterior pituitary, which stores and releases ADH in response to a decrease in blood volume or increased blood osmolarity. ADH increases the number of water channels in collecting duct cells, allowing increased water reabsorption.
- **Angiotensin II** is a hormone synthesised in the liver and activated by the enzyme renin and angiotensin-converting enzyme (ACE). Angiotensin II is highly vasoactive. It has important actions in the control of blood pressure, and it also increases the reabsorption of Na^+ and Cl^- ions in the proximal tubule.

- **Aldosterone** is produced in the adrenal cortex in response to Angiotensin II. Aldosterone acts on the cells of the collecting ducts, promoting Na+ reabsorption and K+ excretion.
- **Atrial natriuretic peptide (ANP)** is produced by cardiac muscle cells in the atria, in response to volume overload. ANP increases the glomerular filtration rate and promotes renal salt and water excretion by interfering with counter current exchange.

1.2 Kidney Disease

1.2.1 Acute Kidney Injury

Acute kidney injury (AKI), previously called acute renal failure (ARF), usually with fairly rapid loss of renal function and potentially reversible, is generally characterised by oliguria (< 400 ml per day in adults) and fluid and electrolyte imbalance. AKI can result from a variety of causes, which are generally classified as: 1) pre-renal – usually associated with hypotension due to blood loss or dehydration; 2) intrinsic – due to direct damage to the kidney, e.g. rapidly progressive glomerulonephritis; or 3) acute interstitial nephritis, and post-renal due to obstruction of urine outflow at any level. The underlying cause must be identified and treated to arrest the progress. Dialysis may be necessary to bridge the time gap between renal injury and recovery. Acute kidney injury can be present on top of chronic kidney disease, a condition called acute-on-chronic renal failure. The acute part of acute-on-chronic renal failure may be reversible. Like AKI, acute-on-chronic renal failure can be difficult to distinguish from chronic kidney disease in the absence of a typical history and/or previous chemistry.

1.2.2 Chronic Kidney Disease

Chronic kidney disease (CKD) implies irreversible loss of kidney function, which usually occurs over a period of months or years. Symptoms of worsening kidney function tend to occur in the later stages and are non-specific, e.g. feeling generally

unwell and experiencing a reduced appetite. CKD is often diagnosed on screening people known to be at risk of kidney problems, such as those with high blood pressure, diabetes, or those with a family history of the condition. CKD may also be identified when it leads to one of its recognised complications, such as hypertension, cardiovascular disease, or anaemia.

1.2.2.1 Aetiology

The aetiology of CKD is varied. In the UK, as in many developed countries, diabetic nephropathy is the most prevalent primary renal disease in patients with advanced kidney disease (Table 3).

Table 3: Primary renal disease in incident renal replacement therapy patients, (1)

Percentage with Co-morbid Diagnosis in Renal Replacement Therapy Patients			
Diagnosis	**Age <65**	**Age≥65**	**All patients**
Diabetes	28.6	22.3	25.6
Glomerulonephritis	17.3	10.4	14.0
Pyelonephritis	6.8	6.4	6.6
Hypertension	6.2	8.8	7.4
Polycystic kidney	10.1	3.1	6.7
Renal vascular disease	1.7	10.9	6.1
Other	17.4	18.0	17.7
Uncertain aetiology	11.8	20.1	15.9

1.2.2.2 Stages of CKD

Stages of chronic kidney disease are shown in Table 4, in which eGFR was estimated from serum creatinine measurements using the Modification of Diet in Renal Disease (MDRD) study equation (4). Individuals with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 for three months are classified by Kidney Disease Outcomes Quality Initiative (K/DOQL) as having moderate to severe CKD (Stages 3-5). Individuals with evidence of kidney disease (e.g. proteinuria, abnormal renal imaging) and higher levels of eGFR are classified as having CKD (Stages 1 or 2) (5).

Table 4: The K/DOQI stages of chronic kidney disease (5)

Stage	Description	Estimated Glomerular Filtration Rate (mL/min/1.73m^2 BSA)
1	Kidney damage, normal or increased eGFR	≥ 90
2	Kidney damage, mildly reduced eGFR	60-89
3	Moderately reduced eGFR	30-59
4	Severely reduced eGFR	15-29
5	Kidney failure / Advanced chronic kidney disease	<15 (or dialysis)

1.3 End-stage Renal Disease (ESRD)

End-stage renal disease (ESRD) refers to the state of reduced kidney function when the kidneys are unable to sustain life without some form of renal replacement therapy (RRT), i.e. Stage 5.

1.3.1 Incidence of ESRD

The UK Renal Registry (http://www.renalreg.com) collects standardised data on incidence, clinical outcomes, and management of patients with ESRD receiving renal replacement therapy from all UK renal services on a quarterly basis. UK Renal Registry data shows that 6,891 patients started renal replacement therapy in 2012 (2).

The incidence has increased over the last 20 or so years, with some levelling off more recently (Figure 1) (1). Incident rates are higher in males and peak in the eighth decade of life (Figure 2) (1).

Figure 1: Incidence of RRT from 1990 to 2012, (1)

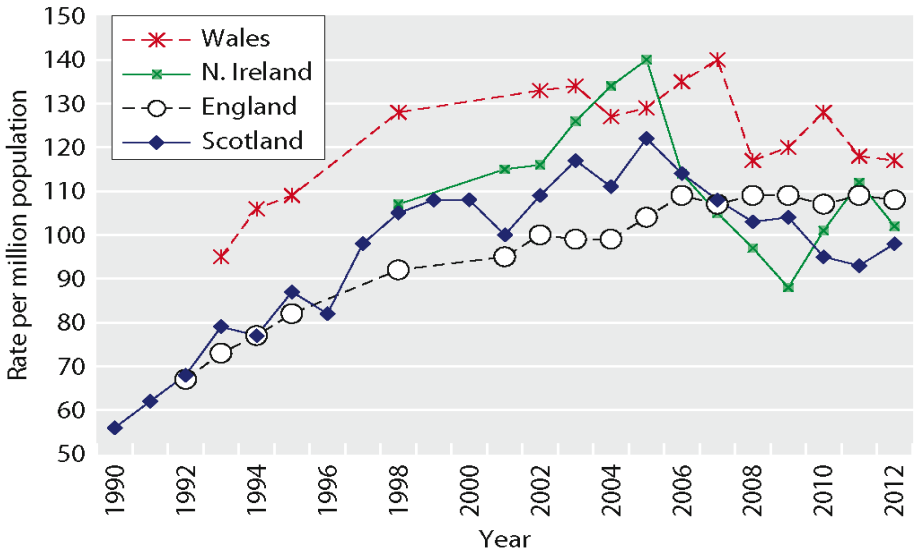
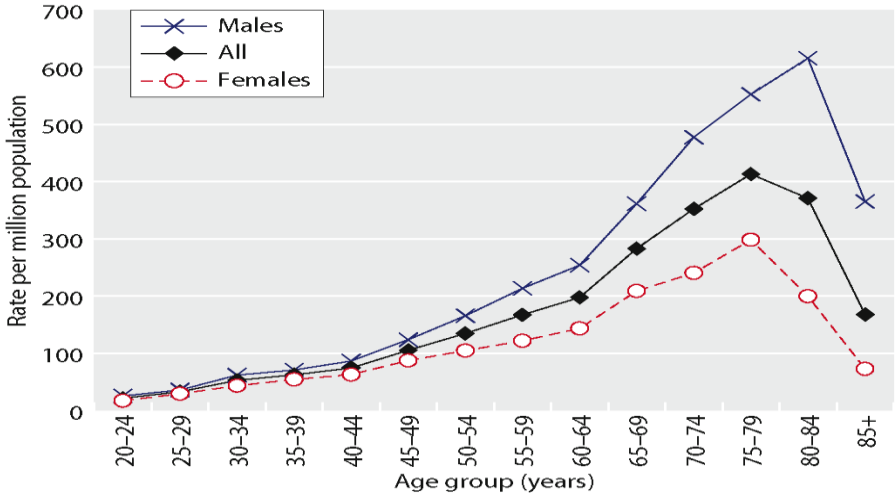


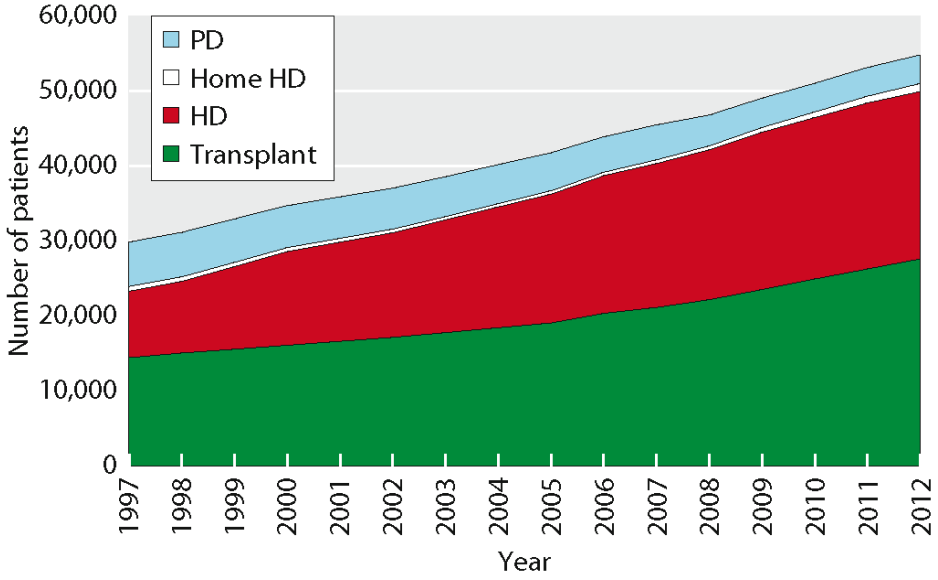
Figure 2: Incidence rate of RRT by age and gender in 2012, (1)



1.3.2 Prevalence of ESRD

There were 54,824 adult patients receiving RRT in the UK on 31 December 2012 (UK Renal Registry (1)). Around half of these patients had a functioning transplant, with the remainder on dialysis – predominantly HD. There has been a significant increase in the RRT population over the last 20 years (Figure 3). There have also been significant demographic changes. The median age of prevalent RRT patients in 2000 was 55 years compared to 58 years in 2012. The percentage of RRT patients aged greater than 70 years increased from 19.2% in 2000 to 24.9% in 2012. This reflects an aging general population as well as improved survival on RRT. The availability of transplantation and HD are continuing to increase, while that of peritoneal dialysis (PD) is declining (Figure 3). The reasons for these changes are complex. The growth in centre-based HD facilities from the early 1990s, improved understanding of the limitations of PD as a long-term therapy, the selection of younger and fitter patients with a better prognosis for transplantation, and the growth in living donor and pre-emptive (before dialysis) transplantation are important factors in understanding these changes. The increasing age has significant implications, with higher proportions of the HD population being frail and dependent.

Figure 3: Growth in prevalent patients by treatment modality at the end of each year 1997–2012, (1)



1.3.3 Uraemic Syndrome

The effects of impaired renal function are manifested in the clinical syndrome termed ‘uraemia’. The term was introduced by Priorry and L’Heritier in 1940 and literally means ‘urine in blood’. Uraemia is the end result of the retention of all of the various substances that are normally excreted in urine. The term uraemia is used to describe a complex clinical syndrome that has many interrelated features.

The syndrome is recognised as a composite problem, involving all of the body’s system and reflecting biochemical alterations in all aspects of the constitution of the internal environment. Uraemia is considered to be a consequence of the accumulation of metabolic end products with associated changes in water, electrolyte, acid-base homeostasis, disturbance in hormone and nutritional status, and abnormalities in the metabolism of fat, carbohydrates, and protein.

The syndrome of uraemia resembles systemic poisoning. Many substances accumulate in uraemia and some of these substances have been established as playing an important role as toxins (Table 2). Many of these metabolites and substances appear to act as enzyme inhibitors, with possible cumulative effects.

1.3.3.1 Implication of Uraemic Toxins

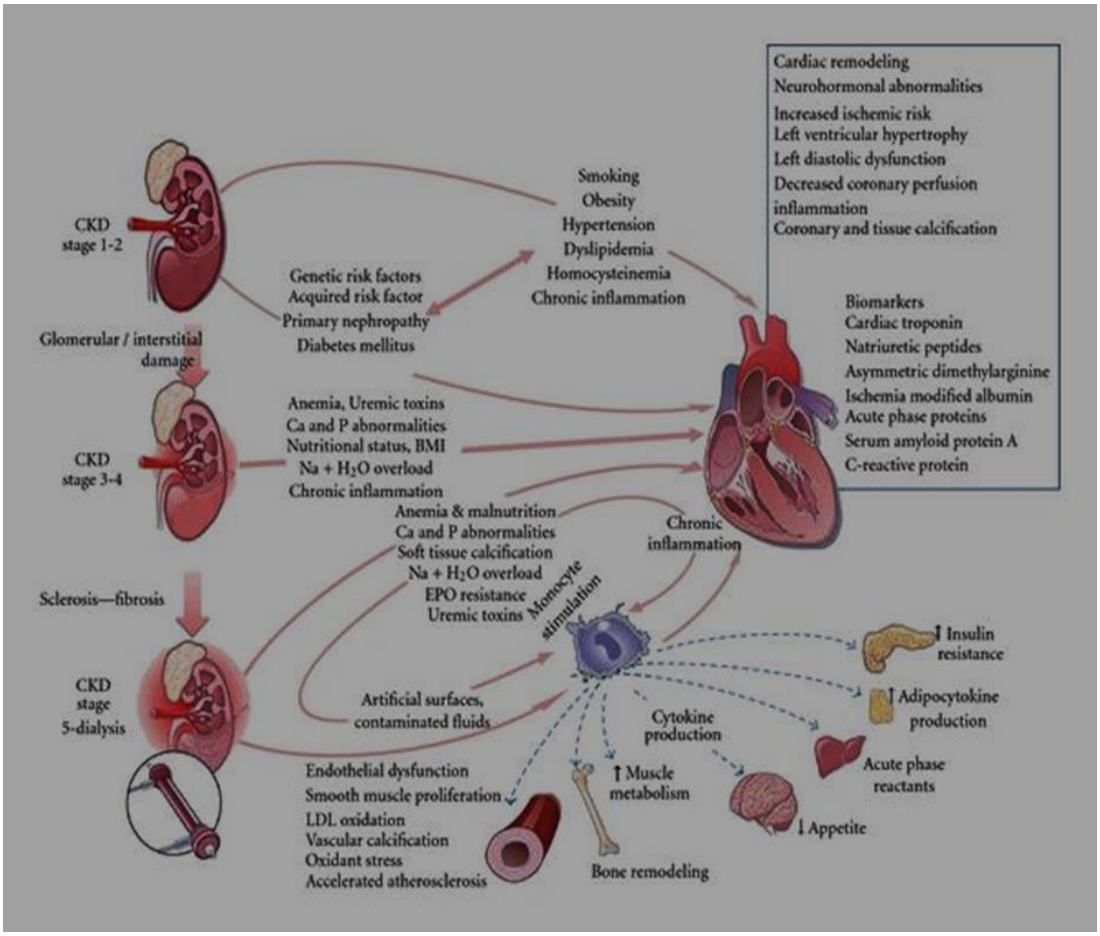
Accumulated uraemic solutes are termed uraemic toxins if they are biologically active. The accumulation of uraemic toxins is associated with negative effects on almost every organ system, as outlined in Table 5.

- **Cardiovascular system:** Heart disease accounts for more than 50% of deaths in uraemic patients (6, 7), and more than 60% of patients starting dialysis have echocardiographic manifestations, including left-ventricular hypertrophy (LVH), left-ventricular enlargement, and/or cardiac dysfunction (8). Risk factors in uraemic patients include bacteremia, extracellular fluid overload, and glycaemic load. This is in addition to anaemia, proteinuria, increases in levels of pro-inflammatory cytokines, oxidative stress, abnormal calcium and phosphate metabolism, and the accumulation of uraemic toxins,

as well as hypertension, diabetes, and dyslipidaemia as primary comorbidities (Figure 4).

- **Fluid and electrolyte imbalance**: Salt and water retention are common in end-stage renal failure (ESRF) due to loss of excretory function. Hyperkalaemia and acidosis are similarly common manifestations of uraemia. Damaged kidneys are unable to excrete the 1mg/kg of acid generated by metabolism of dietary proteins. Bone buffering of the excess hydrogen ions contributes to renal osteodystrophy.
- **Musculoskeletal:** Phosphate excretion is impaired in CKD. Hyperphosphataemia results in impaired renal activation of vitamin D3 and reduced circulating calcitriol levels, leading to reduced intestinal calcium absorption and hypocalcaemia. Loss of functioning of renal mass also results in reduced secretion of calcitriol. Hyperparathyroidism and bone disease can result in bone pain and fractures. Metastatic calcium phosphate deposition occurs especially in heart valves and blood vessels – increasing cardiovascular risk. Renal osteodystrophy typically presents with bony pain and proximal muscle weakness along with spontaneous fractures, which are slow to heal. It involves a number of entities, including hyperparathyroidism, osteomalacia, adynamic bone disease, osteoporosis, and ectopic calcification. It is due to disruption of the complex interplay of calcium, phosphate, vitamin D, PTH, and metabolic acidosis.

Figure 4: Complex pathogenesis of chronic kidney disease (CKD) and cardiovascular disease (CVD) (9)



- **Haematological:** Anaemia is very common in ESRD; the primary cause is insufficient production of erythropoietin. Iron deficiency, B12 deficiency, haemolysis, short red blood cell life, and/or suppressed bone marrow may contribute. The most important effects of anaemia occur within the cardiovascular system and include LVH, exacerbation of heart failure, and a lowered threshold for angina. Other manifestations include decreased aerobic capacity, poor cognition, and diminished overall well-being. Uraemic patients have impaired platelet function so bleeding time is prolonged. Symptoms may be manifested as petechiae, purpura, and increased bruising. There is also an increased risk of bleeding.
- **Endocrine – Endocrine abnormalities include:** hyperparathyroidism, and increased insulin resistance, which may lead to glucose intolerance.

Disturbances of thyroid function ('sick euthyroidism') and pituitary function may also occur.

- **Neurological:** Peripheral neuropathy is very common and related to uraemic toxin retention, and, in patients with diabetes, to diabetic neuropathy. Disturbed cognitive function is common. Uraemic encephalopathy is a rare manifestation of severe uraemia. Symptoms include difficulty in concentrating, lethargy, confusion and, eventually, coma if left untreated.
- **Gastrointestinal:** Metallic taste and loss of appetite are early symptoms of renal failure, and may be followed by nausea, vomiting, anorexia, and weight loss. Altered coagulation may lead to gastrointestinal bleeding, gastritis, and peptic ulcerations. Hiccups are common.
- **Skin:** Uraemia causes pruritis and abnormal skin pigmentation. High plasma phosphate levels may exacerbate pruritis. Yellowish skin pigmentation, also known as uraemic hue, is noted in many patients. This colour change is a result of retained lipochromes and carotenoids. These manifestations are often relieved with dialysis and control of serum phosphate levels.

Table 5 below summarise the manifestation of uraemia complications and symptoms, whether occurring directly from uraemia or secondarily from uraemic complications.

Table 5: Complications and symptoms of uraemic syndrome

Complications of uraemia		
Anaemia	Fluid overload	Cardiac failure
Hypertension	Insulin resistance	Hyperparathyroidism
Coagulation disorder	Osteodystrophy	Immune dysfunction
Inflammation	Coordination disorders	Loss of strength
Tremor	Pericarditis	Polyneuritis
Vascular disease	Skin atrophy	

Symptoms of uraemia	
• Loss of appetite	• Decreased desire for sexual activity
• Nausea and vomiting	• Menstrual irregularities
• Fatigue	• Constipation
• Weight loss	• Diarrhoea
• Itchy skin	• Muscle cramps and twitches
• Confusion	• Shortness of breath
• Trouble concentrating	• Chest pain
• Swelling throughout the body	• Weak, brittle bones
• Low urine output	• Yellowish-brownish skin tone
• Generalized weakness	• Headache
• Multiple bruises	• Frequent hiccups
• Numbness and tingling in the extremities	• Irritability

1.3.4 Comorbidities

One of the consequences of the increasing age of the RRT population is their increasing comorbid burden, though the burden is high in younger patients too. It can

be seen from Table 6 that comorbidities in relation to diabetes and cardiovascular disease are particularly common. Smoking is not considered a comorbidity, though it contributes to many comorbidities, e.g. malignancy, angina, and chronic obstructive pulmonary disease (COPD).

Table 6: Comorbidities in RRT patients in 2012 (1)

Comorbidity	Age <65		Age ≥65			
Overall prevalence	**N**	**(%)**	**N**	**(%)**	**p value***	**(%)**
Any comorbidity present	1,459	(41.6)	2,291	(64.0)	<0.0001	52.9
Angina	194	(5.6)	536	(15.2)	<0.0001	10.4
MI in past 3 months	42	(1.2)	99	(2.8)	<0.0001	2.0
MI >3 months ago	208	(6.0)	467	(13.2)	<0.0001	9.7
CABG/angioplasty**	176	(5.1)	385	(10.9)	<0.0001	8.0
Cerebrovascular disease	231	(6.7)	496	(14.0)	<0.0001	10.4
Diabetes (not listed as PRD*)**	182	(5.2)	476	(13.5)	<0.0001	9.4
Diabetes listed as PRD	1,008	(29.1)	765	(21.7)	<0.0001	25.4
COPD	155	(4.5)	345	(9.8)	< 0.0001	7.1
Liver disease	154	(4.4)	68	(1.9)	<0.0001	3.2
Claudication	142	(4.1)	277	(7.9)	<0.0001	6.0
Ischaemic/ neuropathic ulcers	147	(4.2)	123	(3.5)	<0.0989	3.9
Angioplasty/vascular graft	77	(2.2)	208	(5.9)	<0.0001	4.1
Amputation	110	(3.2)	86	(2.4)	<0.06	2.8
Smoking	516	(15.4)	431	(12.6)	<0.0008	14.0
Malignancy	234	(6.8)	659	(18.6)	<0.0001	12.7

**** p values from Chi-squared tests for differences between age groups in the percentage with the comorbidity***
***** Coronary artery by-pass grafting (CABG)***
******Primary renal disease (PRD)***

Depression can also be considered as comorbidity or a consequence of the illness. Cognitive impairment is also common in patients with CKD (10)and may complicate the diagnosis of depression(11).

1.4 Management of ESRD

1.4.1 Diagnosis of ESRD and Dialysis Initiation

The diagnosis of ESRD is based on the demonstration of severe kidney failure (CKD Stage 5) in blood tests and evidence of irreversibility (e.g. history of progressive decline in renal function, small kidneys on renal ultrasound, and occasionally renal biopsy findings). In general, these criteria are not by themselves an indication for dialysis initiation. In most cases the presence of symptoms attributable to uraemia is

the trigger to start dialysis (12). In suitable patients, transplantation can be carried out pre-emptively, where possible, before symptoms occur.

1.4.2 Interface of Primary and Secondary Care

Many patients with early CKD are cared for in primary care. Most kidney units provide local guidelines to primary care providers regarding referral of patients with CKD to secondary care. Many patients need input from multiple sources in addition to the nephrologist, e.g. cardiologist, diabetologists, and vascular surgeons. Clear communication between professionals is, therefore, crucially important to avoid problems such as duplicated investigations, failure to preserve peripheral vasculature for potential arteriovenous (AV) fistula, and potentially nephrotoxic investigations, e.g. as in contrast studies.

1.4.3 Referral to Nephrologist

Most patients (around 80% in the UK) start dialysis in a planned fashion (‘planned starters’), having been referred to a nephrologist when their glomerular filtration rate (GFR) was around 30 ml/min/1.73 m^2, followed up over a period of time (usually many months or years) until a treatment decision was made. Critically, these patients have had time to adapt, seek support, and be educated (13, 14). However, renal disease can remain asymptomatic for some individuals until the disease is very advanced. Such patients are often termed (‘late presenters’). Other patients may have been seen in primary or secondary care with known kidney disease, yet for some reason referral to a nephrologist was delayed (‘late referral’). Individuals in both categories may present in need of urgent dialysis colloquially referred to as (‘crash landers’). In addition, some patients may have been referred and clinically assessed by a nephrologist, but go on to need dialysis far sooner than initially expected (‘failed planned’). Starting dialysis within 90 days of referral to a nephrologist, and without adequate time to plan, can include patients in all of the above categories, and is captured by the general term (‘unplanned starters’). Such patients constitute around 20% of the incident dialysis population. An unplanned start to dialysis has

been shown in several empirical works to have adverse consequences upon patient outcome (13, 14).

Selecting a point at which to start dialysis is a complex issue with no definitive answer. Dialysis is currently started when eGFR is at a mean of around 8ml/min/1.73m^2 (UK Renal Registry data). K-DOQI guidelines recommend considering starting dialysis when eGFR <15ml/min/1.73m^2 (15) whereas the Renal Association (UK) guidelines recommend dialysis consideration when eGFR <10ml/min/1.73m^2 (16). In both guidelines, the absolute need to initiate dialysis is dictated by the presence of clinical symptoms, including symptoms of uraemia, fluid overload, and declining nutritional status. These symptoms tend to be more important indicators of the need for dialysis than the eGFR. While there is little debate about the survival disadvantage of late referral (17), there is RCT data suggesting no benefit of early planned initiation based on the level of renal function alone (12).

1.4.4 Treatment of ESRD

1.4.4.1 Conservative Treatment

Conservative kidney management provides all the aspects of kidney care support without the dialysis treatment. Conservative treatment includes medical, emotional, social, spiritual, and practical care for both the person with kidney failure and their family. The decision to choose conservative care is made in consultation with a renal multidisciplinary team. It is an appropriate choice for some people when dialysis is very unlikely to improve their quality or length of life and may even reduce aspects of overall quality of life. Studies have shown that the conservative care of frail elderly patients with ESRD can achieve outcomes comparable to those patients receiving HD. Many frail and elderly patients may live just as long being conservatively managed as with dialysis treatment (18).

In such settings, the kidney care team should ensure:

- A medication review to ensure avoidance of drugs likely to damage kidney function such as non-steroidal anti-inflammatory agents.

• Advice on an appropriate diet, though as kidney failure worsens and appetite deteriorates, adherence to a rigid diet becomes progressively less important and/or even feasible.

• Advice on the avoidance of dehydration e.g. associated with inter-current illnesses causing diarrhoea and/or vomiting.

• Adequate symptomatic treatment, e.g. breathlessness, nausea, poor appetite, and itching.

• Adequate community support, such as home help and district nursing.

• Referral to a local palliative care service, with the aim of keeping the patient active and independent for as long as possible, as well as support in the final stages.

1.4.4.2 Renal Replacement Therapy (RRT)

Dialysis replaces *some aspects* of renal function such as the removal of small and middle-sized molecules, while also permitting removal of fluid. There are two basic types of dialysis: haemodialysis (HD) and peritoneal dialysis (PD). Both modalities serve the same purpose, but differ in their application. Figure 5 shows treatment modality in prevalent RRT.

1.4.4.2.1 Haemodialysis

Haemodialysis is the most common dialysis modality and has been in regular use since the 1960s. Haemodialysis can be carried out in a hospital, in a separate clinic, in a self-care centre, and even in the patient's own home. The process normally takes between three to five hours thrice weekly. Preparation is necessary by creating access to the circulation – the optimal being the arteriovenous fistula (AV fistula). Dialysis involves pumping blood from the fistula through the dialyser, where waste products, toxins, and excess fluid are removed by diffusion and convection, and back into the fistula. Anticoagulation is required usually using systemic low molecular weight heparin. Haemodialysis adequacy is assessed by either the urea reduction ratio (URR) or normalised urea clearance (Kt/V, where K is the dialyser clearance, t the duration of the dialysis session and V the total body water). A sessional URR of >65% or sessional Kt/V of 1.2 is the minimum target adequacy for thrice weekly HD

(KDOQI, 2002) (5). These adequacy criteria relate to thrice weekly treatments, which are currently the norm, though it is thought that significant benefits may accrue from more frequent sessions (5).

1.4.4.2.2 Peritoneal Dialysis (PD)

Peritoneal dialysis has been in use since the 1980s, and is now a common home-based treatment for kidney failure patients. PD takes advantage of the peritoneum as a natural semi-permeable membrane. Dialysis fluid is introduced to the abdominal cavity, where waste products transfer through the peritoneal membrane into the fluid. On draining the abdomen, the waste is removed. There are two main versions of dialysis: the first is continuous ambulatory peritoneal dialysis (CAPD), where the patient is able to ambulate while dialysing; the second is continuous cycler-assisted peritoneal dialysis (CCPD), which requires the use of a machine called a cycler to fill and drain the abdomen, usually while the patient sleeps.

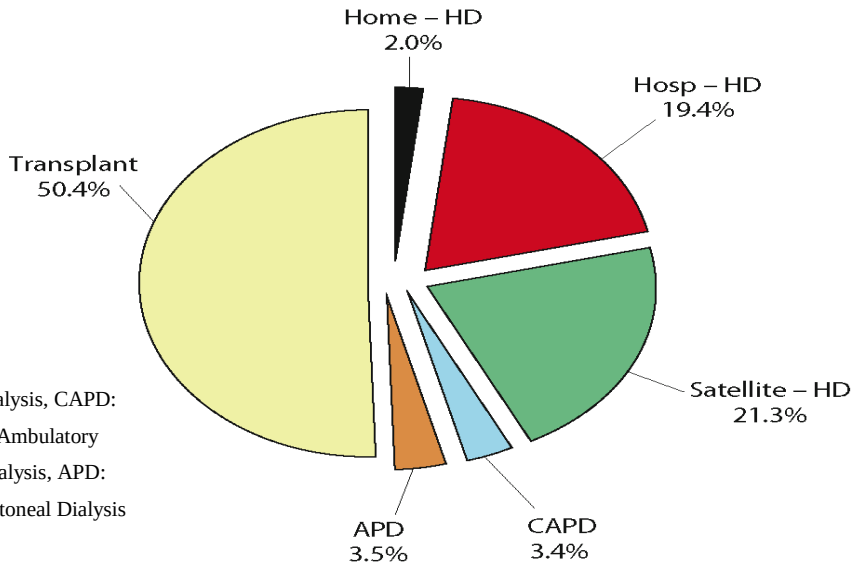
1.4.4.2.3 Renal Transplantation

Renal transplantation is the preferred treatment for ESRD, though only a minority of patients are suitable. In Europe and the US in 2002/3, only 24-55% of dialysis patients under the age of 65 were on the transplant waiting list. The higher prevalence of comorbid conditions suggests that the proportion is very much less in older patients. This selection coupled with better control of uraemia by means of transplantation accounts for the better prognosis compared with dialysis. A successful transplant returns renal function to near normal and frees the patient from dialysis treatment.

There are two sources of kidneys: living donors, either blood relative or unrelated donors, and non-living (cadaver) donors. To manage the risk of the body rejecting the transplant, immunosuppressive medication is required for the duration of the transplant. Use of these agents carries risks – particularly of increased susceptibility to infection. Nevertheless, the benefits of renal transplantation are well established, improving both survival and quality of life. Improved techniques have led to transplanted kidneys surviving longer, with around 50% lasting 10 years or more.

However, the demand for donor kidneys outweighs the supply, which prolongs the patient's reliance upon dialysis therapies.

Figure 5: Treatment modality in prevalent RRT patients (1)



HD: Haemodialysis, CAPD: Continuous Ambulatory Peritoneal Dialysis, APD: Automated Peritoneal Dialysis

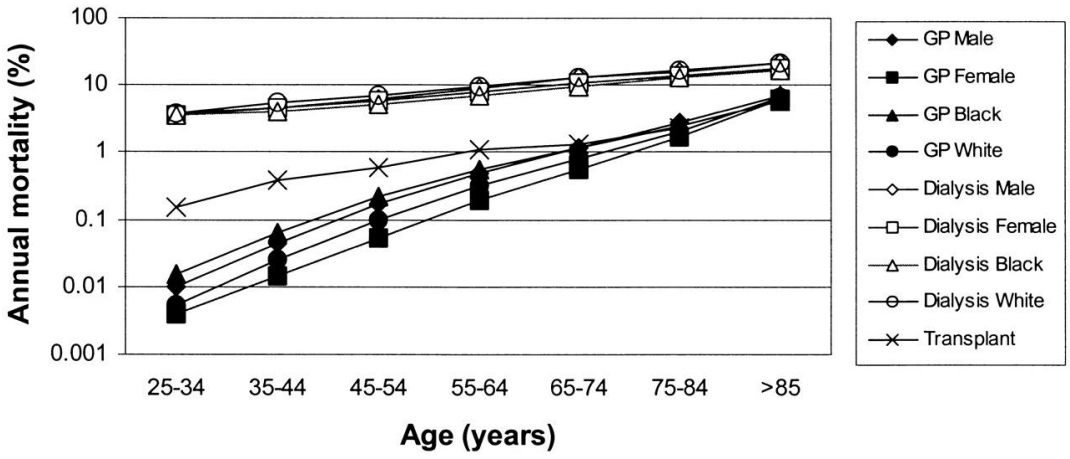
1.5 Life on Haemodialysis

1.5.1 Physical Impact of the Treatment

- **Cardiovascular disease:** The prevalence of cardiovascular disease is very high in the dialysis population. Cardiovascular mortality is dramatically increased in patients on dialysis compared with the aged-matched general population. The risk is particularly magnified in younger patients (Figure 6). The increased prevalence of cardiovascular disease also contributes to morbidity, particularly to increased symptoms of lethargy, breathlessness, and chest pain, increased intradialytic symptoms related to hypotension and dysrhythmias, and increased admissions and interventions for fluid overload, pulmonary oedema, dysrhythmias, and acute myocardial events. Mitral and aortic valve calcification as a result of metastatic calcium deposition is common among patients with ESRD. Patients with ESRD with indwelling haemodialysis catheters are at a particularly increased risk of infective endocarditis. Sudden arrhythmic death accounts for approximately half of the

cardiovascular disease (CVD) mortality in patients with ESRD (19). There is also a well-recognised association between cardiovascular disease and depression, both of which are common in dialysis patients (20).

Figure 6: Cardiovascular mortality defined by death in general population (21)



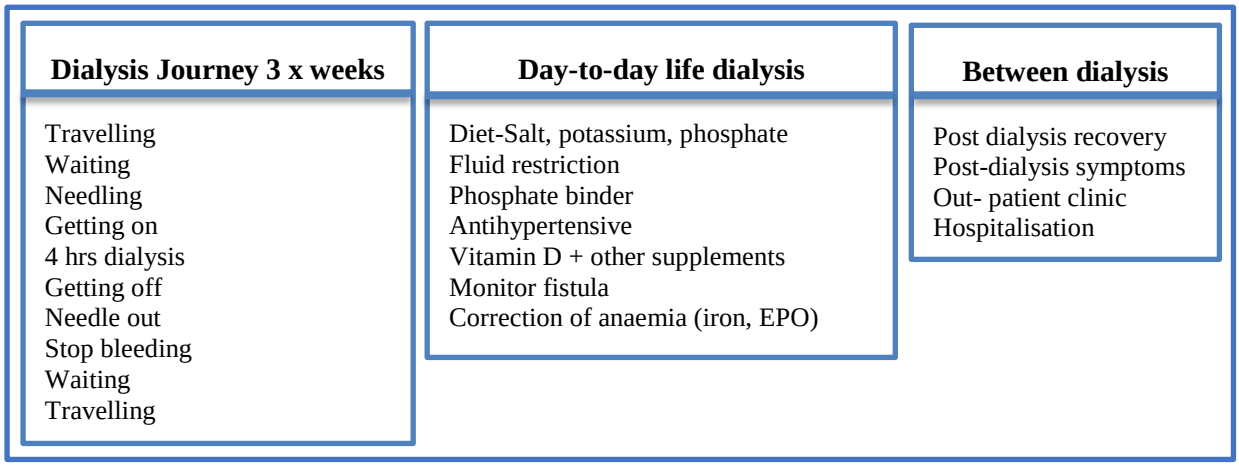
- **Hypertension:** In patients on HD the management of hypertension is less well defined than in the general population. Blood pressure varies throughout the dialysis cycle, i.e. pre- and post-dialysis pressures often being markedly different. Blood pressure targets are not well defined, there being a 'U-shaped' curve relating blood pressure and mortality. The mainstay of treatment is maintenance of a normal extracellular fluid volume by fluid removal on dialysis. Assessing the appropriate 'dry weight' of a patient is difficult. Miscalculations are frequent. Underestimation results in intradialytic hypotension, and overestimation in fluid overload, hypertension, and pulmonary oedema. Most patients also require antihypertensive agents.
- **Anaemia:** Treating a haemoglobin level <11g/dl with erythropoiesis-stimulating agent therapy improves functional capacity, but a reduction in mortality is unproven.
- **Mineral and bone disorders:** Reduced intake of phosphate; use of phosphate binders, calcium, and calcitriol supplements may all be required.
- **Uraemic symptoms**: Many of the symptoms associated with uraemia described earlier are incompletely controlled by dialysis therapy. Symptomatic treatment is required for these problems.

- **Comorbid conditions**: As described earlier, it is common for dialysis patients to suffer from a range of other conditions upon which the dialysis treatment has either no impact or perhaps a negative one. These conditions need specific management in their own right. Clinical management is either pharmacological (antihypertensive, anti-hyperlipidaemia, anaemia, bone and minerals, and cardiac) or non-pharmacological (diet, fluid restriction, psychological support). The 'pill-burden' endured by HD patients is huge, averaging around ten different agents (22).
- **Dialysis-related conditions**: It is common for patients to suffer from a range of symptoms related to the dialysis session. Symptomatic hypotension during the session occurs in up to 15% of sessions. Muscle cramps and headaches are also common. Recovery following the procedure can be prolonged – the mean recovery time being 6-8 hours (23).

1.5.2 Psycho-social Impact

HD is an intrusive treatment. Figure 7 below summarises the journey of a patient receiving HD three times weekly and the challenges they are exposed to. This includes spending 3-4 hours on the dialysis machine, but also accompanying pre- and post-dialysis impact and burdens and day-to-day life constraints secondary to the illness. Additionally, there tend to be multiple hospitalisations, adding to the overall

Figure 7 HD life journey



HD patients have sustained multiple losses, including loss of renal function and mobility, loss of their role within the family and the workplace, loss of physical skills and cognitive abilities, and loss of sexual function (24, 25). Additionally, stressors in the life of a dialysis patient can include dietary and time constraints, functional limitation, loss of employment, changes in self-perception, alterations in sexual function, general and perceived effects of illness, medication used to treat the illness, and fear of death. The demands with HD include potential changes in a patient's status in marital, familial, occupational, and social contexts; the expenses and worries associated with the treatment, illness, uncertainty, anxiety, and the costs entailed while waiting for transplant. Furthermore, treatment within a unit implies a complex relationship with dialysis personnel: physicians, nurses, technicians, and other staff. In the absence of adaptive coping, disabilities, and marital and family dysfunction can occur. The main psychological impact is depression in response to the above losses (25).

Over the past decade, increasing emphasis has been given to quality of life as survival with chronic diseases has increased. The World Health Organisation defines quality of life as 'an individual's perception of their position in life in the context of culture and value systems in which they live and in relation to their goals and expectations, standards and concerns. It is a broad ranging concept affected in a complex way by a person's physical health, psychological state, level of independence and their relationships to salient features of their environment' (26)

In the context of chronic illnesses, the most widely studied aspect of quality of life has been Health-related Quality of Life (HRQL). This construct gives insight into the patients' perceptions of the physical and psychosocial impact of the illness and its treatment on their lives (27).

Depression and anxiety are important independent predictors of low quality of life across HD patients (28-31). Depression not only undermines the patients' mental and physical health but also alter their subjective perceptions of physical status, functional capacity, and social function. It has been proposed that depression and anxiety may be more strongly associated with HRQL than clinical and socio-demographic variables taken together (28, 32).

Due to the nature of dialysis, the combination of chronic dialysis with having a job appears to be difficult. The Dialysis Outcomes and Practice Patterns Study (DOPPS) (33) indicated that the percentage of employed patients was low in the US, Europe, and Japan. The study showed that unemployment is common in ESRD patients, leading to further burdens such as a loss of social support, and low quality of life and reduced self-esteem (34, 35). Moreover, the patient's financial situation declines.

Living with a high symptom burden can be debilitating. The prevalence of pain in patients treated with haemodialysis is often underappreciated (36, 37). Better pain management appears to be a priority to improve QoL. Fatigue is common (38). It impacts on physical functioning (38, 39), family and social roles (39), activity levels (40), and mental and physical QoL (41). It damages patients' abilities to manage everyday activities (42, 43) resulting in feelings of isolation (42). It impairs memory and concentration (43). Some feel too fatigued to communicate and have difficulty maintaining close relationships (42). Fatigue symptoms can lead to poor sleep, poor physical health, and eventually depression (44). Sleep disturbances are highly prevalent (45, 46) and are associated with poor QoL (47-49). Restless leg syndrome (RLS) is also common and is associated with insomnia, mortality, and depression (50-53). In a large cohort of dialysis and transplant patients, RLS was predictive of significant depressive symptoms after controlling for covariates including albumin and co-morbidity (54).

Social support depends on instrumental, emotional, and informational help. Low perceived social support, defined by the quality of social relationships, is also a strong predictor of depression in ESRD (55, 56). ESRD is also associated with more psychological distress in younger patients compared with the elderly as a consequence of larger disruptions to their valued activities, lifestyles, and interests (57, 58). Thus, the dynamic interplay among these biological, social, and psychological factors may intensify or buffer people's feelings of distress.

Psychosocial factors and burdens, as highlighted above, may prevent or trigger depression at any point during the trajectory of CKD. In the early stages of CKD, people may be depressed and anxious because of their changed identity from being healthy to sick, the symptom burden, fear of dialysis, the uncertainty of the disease outcome, and negative experiences with the healthcare system (59). Those on

dialysis often dislike the treatment (or have ambivalent feelings, as it keeps them alive), suffer from the lifestyle disruption it causes, which may be linked to financial struggles, and feel guilty for the burden they perceive they cause for family members (59, 60). Patients' self-concept and self-esteem may also change due to the changes in their physical status, lifestyle, and social roles.

1.5.3 End of Life

For some patients, who have serious and complex illnesses or who are frail and elderly, dialysis treatments may be exceptionally burdensome with little benefit to either survival or quality of life. People who find themselves in this situation are often worried and unsure about what will happen and how long they will live if they choose to stop dialysis treatment. Patients and their families need support in coming to the decision about whether to continue with dialysis. If a decision is made to discontinue dialysis, they require end-of-life care, which should include detailed assessment of preferences for place of care, physical symptoms, psycho-social symptoms, family well-being and planning ahead in order to maximise the quality of remaining life.

Traditionally, it was believed that uraemic death was relatively symptom free; however, evidence does not support this (61). In studies that looked at end-of-life symptoms, it was shown that some patients have a peaceful and symptom-free death; however, a significant minority experience severe or distressing symptoms (61). Pain, breathlessness, nausea, retained respiratory tract secretions, and terminal agitation can all be problematic. These symptoms are relatively well controlled in the majority of patients. Agitation usually responds to low doses of anxiolytics such as midazolam. Retained respiratory tract secretions can be improved by hyoscine. Pain and breathlessness can be effectively managed by low doses of opioid medications.

1.6 Summary

Kidney disease is complex and has many different stages, and ESRD is the final stage. There are different treatment modalities for ESRD, including HD, which

usually involves lengthy out-patient treatment sessions three times a week, placing significant burdens on the patient and their family or carers. Life on HD is challenging, with both physical and psychological challenges. This thesis will concentrate on the psychological impact of ESRD and HD, which can include the presence of depression and high fatigue levels. The diagnosis of depression is complicated by the overlap of the symptoms of uraemia. Additionally, medications used to treat patients with ESRD might also cause depression or have side effects that mimic its symptomatology. When depression and fatigue are identified, alleviation of these symptoms with appropriate management should be attempted.

In the forthcoming chapters, a comprehensive review of both depression and fatigue will be conducted to give a clear understanding of these disorders, as well as an up-to-date review of the literature in order to identify the gaps upon which the thesis and research will be based.

Chapter 2

Depression in End-stage Renal Disease

In this chapter, I will initially focus on major depressive disorder in the general population, then in patients with chronic disease, and finally in ESRD patients on HD.

2.1 Mood Disorder

Mood is a subjective, pervasive, and sustained feeling that is experienced internally and influences a person's behaviour and perception of the world. The external expression of mood is described as 'affect'. Healthy individuals experience a wide range of moods and have an equally large repertoire of affective expression. Mood disorders are a group of clinical conditions characterised by the loss of a sense of control and a subjective experience of distress. Patients with a disorder of elevated mood (mania) present with grandiosity, flight of ideas, decreased sleep, and expansiveness.

Those with a disorder of depressed mood present with loss of energy and interest, a sense of guilt, loss of appetite, sleep disturbance, poor concentration, and thoughts of suicide and death. These mood disorders result in substantially impaired interpersonal, social, and occupational functioning and suicidal activity. Patients who are affected with depressive episodes only are said to have major depressive disorder or unipolar depression. Other disorders of depressed mood include bipolar affective disorder (alternating between severely depressed and elevated moods), cyclothymia (a milder form of alternating mood states) and dysthymia (chronic low-grade depression).

The morbidity caused by these disorders is greatly underappreciated. A survey conducted by the World Health Organisation (WHO) showed that mood disorders currently rank as the world's fourth greatest cause of illness burden. The report estimates these disorders will rank second by 2020 (62). The illness burden associated with day-to-day disability is profound. Depression and bipolar disorders constitute the world's leading cause of disability among adults (63).

In the UK, mental health problems are the largest single cause of disability, accounting for 23% of the total burden of disease. The economic and social costs of mental illness in England are estimated to be around £105 billion/year. This includes £21.3 billion in health and social care costs, £30.3 billion in lost economic output, and £8.4 billion in sickness absence due to mental ill health (62). Depression causes more disability than angina, arthritis, asthma, and diabetes. Both acute and chronic depressive episodes cause greater day-to-day impairment of quality of life than diabetes, high blood pressure, arthritis, or peptic ulcer disease (64). A recent heath economic analysis ranked depression as one of the five most costly brain disorders in the UK, amounting to £19.3 billion per annum (65), of which the majority of the cost was indirect, attributable to illness-related loss of income and revenue.

2.2 Major Depressive Disorder (MDD)

2.2.1 Classification

The two major classifications of mental disorder diagnosis used internationally are the World Health Organisation's International Classification of Diseases (ICD) and the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Health (DSM). Currently used versions are the ICD10 (66) and DSM-IV (67).

The ICD-10 was published in 1992 as an aid to the collection of international statistics about disease.

The DSM-IV is specific to mental disorders only and includes a multiaxial system of classification with five axes incorporating clinical disorders, personality disorder, and intellectual disabilities, and medical, psychosocial, environmental, and childhood factors. It is a hierarchical system that provides operationalised criteria for each diagnosis. It was underpinned by a comprehensive literature review, analysis of data, and field trials to evaluate changes. It has abandoned the psychoses–neuroses distinction, and has some minor differences from the ICD-10, which are outlined in Table 7. The DSM-5 (68) was published in May 2013, and superseding the DSM IV-TR. In most respects, DSM-5 does not differ greatly from DSM-IV. Notable changes

include dropping Asperger's syndrome as a distinct classification; loss of subtype classifications for variant forms of schizophrenia; dropping the 'bereavement exclusion' for depressive disorder; a revised treatment and naming of gender identity disorder to gender dysphoria; and removing the A2 criterion for post-traumatic stress disorder.

Table 7: Differences in the ICD-10 and DSM-IV classification systems

	ICD-10	DSM-IV
Origin	International (WHO) 1992	American Psychiatric Association (APA) 1994
Presentation	Different versions for different settings	Single document
Languages	Available free in all widely spoken languages	English only and not 'licensed'
Structure	Part of overall ICD framework. Single axis in chapter V; separate multiaxial systems available Versions use both operational and clinical prototypes	Multi-axial All categories defined using operational criteria (reliable, easily applied, internationally accepted, easy-to-design interview for research)
Content	Guidelines and criteria do not include social consequences of psychiatric disorder Terms 'neurotic' and 'neurasthenia' preserved	Diagnostic criteria usually include significant impairment in social functions Terms 'neurotic' and 'neurasthenia' discarded

DSM-IV and ICD-10 have virtually the same diagnostic features for a 'clinically important' severity of depression (termed a major depressive episode in DSM-IV or a depressive episode in ICD-10). However, their thresholds differ, with DSM-IV requiring a minimum of five out of nine symptoms (which must include depressed mood and/or anhedonia) and ICD-10 requiring four out of ten symptoms (including at least two weeks of depressed mood, anhedonia, and loss of energy). This may mean that more people may be identified as depressed using the ICD-10 criteria compared with that of DSM-IV (69) , or at least that slightly different populations are

identified (70), related to the need for only one of two key symptoms for DSM-IV but two out of three for ICD-10.

Major depressive disorder is a mental disorder characterised by pervasive and persistent low mood, accompanied by loss of interest and/or anhedonia (the loss of interest in otherwise pleasurable everyday activities, such as hobbies, sex, or work). The severity of the disorder is determined by the number and severity of symptoms, as well as the degree of functional impairment. These are accompanied by other somatic, cognitive, and behavioural symptoms, such as loss of energy, significant changes in body weight, insomnia or hypersomnia, agitation, difficulty concentrating, feelings of worthlessness, hopelessness, helplessness, excessive guilt, and/or thoughts about death and suicide.

Depression is usually categorised on the basis of the severity, duration, and number of symptoms. For example, the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM IV-TR) classifies depressive disorders as Major Depressive Disorder, Dysthymic Disorder, and Depressive Disorder Not Otherwise Specified (67) (Table 8). While much attention has focused on the management of major depression, less severe forms of depression may lead to as much disability as major depression (71). Also, less severe but persistent mental stress may develop into major depression if protective factors are not mobilised (72).

Table 8: Symptoms of depressive disorders (based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition)

Major Depressive Episodes
Five or more of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either depressed mood or loss of interest or pleasure.
(1) Depressed mood
(2) Markedly diminished interest or pleasure in (almost) all activities
(3) Significant weight loss when not dieting, or weight gain, or decrease or increase in appetite
(4) Insomnia or hypersomnia

(5) Psychomotor agitation or retardation

(6) Fatigue or loss of energy

(7) Feelings of worthlessness or excessive or inappropriate guilt

(8) Diminished ability to think or concentrate, or indecisiveness

(9) Recurrent thoughts of death, recurrent suicidal ideation, or a suicide attempt

The symptoms cause significant distress or impairment in social, occupational, or other important areas of functioning.

Dysthymic Disorder

Depressed mood for at least two years. Presence, while depressed, of two (or more) of the following:

(1) Poor appetite or overeating

(2) Insomnia or hypersomnia

(3) Low energy or fatigue

(4) Low self-esteem

(5) Poor concentration or difficulty making decisions

(6) Feelings of hopelessness

The symptoms cause significant distress or impairment in social, occupational, or other important areas of functioning.

Examples of Depressive Disorders Not Otherwise Specified

(1) Minor depressive disorder: episodes of at least two weeks of depressive symptoms, but with fewer than the five items required for major depressive disorder

(2) Recurrent brief depressive disorder: depressive episodes lasting from two days up to two weeks, occurring at least once a month for 12 months

(3) Situations in which the clinician has concluded that a depressive disorder is present, but is unable to determine whether it is primary, due to a general medical condition, or substance-induced

2.2.2 Diagnosis

Diagnostic approaches rely upon professional evaluation typically by structured or semi-structured interviews using diagnostic criteria such as the Diagnostic and

Statistical Manual of DSM-IV, as explained above. The Structured Clinical Interview for Depression (SCID) is one diagnostic assessment based upon the DSM-IV criteria. Other diagnostic methods included, the Diagnostic Interview Schedule (DIS) and the Mini-International Neuropsychiatric Interview (MINI). Formal diagnosis has implications for the management and treatment of depressive disorders.

The Mini-International Neuropsychiatric Interview (MINI): The MINI is a short diagnostic structured interview (DSI) developed jointly by psychiatrists and clinicians in the US and Europe, for DSM-IV and ICD-10 psychiatric disorder. It was designed to meet the need for a short but accurate structured psychiatric interview for multicentre clinical and epidemiology studies and to be used as a first step in outcome tracking in non-research clinical settings. It is fully structured to allow administration by non-specialised interviewers. It focuses on the existence of current disorders. For each disorder, one or two screening questions rule out the diagnosis when answered negatively. Examinations for severity, disability, or medically explained symptoms are not explored symptom by symptom (73). Two joint papers present the inter-rater and test-retest reliability of the MINI and the validity versus the Composite International Diagnostic Interview (CIDI) (74) and the Structured Clinical Interview for DSM-III-R patients (SCID) (75). 346 patients (296 psychiatric and 50 non-psychiatric) were administered the MINI and the CIDI 'gold standard'. Forty-two were interviewed by two investigators and 42 were interviewed subsequently within two days. Interviewers were trained to use both instruments. The mean duration of the interview was 21 minutes with the MINI and 92 minutes for corresponding sections of the CIDI. Kappa coefficient, sensitivity, and specificity were good or very good for all diagnoses with the exception of generalised anxiety disorder (GAD) (kappa = 0.36), agoraphobia (sensitivity = 0.59) and bulimia (kappa = 0.53). Inter-rater and test-retest reliability were good, with the kappa coefficients ranging from 0.88 to 1.0. The main reasons for discrepancies were attributed largely to the coexistence of affective and psychotic symptoms. The MINI provided reliable DSM-III-R diagnoses within a short time frame.

2.2.3 Screening

Screening for depression in the general medical population remains controversial as there is a lack of diagnostic capability and typical self-report scales are used, requiring the patient to rate symptom frequency or severity. Such tools assess the patient's mood based upon a continuum, with higher depression scores often reflecting greater depressive symptoms. Self-report scales are useful research tools that allow depression to be quantified across a population who do, as well as those who do not, meet the diagnostic criteria for depression. Given the high prevalence of depression and its significant impact on morbidity and mortality, a strong case can be made for screening patients with chronic medical conditions, as this could serve to identity patients with significant depressive symptoms or to assess the severity of depression so that the diagnosis of depression is not missed and the opportunity to provide treatment can be considered.

The Beck Depressive Inventory (BDI) is a 21-item self-report questionnaire that uses cut-off levels for depression in the general population: 9, no depression; 10 to 15, mild depression; 16 to 23, moderate depression; 24, severe depression. The 21 items are scored on a four-point scale, where 0 signifies no problem and 3 represents an extreme problem, with a total score range of 0 to 63 (76).

The Cognitive Depression Index (CDI) is a subset of the BDI that consists of items of affective components and excludes the somatic components of the questionnaire. The affective component contains eight items: pessimism, past failures, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts or wishes, and worthlessness. The somatic component consists of the other thirteen items: sadness, loss of pleasure, crying, agitation, loss of interest, indecisiveness, loss of energy, change in sleep patterns, irritability, change in appetite, concentration difficulties, tiredness and/or fatigue, and loss of interest in sex. The two subscales were moderately correlated at 0.57, suggesting that the physical and psychological aspects of depression are related rather than totally distinct (77, 78).

The nine-question Patient Health Questionnaire (PHQ-9) consists of nine questions that assess the severity of depression with each question based on a scale of 0 to 3. Higher PHQ-9 scores correlate with increased depressive affect. The PHQ-

9 has a maximum possible score of 27: 0-4, none; 5-9, mild; 10-14, moderate; 15-19, moderately severe; 20-27, severe (79, 80).

The Centre for Epidemiologic Studies Depression Scale (CES-D) consists of 20 items ranging on a scale of 0 to 60. A CES-D cut-off score of 16 in the general population is used as a screening tool for possible depression (81).

The Zung Self-report Depression Scale (Zung SDS) is a short, self-administered survey to quantify the depressed status of a patient. There are 20 items on the scale, which rate the affective, psychological, and somatic symptoms associated with depression. There are ten positively worded and ten negatively worded questions. Each question is scored on a scale of 1 to 4 (based on these replies: 'a little of the time', 'some of the time', 'good part of the time', 'most of the time'). Scores on the test range from 20 to 80. The scores fall into four ranges; normal range (20-44), mildly depressed (45-59), moderately depressed (60-69), and severely depressed (above 70) (82).

The Hospital Anxiety Depression Scale (HADS) is commonly used to determine the levels of anxiety and depression that a patient is experiencing. The HADS is a 14-item scale. Seven of the items relate to anxiety and seven relate to depression. Each item on the questionnaire is scored from 0 to 3 and this means that a person can score between 0 and 21 for either anxiety or depression. The cut-off point for caseness of anxiety or depression is 8/21 (83, 84).

Quick Inventory of Depressive Symptomatology Self-report (QIDS-SR) The 16-item QIDS measures depressive symptom severity derived from the 30-item Inventory of Depressive Symptomatology (IDS), and is available in both self-report (QIDS-SR(16)) and clinician-rated (QIDS-C(16)) formats. The scoring system for the QIDS converts responses to 16 separate items into the nine DSM-IV symptom criterion domains. The nine domains comprise: 1) sad mood; 2) concentration; 3) self-criticism; 4) suicidal ideation; 5) interest; 6) energy/fatigue; 7) sleep disturbance (initial, middle, and late insomnia or hypersomnia); 8) decrease/increase in appetite/weight; and 9) psychomotor agitation/retardation. The total score ranges from 0 to 27. The cut-off point for depression is $\geq$10 (85).

The Hamilton Rating Scale for Depression (HAMD) is a 17-item clinician-rated questionnaire that is used to assess depressive affect. Each item on the questionnaire is scored on a three- or five-point scale. A score of 0-7 is considered normal. Scores of 20 or higher indicate moderate, severe, or very severe depression, and are usually required for entry into a clinical trial. Questions 18-20 may be recorded to give further information about the depression (such as whether diurnal variation or paranoid symptoms are present), but are not part of the scale (86).

The Montgomery-Åsberg Depression Rating Scale (MADRS) is a 10-item clinician-rated questionnaire used to measure the severity of depressive episodes in patients with mood disorder (87). It was designed as an adjunct to the HAMD as it seems more sensitive to the changes brought on by antidepressants and other forms of treatment than the Hamilton Scale (88). A higher MADRS score indicates more severe depression, and each item yields a score of 0 to 6 (89). The overall score ranges from 0 to 60. Usual cut-off points are: 0-6, normal/symptom absent; 7-19, mild depression; 20-34, moderate depression; >34, severe depression (89, 90). MADRS is less biased by anxiety and physical factors (0 items) than HAMD so is especially useful in the presence of physical illness (91).

The Clinical Global Impression (CGI) rating scales are commonly used measures of symptom severity, treatment response, and the efficacy of treatments in treatment studies of patients with mental disorders (92). Many researchers, while recognising the validity of the scale, consider it to be subjective as it requires the user of the scale to compare the subjects to typical patients in the clinician's experience. They are:

- The Clinical Global Impression – Severity scale (CGI-S) is a seven-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating: 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill.
- The Clinical Global Impression – Improvement scale (CGI-I) is a seven-point scale that requires the clinician to assess how much the patient's illness has

improved or worsened relative to a baseline state at the beginning of the intervention. It is rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.

- The Clinical Global Impression – Efficacy Index is a four-point × four-point rating scale that assesses the therapeutic effect of the treatment as: 1, unchanged to worse; 2, minimal; 3, moderate; 4, marked by side effects rated as: none; do not significantly interfere with patient's functioning; significantly interfere with patient's functioning; or outweigh therapeutic effect.

2.2.4 Epidemiology of MDD

At least 12% of the adult population will suffer from a mood disorder at some point, with some surveys suggesting lifetime prevalence rates as high as 25%. The cumulative risks of the specific major mood disorders are 10.2% for major depressive disorder and 1.3% for bipolar disorder (93-96).

Minor or sub-syndromal forms of major depressive disorder include dysthymia (persistent, unremitting symptoms for at least two years), sub-syndromal symptomatic depression (characterised by neither sufficient duration for dysthymia nor sufficient symptom severity for a major depressive episode), and adjustment disorders with depressive features (onset following a stressor; less severe and persistent than a major depressive episode). The lifetime risk of dysthymia is about 3-5% (97, 98).

The modal age of onset of major depressive disorder is between 25 and 35 years (93, 96, 99), and has decreased over the past four generations (93). Earlier onsets are associated with greater lifetime incidence and higher rates of recurrence (99). A later onset is associated with the absence of family history of mood disorder, alcohol, and antisocial personality disorder. The lifetime risk that someone with dysthymia will develop a major depressive episode exceeds 70% (95). Major depressive disorder and dysthymia are more common among women, who have a morbid risk 1.5-2 times greater than men (93, 96, 99).

For a fortunate minority (30-45%), a single lifetime episode of major depression may have few long-term sequelae. More often, major depressive episodes recur with increasing frequency. After a second lifetime episode, the risk of a third is at least 70% within three years (without prophylactic treatment) (100). Early withdrawal of antidepressant medication before three months results in the return of the symptoms, and as the course of the disorder progresses, patients tend to have more frequent episodes that last longer. Over a 30-year period, the mean number of episodes is five to six (101).

The average depressive episode lasts about nine to 12 months without treatment, although about 20% run a chronic course of two years or longer. Once established, chronic episodes last an average of five to eight years (93). Episodes of major depressive disorder with dysthymia are called double-depressive syndrome (dysthymia plus a superimposed major depressive episode) and are associated with the most disability (102).

Most people who suffer from one episode of depression will develop a recurrence of the disorder. Early in the course of illness, it is not uncommon for an apparently unipolar disorder to switch to bipolar, especially when the onset of depression is before the age of 25 (103). After three or more depressive episodes, however, the onset of mania is much less likely (<5% incidence).

2.2.5 Aetiology

2.2.5.1 Neuro-biological factors

The classical theory to explain depression is the ‘monoamine hypothesis’, which proposes that depression is related to a deficit of monoamines, particularly norepinephrine (NE) and serotonin (5-HT), at critical synapses (104). Additional neurotransmitters implicated include acetylcholine (105), gaba amino butyric acid (106), glutamine, and glycine-N-methyl-d-aspartate (107).

The monoamine neurotransmitters NE, 5-HT, and dopamine (DA) are the main focus of theories and research on the aetiology of depressive disorder. Malfunctioning of monoamine pathways has been difficult to document in depression, but the

antidepressant actions of currently available drugs (i.e. their ability to reduce or eliminate depressive symptoms) are definitely linked to boosting neurotransmission in monoamine pathways (108).

Depression has also been associated with dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis. This may manifest itself in two ways; firstly, activation of the HPA axis and, secondly, blunting of the normal diurnal cortisol profiles. Cortisol is a counter-regulatory hormone and in excess induces visceral/central adiposity, insulin resistance, dyslipidemia (metabolic syndrome), and hypertension. States of depression and stress can result in elevated plasma adreno-corticotrophin hormone (ACTH) and cortisol levels, elevated 24-hour urine free cortisol (UFC) levels, adrenal gland enlargement, and failure to suppress cortisol in response to the dexamethasone suppression test (109). Successful treatment for major depressive disorder can restore the suppressive response to dexamethasone (110).

MDD is also known to be accompanied by clinically significant cognitive functional impairment and is associated with poor response to treatment (111). Neuropsychological dysfunction is often present in the disorder and has been shown to contribute independently to poor functional outcome (112). These includes sustained vigilance and motor functioning (113), visuomotor attention and processing (114), ideational fluency (115) short-term and working memory, verbal and non-verbal learning (116) and general intelligence (117). It has been proposed that executive function may be particularly impaired in individuals with MDD, and that problems in other domains, such as memory, attention, and problem-solving, may arise because these abilities rely heavily on aspects of executive and prefrontal function (118).

2.2.5.2 Psycho-social factors

There are many psycho-social pathways that may lead to depression. The most common involve family relationships, interpersonal relationships, social function, and the discrimination an individual might suffer at the hands of others. Psycho-social factors are:

- **Life events and environmental stress:** Stressful life events are associated with the onset of episodes of major depression. The response to stressful life events is also influenced by genetic factors, which seem to align with those that predispose to major depression. The most compelling data indicate that losing a parent before the age of 11 is often associated with the development of depression (119). Loss of spouse may also precipitate depressive episodes. Other risk factors include female gender, unemployment, living alone, and older age (120). Depression is related to the normal emotions of sadness and bereavement, but it does not remit when the external cause of these emotions dissipates, and it is disproportionate to their cause. Classic severe states of depression often have no external precipitating cause. It is difficult, however, to draw clear distinctions between depressions with and those without psychosocial precipitating events (121).
- **Cognitive impairment:** Both low mood and cognitive impairment are associated with poor psychosocial functioning. Patients usually rated their social or occupational functioning as significantly, severely, or totally impaired (112). Therefore, the remediation of cognitive impairment and alleviation of depressive symptoms each play an important role in improving outcome for patients with depression (11). Cognitive impairment represents a core feature of depression that cannot be considered an epiphenomenon that is entirely secondary to symptoms of low mood .It is widely acknowledged as an important aspect of MDD. Indeed, the DSM-IV criteria for MDD include "diminished ability to think or concentrate, or indecisiveness". Impaired cognition has been estimated to occur in around two-thirds of depressed patients(122). Impairments in cognition have been found to persist beyond acute episodes of depression, and between one-third and one-half of remitted depressed patients are thought to be affected by cognitive impairment (123).
- **Personality factors:** Certain personality types such as obsessive compulsive personality disorder (OCPD), and emotionally unstable (borderline) or histrionic personality disorders are at greater risk of depression, compared to antisocial or paranoid personality disorders since the latter tend to use projection and other externalising defence mechanisms to protect themselves

(124). Beck (125) proposed that depression may occur when persons experience events that represent a perceived loss in a domain that has particular meaning or relevance for them. Thus, for highly sociotropic people (those who need positive interchanges with other individuals), depression is most likely to occur in response to perceived interpersonal loss or rejection. In contrast, highly autonomous people (those who need independence and to attain meaningful goals) are most likely to become depressed in response to perceived failure or lack of control over the environment.

- **Psychodynamic factors:** Sigmund Freud (126) was first to explore the psychodynamic understanding of depression. This was later expanded by Karl Abraham (101) as the 'classic view of depression'. This theory involves four key points: 1) disturbances in the infant-mother relationship during the oral phase (10-18 months) predispose to subsequent vulnerability of depression; 2) depression can be linked to a real or imagined object loss; 3) introjection of the lost object acts as a defensive mechanism to deal with the distress related to the loss; 4) object loss is regarded with a mixture of love and hate; feelings of anger are directed inward at the self.
- **Genetics:** studies comparing concordance rates for major depression between monozygotic and dizygotic twins suggest a heritability of about 37% (127). Kendler et al. (128) showed that although depression is due in part to heritable depression prone personality traits, it is also the result of heritable factors that are independent of personality. Early-onset, severe, and recurrent depression may have a higher heritability than other forms of depression (129). It is clear from studies of families that major depression is not caused by any single gene but is a disease with complex genetic features. Studies of pedigrees with multiple cases of major depression have identified chromosomal regions with linkage to the disorder, and some of these loci have been replicated in more than one study, although no single chromosomal region has been replicated in every family study of genetic linkage in depression. There is evidence of linkage of recurrent, early-onset depression to chromosome 15q25-q26, but the population attributable risk was small. No specific molecular risk factor has been reliably identified (130). One common

polymorphic variant of the serotonin-transporter-linked polymorphic region (5-HTTLPR), which affects the promoter of the serotonin-transporter gene, causes reduced uptake of the neurotransmitter serotonin into the presynaptic cells in the brain (131). Some studies have shown that this polymorphism confers a predisposition to depression (132), but it also confers a predisposition to an anxious and pessimistic personality (131). Brain imaging reveals functional differences in emotion-related areas of the brain among carriers of the different common polymorphisms of *5*-HTTLPR (133), although a direct relation to depression is unclear. In a large, prospective epidemiologic study, Caspi et al. (134) found that 5-HTTLPR predicted depression only in association with defined life stresses. Some environmental factors could confer a predisposition to depression by affecting the genome epigenetically – for example, increased maternal care in rodents causes an epigenetic change in the promoter region of the glucocorticoid receptor gene (135).

- **Frailty:** is a multifactorial geriatric syndrome, which may be influenced by pain, mobility and balance problems, weakness, and poor endurance. All of these risk factors may lead to disability, or functional dependence, and thus lead to depression(136). In a recent meta-analysis there was a "bi-directional relationship between frailty and depression". Approximately 40% of frail people with depression have frailty and a similar proportion of those with frailty have depression. Frail older people are four times more likely to have depression than non-frail people (137). The relationship between depressive symptomatology and increased risk of incident frailty was robust, while the opposite relationship was less conclusive (138). There is evidence that depression is associated with increased weakness, mobility deficits, and fatigue, which may thus increase the risk of frailty and increased mortality over a period of up to 5 years (139).

  Depression may also predict indicators of frailty due to the decrease in social ties, gait speed, and less physical activities, or due to the increase in sedentary life, fall risk, weight loss, and malnutrition, which may increase the perpetuation of affective symptoms typical of depression including sadness,

anhedonia and helplessness (140). Additionally, depression may not only be associated with physical frailty, but also with cognitive impairment as discussed above, which may be long-lasting and may persist even during affective remission (141). Depression related cognitive impairment may contribute to the emergence of frailty. It is also possible that there are shared risk factors and pathophysiological pathways. These are partly explained by overlapping mechanisms such as cerebrovascular disease and sub-clinical vascular diseases that cause pre-frontal white-matter hyper-intensities in patients with late-life depression have consistently been considered a key factor in pre-frailty (142), chronic inflammation, oxidative stress, mitochondrial dysfunction (143), HPA axis dysregulation (144).

There are approaches to prevent frailty or depression which may protect against the other. The potential role of antidepressant medications on frailty has not been clear because geriatric characteristics are rarely taken into account in trials on antidepressant drugs in late-life depression (145). Successful treatment of the depression itself may result in increased behavioural and social activation, thereby increasing physical and social activity levels, improving muscle mass and strength, and the elder's overall energy levels, thereby, reducing frailty (146). Increasing physical activity is an effective intervention for frailty in older adults, and can protect and manage depressive symptoms in the elderly through potential neurobiological changes and as a consequence of social and physical engagement (147, 148).

2.2.6 Comorbidity

Patients with major depressive disorder are at increased risk of developing additional comorbid mental illness. The most frequent disorders are: alcohol abuse/dependence, panic disorder/OCD, and social anxiety (life time prevalence 27%, 10%, 12%, respectively) (149).

2.2.7 Management of Depression

Most patients with depressive disorder are managed in primary care. However, lack of understanding of the recognition and treatment of depression means not all those requiring treatment are recognised (NICE, 2009) (150).

About 50% of patients having their first depressive episode exhibit significant depressive symptoms before the first identifiable full episode (101). Early identification and treatment of symptoms may prevent the development of a full depressive episode. The incidence of relapse is lower in those on prophylactic antidepressants and who had only one or two episodes. However, the more episodes of depression, the less the duration between the episodes and the more severe (101).

Once the diagnosis of clinical depression is made, treatment options need to be tailored to the individual needs of the patient and the resources available to the clinical team. NICE recommends not using antidepressants routinely to treat persistent subthreshold depressive symptoms or mild depression, but rather consider psychological intervention, e.g. cognitive behaviour therapy (CBT), because the risk–benefit ratio is poor. Antidepressants should be considered for people with a past history of moderate or severe depression or initial presentation of subthreshold depressive symptoms that have been present for a long period (typically at least two years), or subthreshold depressive symptoms or mild depression that persist(s) after other interventions. An algorithm depicting a suggested management plan for the use of antidepressants is shown in Figure 8.

There are a variety of treatment options. Firstly, there is pharmacotherapy, which includes different groups of antidepressants (Table 9). Secondly, there are psychosocial therapies, including CBT, a type of psychotherapy developed by Beck (125). CBT is based on the cognitive model, which states that thoughts, feelings, and behaviour are all connected, and that individuals can move toward overcoming difficulties and meeting their goals by identifying and changing unhelpful or inaccurate thinking, problematic behaviour, and distressing emotional responses. According to cognitive therapists, depression is maintained by constant negative thoughts. These thoughts are known as automatic thoughts, which occur without conscious effort, as in depressed patients. CBT involves the individual working

collaboratively with the therapist to develop skills for testing and modifying beliefs, identifying distorted thinking, relating to others differently, and changing behaviours. A course may last from six weeks to six months, with weekly sessions of 45 minutes. The duration will depend on the type of problem and progress. The availability of CBT varies between different areas. Interpersonal therapy, developed by Gerald Klerman (151) is another form of psychosocial therapy. It is time limited (12 to 16 weeks) and focuses on one or two of a patient's current interpersonal problems. It encourages the patient to regain control of mood and functioning through a treatment alliance in which the therapist empathically engages the patient, helps him/her to feel understood, arouses affect, presents a clear rationale and treatment ritual, and yields success experiences. Somatic therapies are also effective and include electroconvulsive therapy (152), vagal nerve stimulation (153), deep brain stimulation (154) and trans-cranial magnetic stimulation (155). In severe/resistant episodes a combination of one or more of the above is considered, depending on the psychiatric assessment and risk.

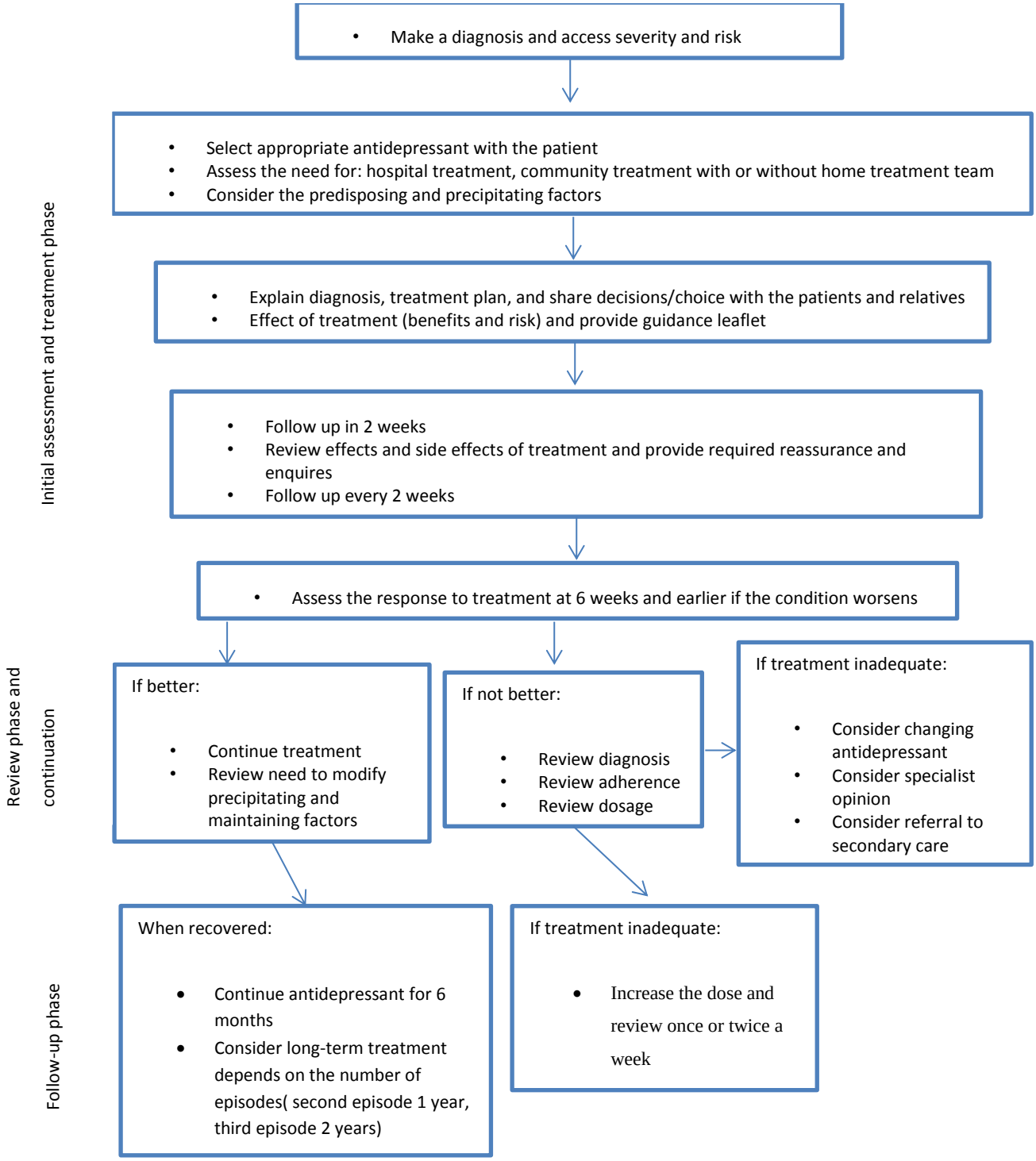
Table 9: Antidepressant pharmacotherapy

Generic name	Usual daily dose (mg)	Common side effects	Clinical caveats
5-HT Reuptake Inhibitor		all SSRIs may cause insomnia agitation, sedation, GI distress and sexual dysfunction.	many SSRIs inhibit various cytochrome p450 isoenzymes they are better tolerated than TCA, high safety in over dose (OD). Shorter half-life SSRIs may be associated with discontinuation symptoms if stopped abruptly.
Citalopram	20-60		
Escitalopram	10-20		
Fluoxetine	10-40		
Fluvoxamine	100-300		
Paroxetine	20-50		
Sertraline	50-200		
NE Reuptake Inhibitor			
Desipramine	75-300	drowsiness, insomnia, OSH, CA, agitation, ↑weight, anticholonergic[1]	dose titration required. over dose can be fatal
Protriptyline	20-60	drowsiness, insomnia OSH, CA, agitation, anticholonergic[1]	dose titration required. over dose can be fatal
Nortriptyline	40-200	drowsiness, insomnia, OSH, CA,↑weight, anticholonergic[1]	dose titration required. over dose can be fatal
Maprotiline	100-225	drowsiness, insomnia, OSH, CA, anticholonergic[1]	dose titration required. over dose can be fatal
NE and 5-HT Reuptake Inhibitor			
Amitriptyline	75-300	drowsiness, OSH,CA, ↑weight, anticholonergic[1]	dose titration required. over dose can be fatal
Doxepin	75-300	drowsiness, OSH,CA, ↑weight, anticholonergic[1]	over dose can be fatal
Imipramine	75-300	drowsiness, agitation, insomnia, OSH, CA, anticholonergic[1]	dose titration required. over dose can be fatal
Trimipramine	75-300	drowsiness, OSH,CA, ↑weight, anticholonergic[1]	dose titration required. over dose can be fatal
Venlafaxine	75-375	sleep changes, GI distress, discontinuation syndrome	higher dose may cause hypertension dose titration is required. Abrupt stop may cause discontinuation symptoms.
Clomipramine	75-300	drowsiness, ↑weight	dose titration required
Duloxetine	30-60	GI distress, discontinuation Syndrome	dose titration required
Pre- and post-synaptic agents			
Nefazodone	300-600	Sedation,	dose titration required, no sexual dysfunction
Mirtazapine	15-45	sedation, ↑weight	dose titration required, no sexual dysfunction
Dopamine Reuptake Inhibitor			
Bupropion	200-400	insomnia, agitation, GIT distress	No sexual dysfunction
Mixed Action Agents			
Trazodon	150-600	drowsiness, OSH, CA, GI distress	Priapism is possible
Amoxapine	100-600	drowsiness, insomnia, agitation, OSH,CA, ↑weight, anticholonergic[1]	dose titration required, movement disorder

CA: cardiac arrhythmia; 5-HT: serotonin, GI: gastrointestinal; NE: norepinephrine; OSH: orthostatic hypotension; SSRI: selective serotonin reuptake inhibitor; [1] dry mouth, blurred vision, constipation, urinary urgency.

Algorithm for the Management of Depression

Figure 8 Management of depression



2.3 Depression in Chronic Physical Illness

The role of depression in physical illness has been recognised and addressed extensively by the National Institute for Health and Clinical Excellence (CG91 Depression with a Chronic Physical Health Problem: NICE Guideline. National Collaborating Centre for Mental Health, London, 2009). Depressive symptoms, particularly when persistent and severe, may be associated not only with impaired quality of life but also with a reduced survival (156). Patients with chronic physical illness who are depressed are at risk because of the difficulty in adhering to complicated treatment regimens or because of suicidality. However, although the presence of major depression has important clinical implications in medically ill patients, the recognition of depression by physicians is poor (157). The failure to diagnose depression may be due to uncertainty about the diagnostic validity of many of the symptoms of depression in the presence of a medical illness and to pessimism regarding the possibilities for therapeutic intervention. Such pessimism may be unwarranted (158).

When depression occurs along with another medical or psychiatric condition, the term ‘compound depression’ is often used (159).

The diagnosis and treatment of depression in patients with physical illness is challenging and the disorder is in general more treatment resistant than depression in patients without other medical or psychiatric comorbidities (24, 160-162).

2.3.1 Clinical Features

Psychological symptoms associated with physical illness are very common but do not always indicate a depressive illness. Adjustment disorders commonly follow the onset of an acute illness. Symptoms of low mood, anxiety, guilt, and hopelessness develop in response to an identifiable stressor but are not persistent. The boundary between adjustment and depressive disorders is not clear-cut, but the key determinant is the severity and duration of symptoms (see next paragraph). Other indicators of a possible mood disorder are failure to adjust to the illness, poorer physical

functioning, slower recovery than would be expected, and reduced social interaction (163).

Depressive syndromes and medical illnesses may relate through several mechanisms. A medical condition may affect self-esteem, body image, or social functioning, or it may alter psychodynamic equilibria. These effects may themselves be sources of stress that can overwhelm coping mechanisms and hence contribute to depression (164). Organic factors in the medically ill may contribute to depression and to symptoms that resemble depression.

Medical conditions may produce both somatic and cognitive-affective symptoms that result in false-positive diagnoses of depression. Biologic factors including metabolic disturbances and the effects of medications may also result in depressive syndromes – referred to as organic affective disorders.

Five or more symptoms of depression that persist over a two-week period are indicative of a depressive illness that warrants specific treatment. Asking about self-harm is essential as chronic physical illness (particularly cancer, HIV and AIDS, renal disease, and chronic pain) is associated with an increased risk of suicide (165).

2.3.2 Epidemiology

Depressive disorders are 1.5-4 times more prevalent in medically ill patients than in the general population (166). Mood disorders can be regarded as the final common pathway arising from the interaction between multiple pathophysiological, psychological, and socioeconomic stressors that chronic illness imposes on the individual (167).

The diseases with the highest prevalence of major depression (95% CI for MD prevalence %) have been reported as follows: chronic fatigue syndrome (32.0-40.7), fibromyalgia (19.4-24.9), inflammatory bowel disease (14.6-18.2), asthma (12.4-14.4), back problems (12.0-13.3), multiple sclerosis (10.9-20.6), epilepsy (10.0-17.2), cancer (9.7-13.8), COPD (8.8-14.6), migraine (8.2-12.3), rheumatic arthritis (9.4-10.6), stroke (6.7- 10.6), diabetes mellitus (6.7 -8.6), heart disease (6.4- 8.2), and Parkinson’s disease (2.2-13.7) (168).

2.3.3 Aetiology

Depression in chronic physical illness can occur as a specific consequence of that illness or as an adverse effect of drug treatment. Additionally, a psychological reaction to physical illness may be precipitated by the exacerbation of an illness or the realisation of its serious or disabling nature. Uncertainty about the future, feelings of loss of control, and a sense of failure are common responses to illness but do not inevitably lead to depression. Risk factors for the development of a mood disorder include: a prior history of depression, low social support, substance misuse, and additional stressful life events such as marital separation or loss of job (169).

2.3.4 Diagnosis

The diagnosis of depression in chronic physical illness is the same as in the general population. There is also a need to consider the illness presentation and medication. There are specific criteria in DSM-IV that need to be taken account in assessing patients with chronic physical illness. A prominent and persistent disturbance in mood predominates the clinical picture and is characterised by either (or both) of the following:

- Depressed mood or markedly diminished interest or pleasure in all, or almost all, activities
- Elevated, expansive, or irritable mood
- In addition to:
    - Evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition
    - Disturbance is not better accounted for by another mental disorder (e.g. adjustment disorder with depressed mood in response to the stress of having a general medical condition)
    - Disturbance does not occur exclusively during the course of a delirium

- Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

Symptoms such as insomnia and appetite change may also be due to physical illness, and in assessing depression there is no evidence that taking account of somatic complaints leads to over-diagnosis (170). In fact, depression comorbid with physical illness is often missed for reasons such as misattribution of symptoms as a normal or realistic response to illness, negative attitudes to a diagnosis of depression, unwillingness of patients to report symptoms, and unsuitability of the clinical setting for the discussion of emotional problems (171).

2.3.5 Management

In the management of depression in chronic physical illness, account should be taken of the patient's age, multiple comorbidities, drug therapy, polypharmacy, and potential drug interactions.

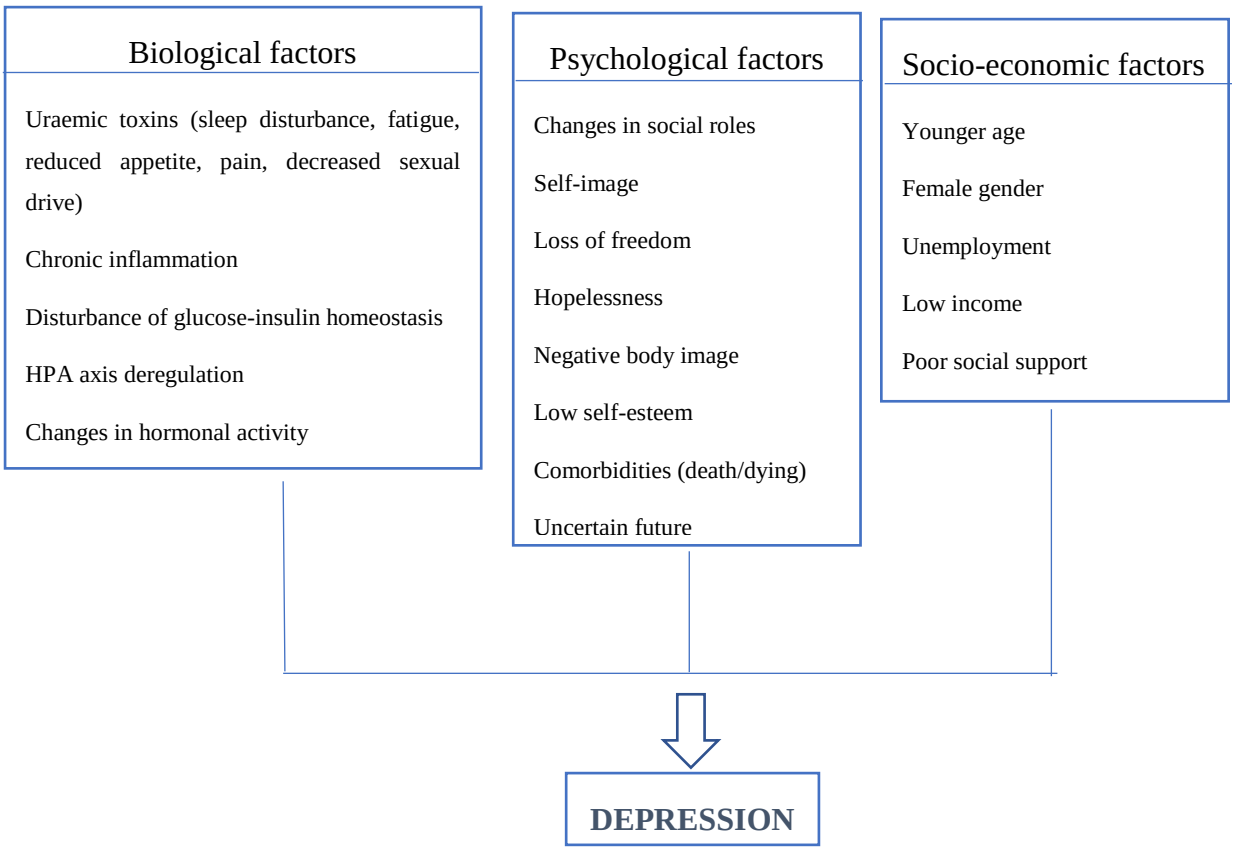
2.4 Depression in ESRD

Most people with ESRD who require dialysis treatment report psychological distress, and people with CKD identify improving psychosocial aspects of living with their illness among their most important research priorities (59, 172). I will discuss the contributing factors to depressive disorder in this group of patients in the following sections.

2.4.1 Contributing Factors to Depressive Disorders in ESRD

There are multiple factors that contribute to depression in ESRD. These are summarised in the Figure 9 and were explained in the previous kidney chapter.

Figure 9 Factors contributing to depression



2.4.2 Prevalence of Depression in CKD

In a systematic review and meta-analysis of observational studies (173), the point prevalence of depressive symptoms ranged between 1.4% and 94.9%, with an overall meta-analytical prevalence of 34.0%. The point prevalence of depressive symptoms when using self-rating scales was statistically different in each stage of CKD, with dialysis patients experiencing the highest rate of depressive symptoms. The point prevalence of depression was markedly lower when adjudicated by clinical interview using specified diagnostic criteria (Table 10).

Table 10: Prevalence of depression in CKD, (173)

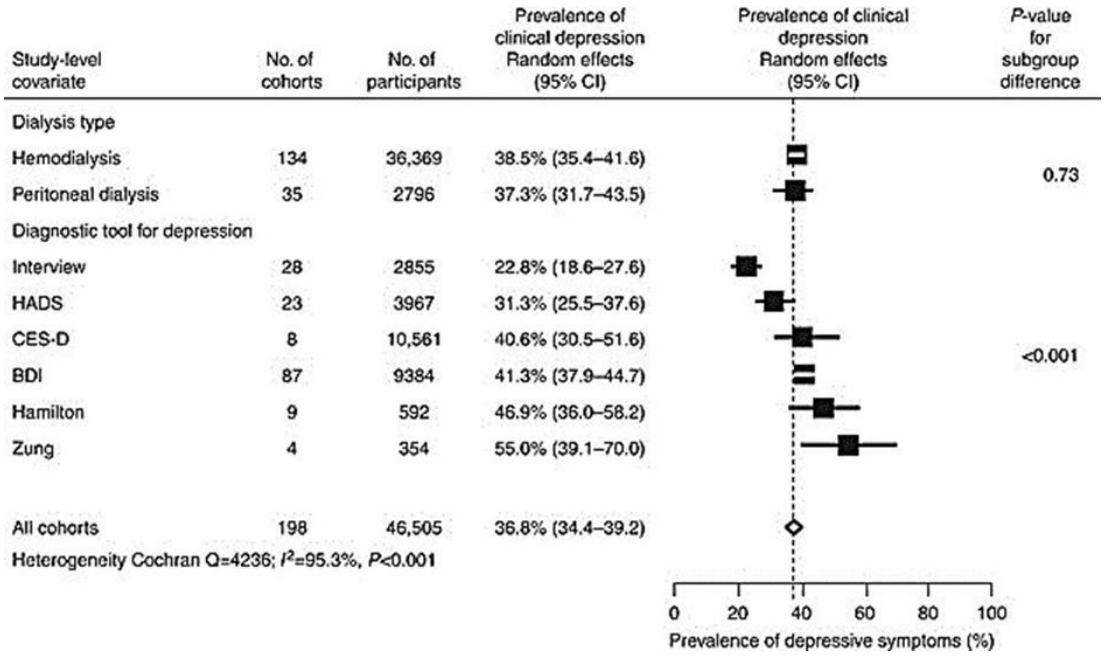
	No. of study populations	No. with symptoms/ no. at risk	Prevalence of clinical depression Random effects (95% CI)	Heterogeneity I^2	*P*-value for subgroup difference
Patient- or clinician-administered questionnaire					
Stage 5D	170	15,085/43,650	39.3% (36.8–42.0)	95.6%	
Stages 1–5	12	521/2121	26.5% (18.5–36.5)	94.9%	<0.001
Transplant	22	1195/4640	26.6% (20.9–33.1)	93.6%	
Interview-based assessment					
Stage 5D	28	609/2855	22.8% (18.6–27.6)	79.8%	
Stages 1–5	4	259/1388	21.4% (11.1–37.2)	74.1%	0.82
Transplant	3	33/122	25.7% (12.8–44.9)	55.2%	

Abbreviations: CI, confidence interval; CKD, chronic kidney disease.
Heterogeneity interpretation: I^2 >80% = moderate; I^2 >90% = high.
CKD stage 5D = estimated glomerular filtration rate <15 and treated with dialysis.

2.4.3 Prevalence in the Dialysis Setting

The prevalence of depression in haemodialysis patients as adjudicated by clinical interview was 22.8% (Table 11). When assessed using self- or clinician-administered questionnaires, the overall estimated prevalence of depressive symptoms was statistically higher than reported in interview studies (39.3%). The prevalence of depressive symptoms varied by screening tool used in the order of increasing prevalence: the HADS, Center for Epidemiological Studies – Depression scale, the BDI, the Hamilton Depression Scale, and the Zung SDS (Table 11).

Table 11: Prevalence of depressive symptoms in people with ESRD on dialysis, (173)

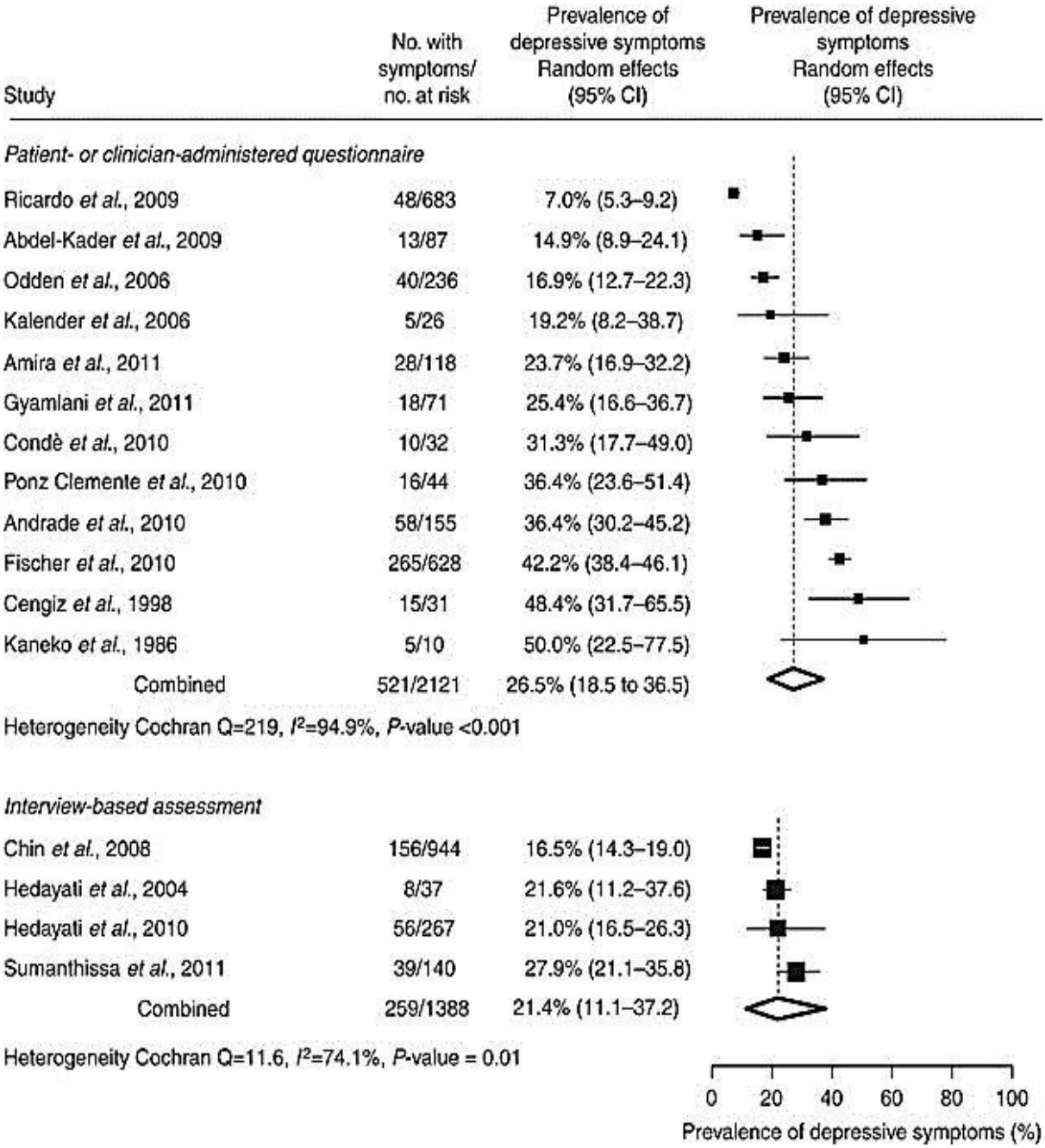


CI, confidence interval; BDI, Beck Depression Inventory; CES-D, Center for Epidemiological Studies Depression Scale; HADS, Hospital Anxiety and Depression Scale; Hamilton, Hamilton Depression Scale.

2.4.4 Prevalence in CKD

In the setting of earlier stages of CKD (Stages 1-5), prevalence of depressive symptoms in individuals ranged from 7.0% to 50.0% (Table 12). In reporting depression assessed using clinical interview and patient- or clinician-completed rating scales, the pooled prevalence was 21.4% and 26.5%, respectively.

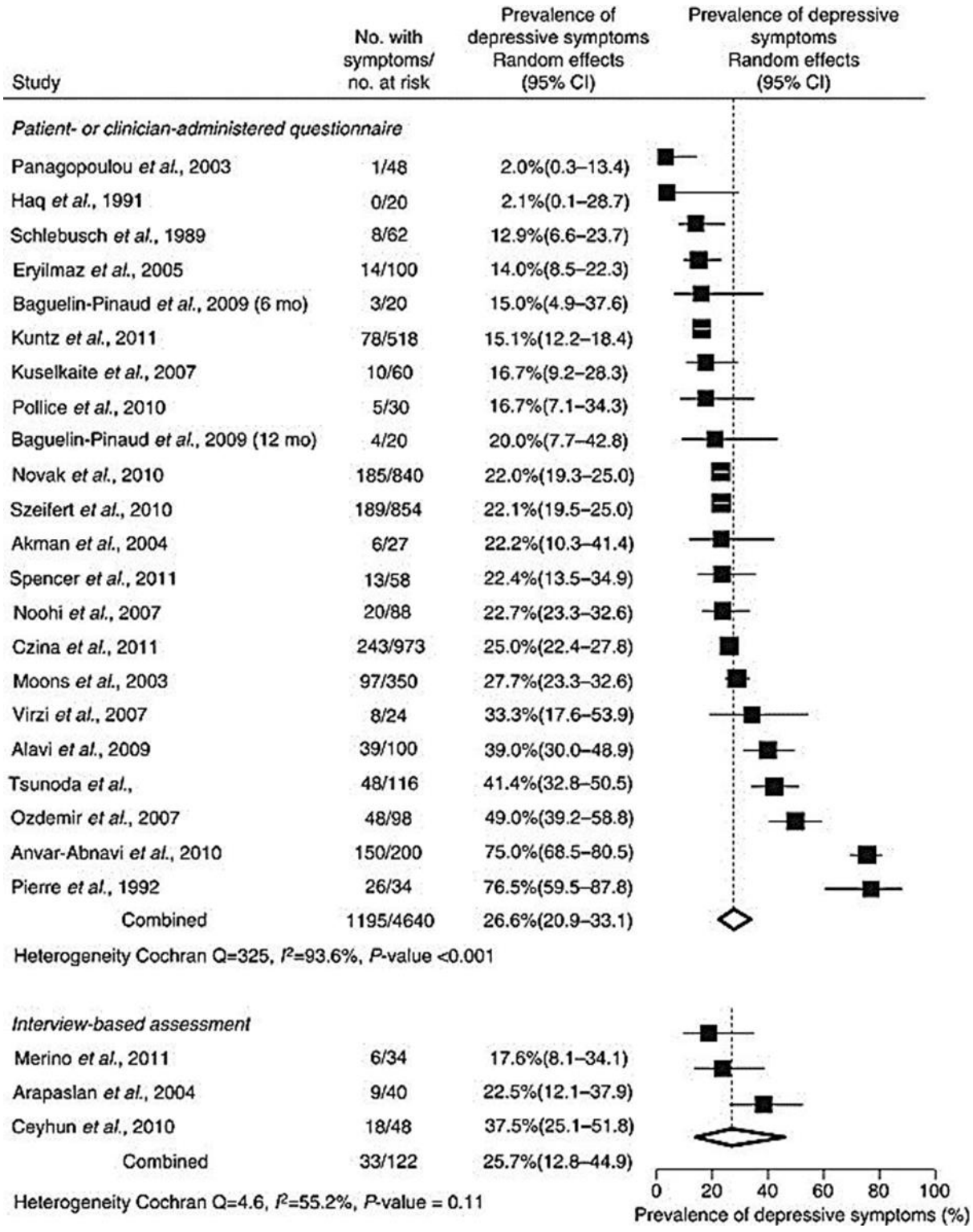
Table 12: Prevalence of depressive symptoms in people with chronic kidney disease Stages 1-5, (173)



2.4.5 Prevalence in Transplant

In the transplant setting, the reported prevalence of depressive symptoms ranged between 2.0% and 76.5%. The prevalence of depression assessed by interview was 25.7% and that assessed by self-rating scales was 26.6% (Table 13).

Table 13: Prevalence of depressive symptoms in kidney transplant recipients, (173)



2.4.6 Screening

Self- or clinician-completed assessments for depression are generally used in clinical settings for screening and in clinical research for pragmatic reasons to reduce time and financial costs. In addition, numerous cut-off point scores have been described for the available rating scales to identify patients in the ESRD population as having clinically relevant depressive symptoms and to estimate sensitivity and specificity of cut-off points in this setting. Self-administered diagnostic tools tend to overestimate the prevalence of depression in CKD, particularly for patients with ESRD, compared with clinical interview. Self-report measures are likely to assign symptoms commonly experienced in severe CKD (such as fatigue, sleep disturbance, and poor appetite) as indicative of the somatic symptoms of depression and may inappropriately classify such patients as depressed. Interviews to adjudicate depression based on specific diagnostic criteria such as the DSM-IV may provide a more accurate estimate of depression prevalence. Although self-reporting scales are efficient and require fewer clinical resources to administer, in the dialysis setting particularly, interview-based diagnosis is the most appropriate for the assessment and management of depression (173). This is due to the multiple factors, including the uraemic syndrome, as previously discussed in the kidney chapter.

A number of measures have been used to screen for depressive symptoms in patients with ESRD, including: BDI version II (BDI-II), 16-item QIDS-SR, CESD, HADS, and the PHQ-9, as in Table 14. The optimal screening tool and diagnostic method to identify depression and depressive affect in patients with renal disease remain unknown, although several studies have been performed to determine the validity and accuracy of these tools in the ESRD population (174-176). I will cover comprehensively the use of both the BDI-II and PHQ-9 as the screening tools used in this empirical study.

Table 14: Screening tools used in advanced kidney disease

Scale	No of items	Score , range	Cut-off score in general population	Cut-off score in CKD (sensitivity, specificity)	Cut-off score in ESRD (sensitivity, specificity)	Ref
BDI	21	0-63	≥10	≥11 (89%, 88%)	≥14-16 (62-91%, 81 86%)	(174-178)
QIDS-SR	16	0-27	≥10	≥10 (91%, 88%)		(178)
CESD	20	0-60	≥16		≥18 (69%, 83%)	(176)
PHQ-9	9	0-27	≥10		≥10 (92%, 92%)	(175)
HADS	14	0-21	≥8		≥12 (81%, 90.2%)	(179)

BDI: The BDI-II is a revision of the original BDI-1A to correspond with the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition (DSM-IV) criteria for Major Depressive Disorder. The BDI-II includes four new items not present in the BDI-1A: agitation, worthlessness, loss of energy, and concentration difficulty. Four items on the BDI-1A (weight loss, body image, work difficulty, and somatic preoccupation) are not included in the BDI-II. In addition, the BDI-II asks patients to answer questions regarding how they have been feeling over the 'past two weeks, including today', reflecting the timeframe for symptoms described in the DSM-IV. The BDI-II has been found to have good reliability (α=0.91) in outpatient samples with various psychiatric disorders (180, 181).

The BDI-II was chosen for use in the studies to be presented because it conforms to current diagnostic criteria for MDD (DSM-IV) and because its properties in general and clinical samples have been well examined (77, 180, 181). Furthermore, the original BDI has also been used with the ESRD setting and more recent work has shown that the original compares well with diagnostic standards, if cut-off scores are adjusted upwards (182). In one of the first empirical studies to test the BDI in ESRD patients, Craven et al. (174) evaluated the measure against DSM-III criteria for

depression in 99 patients. They found that a BDI ≥15 produced optimal sensitivity (0.92) and a negative predictive value (0.99). The authors note that increasing the cut-off above ≥15 decreased sensitivity and did not produce a meaningful increase in positive predictive value.

More recent data confirms that the cut-off on the BDI needs to be adjusted upwards for use in ESRD patients, presumably due to increased somatic symptoms encountered in this population. For example, a BDI cut-off ≥16 was shown to compare well with diagnostic standards, revealing 91% sensitivity and 86% specificity for depression when compared to the SCID in ESRD patients, and revealed utility for the shorter PHQ where a cut-off score of ≥10 was associated with 92% specificity and sensitivity (175).

The BDI and CES-D measures were compared against the SCID in 98 HD patients (176). A CES-D score >18 gave 69% sensitivity and 83% specificity for depression. A BDI cut-off of 14 yielded 62% sensitivity and 81% specificity. A study in UK dialysis patients compared the BDI against the ICD-10 diagnostic criteria for MDD (182). Analysis of 57 dialysis patients' BDI scores against the diagnostic criteria found that a BDI ≥15 produces 78% specificity and 100% sensitivity, whereas a BDI ≥20 produces 92% specificity and 71.4% sensitivity. Interestingly, these studies have utilised the original BDI and not the BDI-II. Given that the BDI-II leads to slightly higher mean total scores compared to the BDI, it could be assumed that a cut-off score based on the BDI-II in ESRD would be marginally higher that the 14-15 cut-off scores reported in studies that used the BDI. However, it should be noted that some confusion has been reported within the wider literature regarding the correct citation of versions of the BDI (183). For example, in one ESRD study, the authors failed to cite the version of the BDI used, instead citing apparent 'validation' studies (184). The failure to adequately describe the questionnaire version inhibits the reliable comparison of scores between studies (and estimated prevalence based upon cut-off scores that differ between versions) and may misinform as to which version to use in subsequent studies.

PHQ: The PHQ and subsequent variants (including the Brief PHQ, PHQ-9, PHQ-8, and PHQ-2) were developed from the Primary Care Evaluation of Mental Disorders (PRIME-MD). The PHQ was validated using 3,000 primary care patients in eight

different clinics and 3,000 obstetrics/gynaecology patients in seven different clinics (185). Shortened versions combined the two original components into a self-administered version called the PRIME-MD PHQ (186).

The PHQ-9 and the shorter PHQ-2 are the depression modules of the PHQ and currently the most widely used versions in clinical settings. Another variant, the PHQ-8, is used primarily in research studies and includes all items of the PHQ-9 except the ninth item that pertains to self-harm. The PHQ-9 detects and measures depression and severity in medical populations in clinical settings. Higher PHQ-9 scores correlate with increased depressive affect (79).

The nine items on the PHQ-9 consist of the nine criteria on which the DSM-IV depressive disorder diagnoses are based. Interpretive guidelines for the PHQ-9 as a severity measure: 1-4, no depression; 5-9, mild depression; 10-14, moderate depression; 15-19, moderately severe depression; and 20-27, severe depression (79).

A diagnosis of MDD is considered if ≥5 of the nine symptom criteria have been present at least ‘more than half the days’ in the past two weeks, and if one of the symptoms is depressed mood or anhedonia or the criteria of ‘thoughts that you would be better off dead or of hurting yourself in some way’ is present at all. Consideration of other depressive disorders is recommended if two, three, or four of the nine symptom criteria have been present at least ‘more than half the days’ in the past two weeks, and one of the symptoms is depressed mood or anhedonia. The recommendation is that a clinical evaluation be the final determination of depressive disorder diagnosis (79).

Severity of depression as measured by the PHQ-9 was found to be highly correlated with scores on the BDI in the general population (r= 0.73). Strong associations were also found between the PHQ-9 and 20-item Short-form Health Survey (SF-20) scores, particularly those scales most strongly related to depression (e.g. mental health), as well as with self-reported disability days, clinic visits, and the amount of difficulty self-attributed to symptoms (187). Similarly strong correlations were found between PHQ-2 and SF-20 scores, with the strongest correlation again with mental health (range 0.63-0.70) (188). Test characteristics (sensitivity, specificity, likelihood ratio, and area under the receiver operator characteristic (ROC) curve) were found to

be similar for the PHQ-2 in comparison to the Symptom-Driven Diagnostic System for Primary Care (SDDS-PC), Medical Outcomes Study (MOS), CES-D, 10-item CES-D, BDI, and 13-item BDI-II (189).

2.4.7 Complexity of Diagnosing Depression in ESRD Population

A distinction must be made between depressive affect, as assessed by self-report questionnaires, and a psychiatric diagnosis of depressive disorder based on DSM-IV criteria (176, 190). High levels of somatic/uraemic symptoms, such as fatigue, poor appetite, and sleep disturbance reported by chronically ill ESRD patients on self-administered depression scales may be misclassified as symptoms of depression and lead to a false diagnosis of depressive disorder (25, 191-193). Cognitive impairment is common in depression and ESRD and impairments in cognition have been found to persist beyond acute episodes of depression, and between one-third and one-half of remitted depressed patients are thought to be affected by cognitive deficits (123). Patients who had cognitive impairment while depressed continued to experience deficits in cognition when remitted from depression(194). Formal diagnosis of depression requires a structured clinical interview based on agreed criteria, e.g. MINI.

2.4.8 Association and Consequences of Depression in ESRD Population

As mentioned earlier, depression has been associated with the response to a loss of some kind (195). ESRD patients have sustained multiple losses, including loss of role within the family and workplace, loss of renal function and mobility, loss of physical health and cognitive abilities, and loss of sexual function (24). Medications used to treat patients with ESRD might also cause depression or have side effects that mimic its symptomatology.

- **Quality of Life (QoL):** Over the past decade, increasing emphasis has been given to quality of life as survival with chronic diseases has increased. The World Health Organisation defines quality of life as ‘an individual’s

perception of their position in life in the context of culture and value systems in which they live and in relation to their goals and expectations, standards and concerns. It is a broad ranging concept affected in a complex way by a person's physical health, psychological state, level of independence and their relationships to salient features of their environment' (26). Clinical and socio-demographic factors in the context of HD, such as the presence and severity of anaemia, malnutrition, inflammation, sleep disorders, sexual dysfunction, unemployment, and low socio-economic status, have been shown to be associated with impaired quality of life (196). Importantly, however, these clinical and socio-demographic factors account for only a fraction of the variance in HRQL scores (28).

Depression and anxiety are important independent predictors of low quality of life across all RRT modalities. Depression not only undermines the patient's mental and physical health but also alters their subjective perception of physical status, functional capacity, and social function. It has been proposed that depression and anxiety may be more strongly associated with HRQL than clinical and socio-demographic variables taken together (28-32).

In the context of chronic illnesses, the most widely studied aspect of quality of life has been Health-related Quality of Life (HRQL). This construct gives insight into the patient's perception of the physical and psychosocial impact of the illness and its treatment on their lives. Due to each patient's idiosyncratic perception of his/her illness, skills for adaptation, and socioeconomic background, people with the same health status may have very different HRQL.

- **Treatment and dietary adherence:** As with most chronic illnesses, non-adherence to a prescribed medical treatment regimen is pervasive in patients receiving HD (197). In addition, dialysis patients need to adhere to a multifaceted treatment regimen, undergo regularly scheduled and time-consuming dialysis treatments, as well as follow a strict medication and dietary regimen. Regular doses of phosphate-binding medication are required to reduce intestinal absorption of phosphorus-rich foods (e.g., dairy products) due to the body's inability to excrete phosphorus (P). Sustained elevations in

serum P are associated with a variety of complications, including hypocalcaemia, hyperparathyroidism, and vascular calcification.

There are also major limitations on the amount of fluid that can be safely consumed due to the intermittent nature of haemodialysis. Prolonged fluid overload is associated with hypertension and heart failure, and is potentially life-threatening. Interdialytic weight gain is typically used to define adherence to the fluid-intake restrictions (198). Higher values are interpreted as reflecting poorer patient adherence, with values over 2.5 kg (or over 4% of the patient's body weight) generally indicative of problematic adherence (199). High interdialytic weight gains lead to increased requirement for ultrafiltration during dialysis and can result in cramps and hypotension (200). Studies examining the prevalence of non-adherence among renal dialysis patients have typically observed that between 30% and 50% of dialysis patients do not adhere to diet, fluid-intake, and medication regiments (199, 201-204).

- **Mortality and hospitalisation:** Though depression has been associated with increased mortality in the general medical population (205-210), the relationship between depression and mortality in CKD patients has proved difficult to clarify. Early studies with relatively small sample sizes, using a variety of self-report questionnaires for cross-sectional assessment of depressive symptoms, did not find any association (211-215) in contrast to others (193, 216-219). Such studies have often compared means between groups of deceased and surviving patients without accounting for potentially confounding medical and demographic factors. However, in a large multinational sample in the DOPPS I, ESRD patients treated with haemodialysis who were classified as depressed and those who reported frequent depressive affect had higher risk of mortality, withdrawal from therapy, and hospitalisation (220). Persistent or worsening depressive symptoms over repeated assessments (rather than a single depressive episode) also predicted long-term CKD mortality (221). Kimmel et al. assessed depressive symptoms in 295 chronic HD patients over 20 to 60 months, and found that though baseline depressive affect did not predict mortality over

this period, changes of depressive symptoms did (211). Also, physician-diagnosed clinical depression may predict mortality more strongly than self-reported depressive symptoms (221).

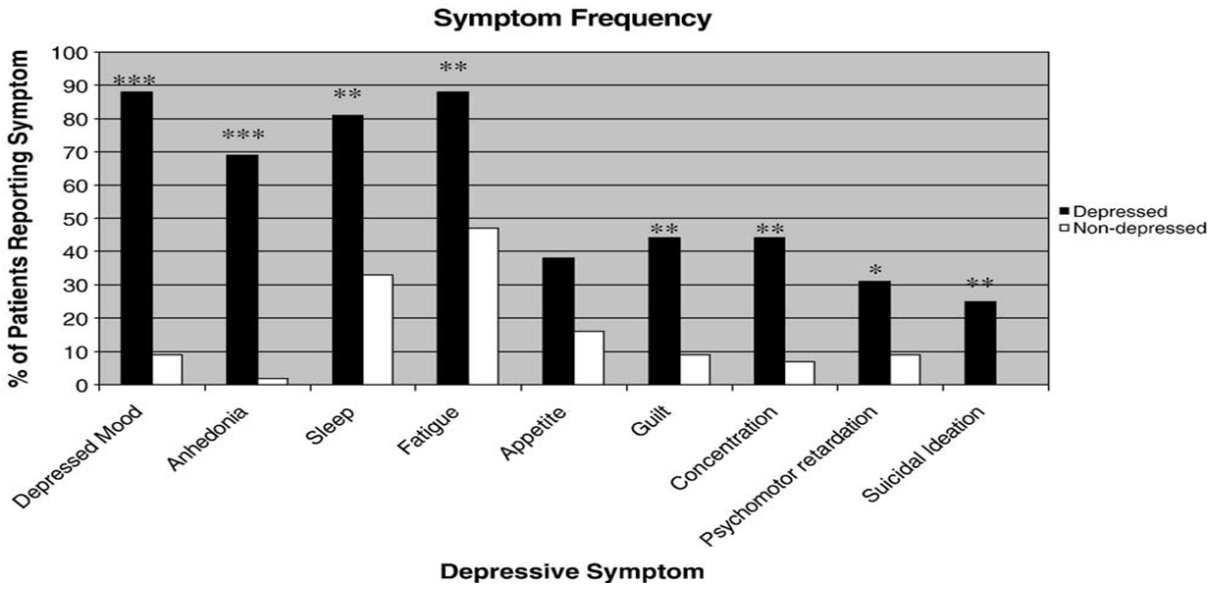
Boulware and colleagues evaluated baseline and longitudinal data from the Choices for Healthy Outcomes in Caring for End-stage Renal Disease (CHOICE) study, with a large cohort of 1,041 incident patients starting peritoneal dialysis and haemodialysis (222). They determined that levels of depressive affect at the beginning of their study were not associated with increased overall mortality. However, using several different time-dependent analyses, they demonstrated that persistently higher levels of depressive affect over time were associated with increased risk of death and cardiovascular events in both adjusted and unadjusted analyses. A recent meta-analysis has supported the relationship between depression and mortality in CKD (223).

Haemodialysis patients with depression are twice as likely to require hospitalisation within a year compared with those without depression (221). They had a 30% increase in both number of hospitalisations and cumulative hospital days (224). In a prospective observational cohort study of 267 consecutively recruited patients with Stage 2-5 CKD pre-dialysis patients, a diagnosis of current major depressive episode at baseline was associated with an increased risk (adjusted hazard ratio 1.86) of a composite of death, hospitalisation, or progression to dialysis, independent of comorbidities and kidney disease severity (225).

- **Fatigue:** Fatigue is a symptom commonly experienced in the general population. Although fatigue is often a consequence of medical or psychiatric illness, many people experience fatigue related to lifestyle or situational factors, such as lack of sleep or stress. Fatigue is a psychosomatic syndrome that is also common in HD patients, and a key area of overlap with depression. Its prevalence ranges from 42% to 89% according to treatment modality and assessment instruments employed (226). Fatigue was as common as depressed mood in 62 patients on HD interviewed and followed for a mean of 29 months, as shown in Figure 10 (29). There is a joint

relationship between fatigue and frailty mediated by the common biomedical determinants shared by frailty and fatigue (227). Forty percent of individuals with depression have frailty and a similar proportion of those with frailty have depression (137). A full review of fatigue in ESRD will be covered in the fatigue chapter.

Figure 10 Symptoms frequency in HD patients, (29)



2.4.9 Management

Despite the high prevalence of depressive symptoms as well as depressive disorder among patients with ESRD and its association with poor outcomes, only a minority of chronic dialysis patients receive adequate diagnosis and treatment for depression (176, 184, 228). For example, in a retrospective analysis of the African American Study of Kidney Disease and Hypertension Cohort Study, only 20% of CKD participants with a BDI score of >14 (above the threshold validated for depression) were prescribed antidepressant medications (229). Similarly, Watnick et al. (184) reported that only 16% of ESRD patients initiating chronic HD with BDI scores of ≥15 were on antidepressants. In a prospective observational cohort of 98 prevalent HD patients, nephrologists were informed about a current diagnosis of depressive disorder based on DSM-IV diagnostic criteria in 26% of cases (221). However, interventions were carried out in less than a quarter of these patients.

Once the diagnosis of clinical depression is made, treatment options need to be tailored to the individual needs of the patient and the resources available to the clinical team or dialysis facility. There are a variety of treatment options available. NICE recommends that chronically ill patients with comorbid depression be treated with CBT and/or SSRIs (150). Despite their proven efficacy among the physically well population, there are factors that may prevent SSRIs from being effective in the ESRD population. NICE recommends conducting a placebo-controlled trial of at least six months duration in patients with COPD because of the dearth of published data (150). Similar comments have been made with respect to ESRD (230).

2.4.9.1 Antidepressant Pharmacotherapy in ESRD

Antidepressant medications are generally highly protein bound and not removed significantly by the dialysis procedure (231). They commonly undergo hepatic metabolism, but many have active metabolites that are renally excreted, leading to accumulation of potentially toxic metabolites in patients with decreased glomerular filtration rates (232). In addition, there is a significant risk of drug–drug interactions in ESRD patients who, because of a large burden of comorbidities and metabolic derangements, may already be taking other medications.

Several classes of antidepressants such as serotonin modulators, tricyclics, and tetracyclics have cardiac side effects such as QTc prolongation, arrhythmias, and orthostatic hypotension. Given that a large proportion of patients with ESRD suffer from CVD, use of such medications without clinical trials to advocate safety must be carefully considered. Central nervous system depression is also a common adverse event. Increased bleeding risk was reported in association with SSRIs (231), which may become problematic in ESRD due to underlying platelet dysfunction related to uraemia. Finally, the serotonergic gastrointestinal activity of SSRIs, one of the most commonly used antidepressant classes, can result in nausea and vomiting, which again may exacerbate these symptoms in patients with ESRD (61, 232).

A preferred group of antidepressant medications from the clinicians view was developed, as outlined in Table 15 (233, 234), and the appropriate medication selected after discussion with the nephrologist

Table 15: Preferred antidepressants in patients with chronic physical illness

Antidepressant	Initial dose in mg/day	Usual dose in mg/day	Most common side effects
SSRIs			
Sertraline	25	25-150	Gastrointestinal symptoms, central nervous system symptoms, sexual dysfunction
Citalopram	10	10-40	Gastrointestinal symptoms, central nervous system symptoms, sexual dysfunction
Paroxetine	10	10-20	Gastrointestinal symptoms, central nervous system symptoms, sexual dysfunction
Tricyclic drugs			
Nortriptyline	10-25	50-100	Cardiac arrhythmia, central nervous system symptoms, orthostasis
Other drugs			
Buptopion	75	300	Central nervous system symptoms
Nefazodone	300	600	Gastrointestinal symptoms, central nervous system symptoms

There are insufficient data to clearly suggest that treatment of major depressive disorder is either efficacious or changes outcomes in ESRD patients (235, 236). Few studies have examined this issue and are fraught with serious limitations, including small sample sizes (237-241), lack of placebo control (236-239, 241, 242), and lack of DSM-IV-based criteria for major depressive disorder (239, 240).

Only a few studies have examined the potential utility of pharmacologic therapy for depression in ESRD patients (237, 238, 240, 243). Streltzer (244) reviewed his

experience with tricyclic antidepressants in five HD patients; three of these patients had a good clinical response. Kennedy et al. (238) identified 10 dialysis patients with major depressive illness. Treatment with desipramine or mianserin was instituted in eight of these patients; two patients were felt to have medical contraindications to therapy. Six of the eight treated patients had a clinical response and two patients discontinued therapy.

Blumenfield et al. (240) organised a randomised trial of fluoxetine therapy in 14 HD patients with major depressive illness. Six of seven patients treated with fluoxetine completed a course of therapy and reported no significant side effects. Depressive symptoms were improved at four and eight weeks after the start of therapy, but the difference was only statistically significant at four weeks. No patients discontinued the study drug because of adverse events, all of which were reported as minor. Furthermore, all patients in the intervention arm had serum plasma concentrations of fluoxetine and norfluoxetine <250 ng/ml at eight weeks, similar to reported levels in patients with normal renal function. Although this study suggests promise for use of SSRIs in HD patients, the short duration and small sample size did not allow for adequate assessment of adverse effects.

Atalay et al. (245) reported that treatment with SSRI sertraline at 50mg per day for 12 weeks was associated with a decrease in depressive symptoms in 25 chronic peritoneal dialysis patients, with BDI scores decreasing from 22 to 15 (P<0.001). Lack of a control group and the small sample size were major limitations. In addition, mean post treatment BDI score was still above the cut-off for depression.

Koo et al. (241) reported treatment of 34 dialysis patients with another SSRI, paroxetine, at 10mg per day for eight weeks concurrently with psychotherapy. Although the authors reported a statistically significant decrease in Hamilton Depression Rating Scale scores (from 16.6±7.0 to 15.1±6.6, P<0.01), the clinical relevance of a 1.5 unit decrease in score is unclear. This study also suffered from the lack of a placebo control group and short-term follow-up.

Non-randomised observational studies of antidepressant medications in ESRD patients on chronic peritoneal dialysis reported some improvement in depressive symptoms; however, major limitations included the lack of a control group, selection

and refusal bias, and a 50% medication discontinuation rate. Of a total of 136 patients with ESRD on chronic peritoneal dialysis who scored ≥11 on the BDI depression questionnaire were studied, only 51% agreed to be further evaluated, and of those, only 72% agreed to have pharmacologic treatment. Finally, merely 23 of 44 (52%) of patients who agreed to treatment completed a 12-week course of antidepressant medications. Although a mean decrease in BDI scores from 17.1±6.9 to 8.6±3.2 was reported in completers, this study does underline the fact that even when ESRD patients were given a diagnosis of depression and treatment was recommended, not all agreed to medical management (236, 237).

Until more data are available for treatment of depression in ESRD, nephrologists are left with the challenge of adding another medication to the growing list prescribed to patients with ESRD, considering non-pharmacologic therapy, or worse yet, dismissing depressive symptoms as nonspecific symptoms of chronic disease or uraemia. However, data clearly suggest that both depression diagnosis and depressive symptoms independently predict poor outcomes in these patients. Therefore, such symptoms should not be ignored. Based on the data available, if a trial of medication is considered, SSRIs would likely be a prudent choice because of established safety in patients with CVD (246).

2.4.9.2 Non-pharmacotherapy

Given the concerns and potential problems with pharmacologic treatment of depression in patients with ESRD, potential non-pharmacologic interventions have been considered. These approaches, however, are likely to challenge healthcare providers given the organisation and structure in ESRD care and mental health services in most countries (that is, the limited resources available for and limited recognition of the significance of providing psychosocial support). Importantly, several studies have now suggested an improvement in depressive symptoms in ESRD patients treated with various non-pharmacologic regimens.

2.4.9.2.1 CBT

In a six-month randomised trial of CBT versus the wait lists from two centres in New York, 59 HD patients were assigned to the treatment-first group (n=33) or the wait-list control group (n=26) (247). In the intervention phase, CBT was administered during dialysis treatments for three months; participants were assessed three and six months after randomisation. Compared with the wait-list group, the treatment-first group achieved larger reductions in BDI-II (self-reported, P=0.03) and HDRS (clinician-reported, P= 0.001) scores at three months. The BDI scores did not decline any further at the six-month follow-up. Among participants with depression diagnosed at baseline, 89% in the treatment-first group were not depressed at the end of treatment compared with 38% in the wait-list group (Fisher's exact test, P=0.01). The treatment group experienced greater improvements in quality of life, assessed with the Kidney Disease Quality of Life Short Form (KDQOL-SF) (P=0.04), and interdialytic weight gain (P=0.002) than the wait-list group, although no effect on compliance was evident at the six-month follow-up.

In another nine-month randomised trial of CBT in Brazil, 85 HD patients with a major depressive disorder on standardised interviewing were randomised to receive standard care (control group) or CBT with a trained psychologist (248). Group sessions were held weekly for 12 weeks, and then monthly maintenance sessions were continued. Baseline BDI scores decreased from 25 in both groups to 10.8±8.8 in the treatment group versus 17.6±11.2 in the control group (between-group comparison P<0.002) at nine months. These significant improvements in depressive symptoms in the treatment group were confirmed with standardised patient interviews.

2.4.9.2.2 Alterations in the Dialysis Treatment

Trials have focused attention on the impact of alterations in the dialysis treatment regimen on depressive symptoms in HD patients (249, 250). The Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements (FREEDOM) study is an observational cohort study of patients changing to six times per week HD with the NxStage machine with targeted standardised weekly KT/V of

a minimum of 2.1 (251). In all, 239 participants were enrolled (intention-to-treat cohort), but only 128 completed the study (per-protocol cohort). In the per-protocol group's analysis after conversion to six times per week HD, BDI scores decreased from baseline values of 11.2±0.8 to 7.4±0.6 at four months, and this improvement was sustained at 12 months (7.8±0.7; $P<0.001$) However, the intention-to-treat analysis revealed less robust results, and BDI scores decreased from 12.8 to 10.7 ($P<0.001$). One criticism of this study was that the percentage of prescribed antidepressant and anxiolytic medications also increased during the course of the study from 26% to 35% ($P = 0.02$). However, after adjustment for antidepressant use, the improvement in BDI scores remained statistically significant. Given the lack of a control group, the improvement in BDI scores may have occurred for reasons other than the intervention alone.

The Frequent Haemodialysis Network (FHN) was a 12-month randomised trial comparing six-times-per-week in-centre HD with three-times-per-week conventional HD (250). Dialysis adequacy (Standardised Kt/V) was higher in the frequent HD group (3.54±0.56 v 2.49±0.27). Significant improvements in the physical health composite score of the Short Form-36 (SF-36) health-related quality-of-life questionnaire were observed. BDI scores were lower in the six-times-per-week HD patients, but the difference was not statistically significant.

2.4.9.2.3 Exercise Training Programmes

The impaired physical functioning of ESRD patients is well documented, the causes of which are multifactorial (252). An association between physical functioning impairments and various health-related quality-of-life measures has been well established (253). Thus, recent studies suggesting a beneficial effect of exercise programmes on depressive symptoms in ESRD are of interest (254, 255).

A randomized 2 × 2 factorial trial of anabolic steroid administration and resistance exercise training was conducted in 79 maintenance HD patients (256). Interventions included double-blinded weekly nandrolone decanoate or placebo injections and lower extremity resistance exercise training for 12 weeks during HD using ankle weights. Exercise was associated with an improvement in self-reported physical

functioning on the physical functioning scale of the SF-36 (P = 0.03). In addition, there was a trend toward a reduction in fatigue in the groups that were assigned to exercise (P = 0.06). In another trial of HD patients with reduced aerobic capacity (measured as VO2 max (volume per time, oxygen, maximum), 35 patients were randomised to a 10-month intradialytic exercise training programme. There was a 21% increase in VO2 max in the exercise group and a 39% reduction in BDI scores – significantly different than in the control group, in whom there was no change in either exercise capacity or BDI scores (254). Finally, BDI scores decreased by 34.5% (P<0.001) in 24 HD patients randomized to a one-year intradialytic exercise training programme versus 20 patients randomised to the control group (257).There was an inverse correlation between BDI scores and heart rate variability indices before and after exercise training, suggesting that decreased heart rate variability may play a mechanistic role in the association of depression with poor CV outcomes.

2.4.9.2.4 Others

Alternative interventions to treat depression in ESRD patients include addressing marital and family discord and barriers to social interactions. Marital and family tensions in ESRD patients are well documented, related at least in part to the stress of illness (258, 259). These tensions have been associated with the presence of a depressive affect (258). Problems with social interactions of ESRD patients are also well documented and have been associated with poor outcomes (259). Involvement of community and religious organisations could be explored (24, 55, 259). Addressing the concerns of caregivers of patients with disabilities may also be helpful in relieving stress in difficult relationships (260).

Future directions could include exploring the possible association of depression with inflammation in ESRD patients. Data suggest that the reduction in cytokine activation associated with inflammatory conditions alone without the concomitant administration of antidepressant medications can result in amelioration of depressive symptoms. For example, in 618 patients with psoriatic arthritis treated with etanercept, there was marked improvement in depressive symptoms, independent of an improvement in associated skin or joint problems (261).

2.5 Summary

Depression is common in general medical patients, approaching the prevalence of hypertension. It is often unrecognised and undertreated in patients with chronic medical illness, often leading to negative outcomes. It is particularly unlikely to be recognised in patients with ESRD because symptoms of depression overlap with those of uraemia. Consequently, prevalence estimates of depression in this population vary widely from 15% to 69% depending on the diagnostic instrument and the cut-off point used.

Depression has now become a public health priority and it is important to consider instituting strategies to screen for and diagnose depression in CKD patients. What needs to be determined before this is whether or not treatments are efficacious and safe in this patient population. Importantly, the impact of treating depression on morbidity and mortality needs to be established though successful improvement of clinical depression and its symptoms.

Overlapping symptoms of ESRD and depression may obscure the effects of treatment in this population. Fatigue is the major overlapping symptom. Data on fatigue in ESRD patients is sparse. The next chapter will give an overview on fatigue in ESRD.

Chapter 3

Fatigue in End-stage Renal Disease

3.1 Definitions of Fatigue

The term ‘fatigue’ is Latin in origin. According to the *Oxford Dictionary of English Etymology* (262), the Latin word ‘fatigare’, from which the word fatigue is derived, means ‘to exhaust as with riding or working, to weary or to harass’. The definition of fatigue provided by Mosby’s (1990) *Dictionary of Medical, Nursing and Allied Health* is similar (263), which is a state of exhaustion or loss of strength and ability that follows an episode of physical activity or a period of emotional and mental pressure.

Subjective fatigue is a sense of weakness, lack of energy, and tiredness. It can be conceptualised as located on a continuum of exhaustion and tiredness at one end, with energy and vitality at the opposite (43). This position has been supported by the National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS). It was also suggested that fatigue is ‘an unrelenting overall condition which interferes with individuals’ ability to function to their normal capacity’ (264).

Objective fatigue is the inability to sustain a specified force output or work rate during exercise (265). Objective fatigue can also be experienced by patients with circulatory disorders, as in ischemic heart disease and left ventricular failure (266).

Physical fatigue, or muscle fatigue, is the temporary physical inability of a muscle to perform optimally. The onset of muscle fatigue during physical activity is gradual, and depends upon an individual's level of physical fitness, and also upon other factors, such as sleep deprivation and overall health. It can be reversed by rest. It should not be confused with chronic fatigue syndrome (CFS), which is the complaint of fatigue, not relieved by rest, and lasting at least six months in the absence of chronic physical illness. Musculoskeletal structures may have co-evolved with their

corresponding brain structures in a way that allows them to adapt to environmental conditions (e.g. proprioception).

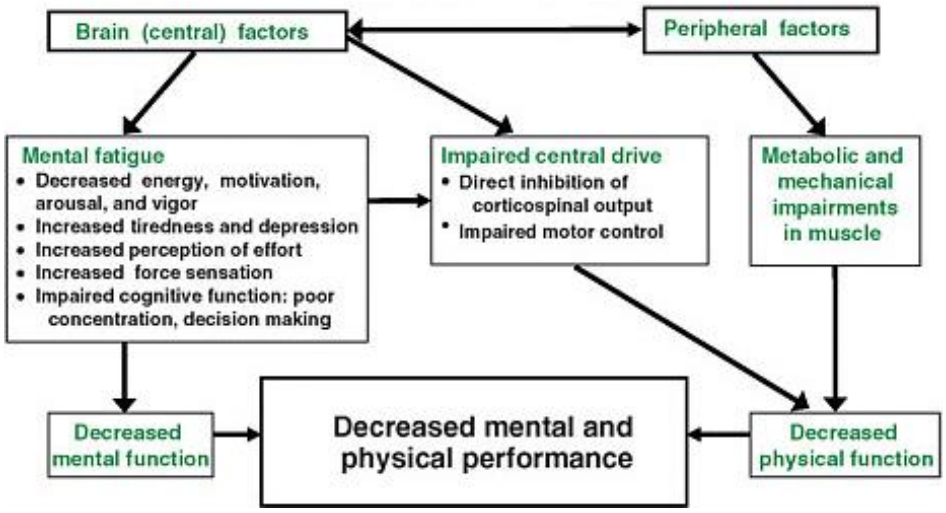
Mental fatigue is a temporary inability to maintain optimal cognitive performance. The onset of mental fatigue during any cognitive activity is gradual, and depends upon an individual's cognitive ability, and also upon other factors, such as sleep deprivation and overall health. Mental fatigue has also been shown to decrease physical performance. It can manifest as somnolence, lethargy, or directed attention fatigue.

Central fatigue may be defined as the failure to initiate and/or sustain attentional tasks (‘mental fatigue’) and physical activities (‘physical fatigue’) requiring self-motivation (as opposed to external stimulation). This should exist in the absence of any clinically detectable motor weakness or dementia. Diseases that lead to the loss of endurance in both physical and mental tasks in the absence of serious weakness or dementia will therefore cause (‘central fatigue’). Central fatigue represents a failure of physical and mental tasks that require self-motivation and internal cues in the absence of demonstrable cognitive failure or motor weakness. Patients with central fatigue have less difficulty to perform when stimulated externally or cued in advance, though they have a much higher perceived effort for the executed tasks. These patients may also fail to complete the execution of incremental or serial tasks that require sustained motivation and attention. This failure of focused attention, which normally provides the unconscious (‘automatic’) link between the self-guided voluntary effort, performance of sequential motor or cognitive tasks and sensory input, is a characteristic feature of central fatigue.

Peripheral or motor fatigue is due to fatigue in either the muscle itself or due to brain control over the muscle. Lee et al. (43) categorised the multi-dimensional fatigue experience of HD patients in Taiwan into three inextricably linked domains: physical, affective, and cognitive. These theoretical frameworks underscore the multi-dimensional aspects of fatigue and suggest that physiological, psychological, and socio-demographic factors contribute to fatigue. Figure 11 illustrates the most likely interaction between central and peripheral fatigue.

In clinical terms, fatigue is a non-specific symptom, with many possible causes. Fatigue is considered a symptom, rather than a sign, because it is a subjective feeling reported by the patient, rather than an objective one that can be observed by others.

Figure 11 Schematic diagram illustrating the likely interactions between central and peripheral components of fatigue, (267)



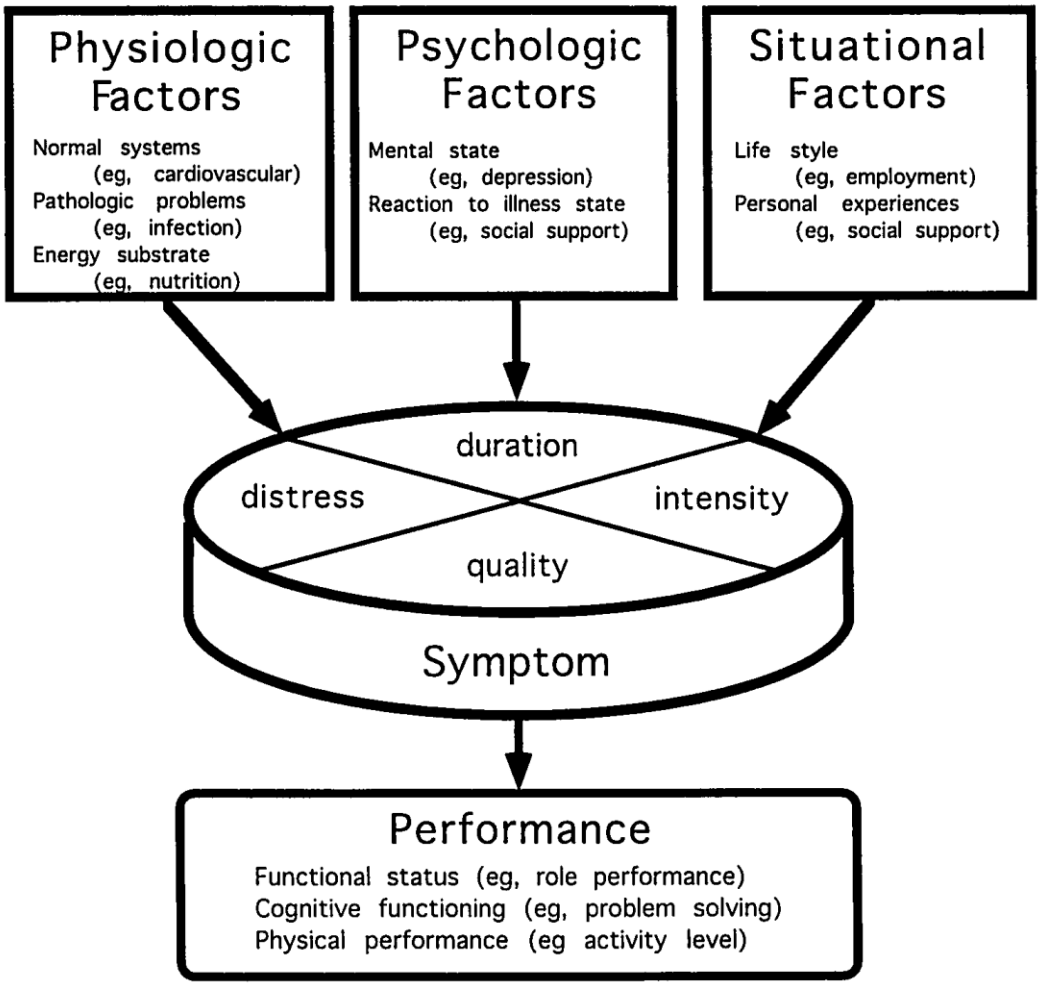
3.2 Aetiology of Fatigue

The exact aetiology of fatigue is unknown; however, the factors contributing to fatigue can be categorised as physiological, psychological, and situational factors, as illustrated in Figure 12, all of which have multiple complex and reciprocal interactions with fatigue. There are a variety of interactions among the contributing factors and various symptoms, resulting in a synergistic impact on performance, which in turn reciprocally influence the symptoms and contributing factors.

The criteria defining cancer-related fatigue (268) could be extrapolated to develop criteria specific for ESRD-related fatigue. The criteria include the presence of significant fatigue every day or nearly every day during the same two-week period in the past month. In addition, there should be the presence of five or more of following symptoms – generalised weakness or limb heaviness, diminished concentration, decreased interest in engaging in usual activities, insomnia or non-refreshing sleep, perceived need to struggle to overcome inactivity, marked emotional reactivity to

feeling fatigued, difficulty completing daily tasks, perceived problems with short-term memory, and post-exertional malaise lasting several hours. The use of such criteria to define clinically important fatigue would help to better understand the prevalence and predictors of fatigue in the ESRD population.

Figure 12: Theory of unpleasant symptoms, (269)



3.3 Measurement of Fatigue

There are a number of choices when selecting a brief assessment tool for fatigue in patients with ESRD. Measures of fatigue can be categorised in a number of ways. Some are generic, others disease-specific. Some measures are evaluative, designed to measure the severity of fatigue, while others have a discriminative purpose, designed to differentiate fatigued from non-fatigued individuals. The most widely used

instrument in the dialysis population is the vitality scale of the SF-36 (270). The SF-36 vitality subscale, which consists of four items, is considered to be at one end of a spectrum of fatigue. The vitality construct captures a mild reduction in energy level but fails to capture the negative aspects of fatigue such as weakness, lack of motivation, and difficulty with concentration. In addition to the SF-36, a number of symptom indices use single items to measure the presence and severity of fatigue. Fatigue scales vary in brevity, reliability, and responsiveness to interventions and most of them have not been validated in the CKD population, although the Revised Piper Fatigue Scale (271), comprised of 22 items, has been shown to be reliable. The Multi-Functional Fatigue Inventory (MFI-20) (272) has also been used to capture overall fatigue. Multiple aspects of fatigue and its impact on daily life are measured by the Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F). In patients with cancer and rheumatoid arthritis, the FACIT-F scale has shown excellent reliability and strong association with the vitality scales of the SF-36. While most fatigue instruments measure the overall experience of fatigue over a period of time ranging from weeks to months, dialysis patients also experience day-to-day and diurnal variation in fatigue. Fatigue assessments using traditional instruments may fail to capture this variability due to recall bias.

Ecological momentary assessment (EMA) (273) provides an important measurement tool to assess subjective fatigue repeatedly and reliably while avoiding recall bias. EMA incorporates repeated real-time measurement of phenomena such as symptoms, behaviours, or physiological processes as they occur in naturalistic settings. It may be that a real-time or experiential assessment of fatigue would provide additional information on the experience of dialysis patients, leading to improved treatment of severe fatigue.

Common instruments include:

- **Unidimensional:** Self-report scales that focus on one dimension, typically severity (Table 16)

Table 16: Unidimensional fatigue measures

Name	Scale type	Subscale/ Factor	Time frame	Target population	Reliability	Validity	Robust psychometric properties
Brief Fatigue Inventory (BFI) – nine items	Eleven point Likert	1: severity	Mainly last 24hrs, past week and present time	Generic although not validated in a non-cancer population	Internal consistency 0.89-0.96 Test-retest: r=0.70-0.91	Construct: factor analysis verified 1 factor Convergent: Correlation with cancer fatigue scale (r=0.64-0.76), POMS fatigue (r=0.60-0.70)	Moderate
Fatigue Assess Scale (FAS) – 10 items	Five-point Likert	1: severity	How a person usually feels	General population also used in sarcoidosis	Internal consistency: 0.9	Convergent: with CIS (r= 0.83, P < 0.001), with FS (r = 0.82, P < 0.001)	Moderate
Fatigue Severity Scale (FSS) - One item	Seven-point Likert	1: impact	Past week	None specified	Internal consistency: 0.88e0.95 Test-retest: 0.84	Convergent: Pearson correlation with MAF (r = 0.74,P < 0.05), VAS-F (r = 0.37,P < 0.05), and Rhoten Fatigue Scale (RFS) (r=0.03, P> 0.05) Discriminative: Between patients with MS or SLE and healthy subjects and cut-off for severe fatigue	Good
Pearson-Byars Fatigue Feeling Checklist – 13 items	Two check list	1: severity	Present time	General population, cancer, pregnancy related fatigue		Concurrent: Rating of nausea 105 Discriminative: Nonclinical sample after fatigue-inducing task from control group	Poor
Rhoten Fatigue Scale – One item	10/11 point self-rating	1: severity	Present time	General population although only validated in cancer	Test-retest: not Reported	Construct: did not show a difference between patient and control group Convergent: Correlated with POMS fatigue subscale (r=0.636); correlated with the Lee Fatigue Scale (r= 0.80)	Poor
Schedule of Fatigue and Anergia (SOFA)- 10 items	Five-point Likert	1: nature and severity	Past few weeks	General population		Discriminative: Between patients with CFS and primary care patients	Moderate

- **Multidimensional** self-report scales gather information on more than one dimension of fatigue; for example, severity of fatigue and nature of fatigue, allowing for the calculation of a number of scores and a global score (in most cases) (Table 17)

Table 17: Multidimensional fatigue measures

Name	Scale type	Subscale/ Factor	Time frame	Target population	Reliability	Validity	Robust psychometric properties
Fatigue Impact Scale – 40 items	Five-point Likert scale	3: physical, cognitive, psychosocial	Present some items related to last month	General validated with MS and liver disease	Internal consistency: 0.93	Concurrent: Sickness impact profile Discriminative: Significant difference between scores of MS and hypertensive patients on all scales	Moderate
Fatigue scale – 11 items	Yes/no response or four-point Likert scale	2: physical fatigue and mental fatigue		General population	Internal consistency: 0.88-0.90	Concurrent: Revised Clinical Interview Schedule (CIS-R) fatigue question Discriminative: between patients with and without fatigue assessed on the CIS Ceiling effect Noted	Moderate
Fatigue Symptom Inventory (FSI) – 13 items	Eleven point Likert scale	3: intensity, duration, impact on quality of life	Past week	General pop	Internal consistency: 0.88-0.90	Concurrent: Revised Clinical Interview Schedule (CIS-R) fatigue question Discriminative: Between patients with and without fatigue assessed on the CIS Ceiling effect Noted	Moderate
Multi-dimensional Assessment of Fatigue (MAF) – 14 items		4: degree, severity, distress, impact on activities	Past week	General	Internal consistency: 0.93 Test-retest: R= 0.47-0.73 and 0.87	Construct: factor analysis did not support four factors Convergent: correlated with POMS fatigue (r= 0.78-0.84) and vigour (r=0.60-0.62) subscales Correlated with FSS (r= 0.74)	Moderate

						Discriminative: detects significant differences in fatigue between patients and controls The sensitivity of the scale has not been fully explored, but the scale did not appear to be able to detect small changes in fatigue	
Multi-dimensional Fatigue Inventory (MFI-20) – 20 items	Five-point Likert scale	5: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue	Previous days	General: validated with a wide range of conditions Cancer, people with chronic fatigue syndrome, psychology students, medical students, army recruits, and junior physicians	Internal consistency: range 0.53-0.93 (mean 0.84), Test-retest: r= 0.76 (total), 0.60-0.72 (subscales)	Factor analysis confirmed the five-factor model and 74.2% variance Convergent: with a VAS measuring fatigue (r= 0.22-0.78) and the RFS (r= 0.44=0.59) Some limitations in the general fatigue scale that failed to discriminate between people with cancer and students. Mental fatigue was found to be less severe in patient group compared with the student sample	Moderate
Piper Fatigue Scale (PFS) – 76 items	Visual analog	7: temporal, affective, and sensory dimensions of fatigue and fatigue severity	Now	General	Internal consistency: 0.85	Concurrent: With POMS-I	Poor
Revised Piper Fatigue Scale (PFS-R) – 22 items	Eleven point numerical self-report and five open-ended	4: sensory, affective meaning, cognitive/ mood, behavioural/ severity	Now	General: also validated with HIV	Internal consistency: 0.80-0.99	Construct: factor analysis verified four factors. Convergent: correlated with Fatigue Symptoms Checklist (r=0.55) and Fatigue Subscale of POM (r=0.42)	Moderate
The Visual Analog Fatigue Scale (VAS-F) – 18 items	100mm VAS	2: energy, fatigue	Now	General population	Internal consistency: 0.96 and 0.91, respectively, for fatigue measured in the morning and evening. Internal consistency: r=96 for both mothers and fathers over five data collection times	Concurrent validity was established using the Stanford Sleepiness Scale and the Profile of Moods States Fatigue subscale	Moderate

I will focus below in the description of the two fatigue screening questionnaires that were used in the empirical studies.

1. Description of the MFI-20

The Multidimensional Fatigue Inventory (Appendix 6) is a self-report instrument. The current version contains 20 statements that cover different aspects of fatigue. These 20 items are organised into five scales. Each scale contains four items. The scales are balanced to reduce the influence of response tendencies as much as possible; each scale contains two items indicative for fatigue and two items contra-indicative for fatigue. Indicative items (e.g. 'I tire easily') are formulated in such a way that a high score suggests a high degree of fatigue. In the case of contra-indicative items (e.g. 'I feel fit'), a high score indicates a low degree of fatigue.

The respondent must compare each of the 20 statements with how he or she has felt lately. The choice for this timeframe was made on the basis of the considerations that a) the instrument has to measure persistent fatigue contrary to acute fatigue resulting from effort, and b) the instrument has to be sensitive to changes resulting, for example, from treatment. Because of the latter, the timeframe cannot be too long.

The response scale consists of five boxes and runs from agreement with the accompanying statement 'yes, that is true' to disagreement, 'no, that is not true'. The respondent must mark the box that intuitively corresponds most with his or her own condition.

MFI-scales: General Fatigue (GF) (items: 1, 5, 12, 16), Physical Fatigue (PF) (items: 2, 8, 14, 20), Reduced Activity (RA) (items: 3, 6, 10, 17), Reduced Motivation (RM) (items: 4, 9, 15, 18), and Mental Fatigue (MF) (items: 7, 11, 13, 19).

The instrument can be presented as a written questionnaire, to be completed in the absence of a researcher or interviewer. The instructions for completing the questionnaire are printed on the instrument. The respondent must read these instructions carefully. If the instrument is used orally in an interview situation it may be recommended that the interviewer reads the instructions out loud. It must be

stressed that all questions need to be answered and that the statements refer to the situation of the last few days.

The scores per item run from 1 to 5. A higher score indicates more fatigue. Therefore, the items indicative for fatigue need to be recoded (1=5, 2=4, 3=3, 4=2, 5=1). This concerns items 2, 5, 9, 10, 13, 14, 16, 17, 18, 19.

For each scale a total score is calculated by summation of the scores of the individual items. Scores can range from the minimum of 4 to the maximum of 20. After all, when a total score obtained by summation is interpreted as a global judgement concerning the degree of fatigue, the question remains as to whether the separate dimensions contribute by a similar degree to this global judgement.

2. Description of the SF-36 energy/fatigue subscale

The vitality (energy and fatigue) category is one of the eight health concepts (number 7) of the SF-36. It is a 36-item short form (SF-36) constructed to survey health status in the Medical Outcomes Study. The SF-36 was designed for use in clinical practice and research, health policy evaluations, and general population surveys. The SF-36 includes one multi-item scale that assesses eight health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. The survey was constructed for self-administration by persons 14 years of age and older, and for administration by a trained interviewer in person or by telephone.

The energy and fatigue subscale comprises four questions (Appendix 6). They are question numbers 23, 27, 29, and 31 in the SF-36. It is a six-point Likert scale, with each item scored on a 0-100 range so that the lowest and the highest possible scores are set at 0 and 100 (0, 20, 40, 60, 80, 100); extreme limitation is represented with a high score and absence of limitation with a low score. Scores represent the percentage of total possible score achieved; the reliability, central tendency, and variability (alpha is 0.86, mean is 52.15, and SD is 22.39).

3.4 Fatigue Associated with Chronic Medical Disorders

Studies of fatigue associated with medical disorders have shown a high degree of correspondence between fatigue and depression. For example, 'vital exhaustion', defined as unusual fatigue, demoralisation, and increased irritability, and associated with the pathogenesis of cardiovascular disease, shares many features with depression and is highly correlated with this condition in patients with cardiovascular disorders (274, 275). Results of studies that have attempted to identify possible differences between depression and vital exhaustion have been conflicting, and questions remain about whether depression and vital exhaustion are independent risk factors for cardiovascular disorders and morbidity (275). Fatigue has also been highly correlated with depression in patients with rheumatological disorders (276, 277) and other medical disorders, such as multiple sclerosis (278), cancer (279), heart failure (280), and HIV/AIDS (281).

The symptomatic overlap between fatigue and depression might have confounded the findings of the high correspondence between fatigue and depression in medical disorders. This problem has been addressed in studies of cancer-related fatigue. Though the assessment of depression was limited to its mood components, there was still a high correlation between depression and fatigue. Furthermore, the association between fatigue and depression remained high even after items reflecting symptoms of fatigue were removed from measures of depression (282, 283). The strong association between fatigue and depression in cancer patients is not simply a function of overlap in their assessment. There is some evidence that depression is a secondary response to the experience of fatigue produced by cancer and indirect evidence to support the possibility that fatigue associated with cancer occurs as a consequence of depression (279) However, the most compelling data suggest that fatigue and depression share etiologic factors, e.g. pancreatic tumours may secrete neuropeptides and neuro-hormones that contribute to the development of both depression and fatigue (279). Having said this, the relationship between unexplained chronic fatigue and depression is still unclear (161).

Numerous studies in a range of medical settings have shown a strong association of medically unexplained chronic fatigue and depression (284-287). Furthermore, a

lifetime history of major depressive disorder occurs in approximately 50-75% of individuals with CFS (288). Even after removing fatigue symptoms as criteria for depression, the majority of patients with CFS meet criteria for a lifetime history of major depressive disorder, suggesting that the comorbidity is not simply a consequence of diagnostic overlap between major depression and CFS (288, 289).

The strong association of chronic fatigue and depression and the high rates of lifetime major depressive disorder in persons with CFS suggest that it may be a manifestation of major depressive disorder. One of the main arguments against this possibility is that about one-quarter to one-half of patients with chronic fatigue do not have a history of major depressive disorder (290). It is, however, important to consider that the presence of only one subtype of depression, melancholic major depressive disorder, excludes a patient from a diagnosis of chronic fatigue syndrome according to the Centres for Disease Control and Prevention (CDC) definition (291, 292). It is possible that patients with CFS may have sub-threshold symptoms of depression, which, as discussed above, represents an important but understudied clinical problem. Furthermore, other subtypes of depression, such as atypical depression, are not excluded when making a diagnosis of CFS. As reviewed above, atypical depression is characterised by prominent fatigue and, like CFS, predominately affects women and is associated with a history of abuse (physical and/or psychological) (293). Unlike melancholic depression, both atypical depression and CFS are associated with reduced activation of the HPA axis (294).

3.4.1 Prevalence of Fatigue in Community and Medical Setting

Fatigue is a common symptom in the community, with up to half of the general population reporting fatigue in large surveys (295, 296) . It also is reported by at least 20% of patients seeking medical care (39, 297-300).

Typically, the fatigue is transient, self-limiting, and explained by prevailing circumstances. However, a minority of persons experience persistent and debilitating fatigue. When the fatigue cannot be explained by a medical condition such as anaemia or hypothyroidism, it may represent CFS (291).

Data from the Epidemiologic Catchment Area (ECA) study shed light upon the relationship between fatigue and psychiatric disorders, in terms of current and lifetime comorbidity (301).

The prevalence of fatigue in general practice attenders, using an extensive fatigue questionnaire, was 10.2% of men and 10.6% of women, all of whom complained of feeling tired all or most of the time for more than a month (298).

Prolonged and excessive fatigue had 13.2% prevalence in a study by Hickie et al. (302). In the majority of cases the symptom of fatigue was clinically significant and not caused by drugs, alcohol, physical illness, or injury. In addition, as a common symptom in the community, fatigue is also a highly prevalent complaint in primary-care medicine (303).

3.4.2 Prevalence of Frailty in Haemodialysis and its Relationship to Fatigue

Ageing and demographic changes are worldwide. Although a large proportion of older adults consider themselves as in good health and lead independent lives, 91% of this population has one or more chronic conditions, 40% live with a disability as reported by the National Advisory Council on Aging (304), and a significant proportion (10%–25%) are considered frail (305).

The prevalence of frailty for adults undergoing haemodialysis is 41.8%. Frailty is associated with a 2.6 times higher risk of mortality and a 40% increased risk of hospitalization (306). The prevalence is 5-7 times higher than community estimates and compares with a frailty prevalence of 7% in adults with cardiovascular disease (307).

There is a direct relationship between fatigue and frailty. The hypothesis is supported by the common biomedical determinants shared by frailty and fatigue, as well as by the established relationship of fatigue with the core elements of the cycle of frailty (227).

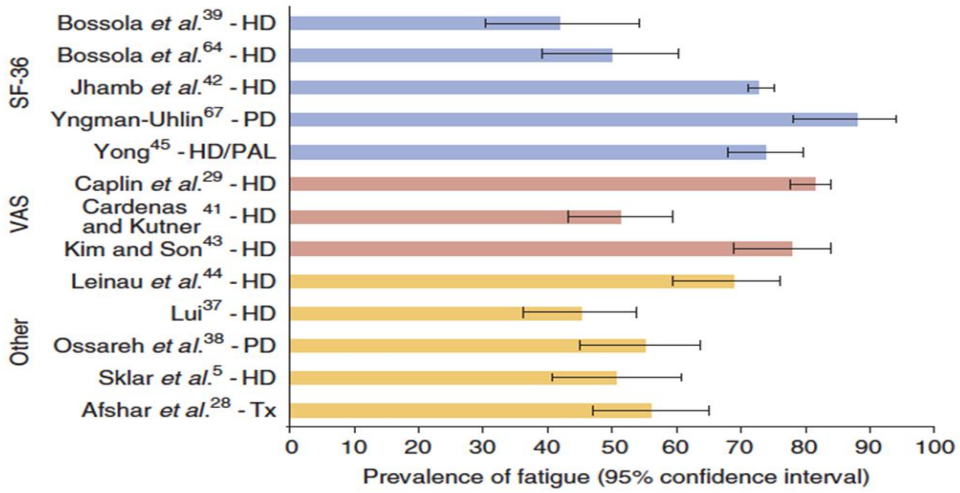
Frailty is increasingly recognized as a geriatric syndrome that is distinct from disability and comorbidity and shares common biomedical determinants with rapid

fatigue, aging, disease, inflammation, physical inactivity, malnutrition, hormone deficiencies, and changes in neuromuscular function and structure .This syndrome is a result of cumulative declines across multiple physiological systems and represents the failure of one's functional reserve capacity to sustain homeostasis to meet the demands of everyday life (308). In addition, there is an established relationship between fatigue and core elements of the cycle of frailty including aging, disease, gender, nutrition, physical activity, inflammation, muscle strength, size, structure, metabolism, and blood flow, and neural and hormonal factors (309). The cycle of frailty in which the biological and physiological determinants of frailty were sarcopenia, neuroendocrine dysregulation and immunologic dysfunction, results from the interaction of these three systems (310). Frail older adults are vulnerable to physiological and psychological stressors, and are at risk for a range of adverse health outcomes, including falls, fractures, disability, death, and increased utilization of medical and social resources in the community, hospital, home, and long-term care institutions (136).

3.5 Fatigue in ESRD

Fatigue is one of the most frequently reported symptoms in renal patients (311, 312). As shown in Figure 13, a significant proportion of patients with renal disease report fatigue, rates that are comparable to other physical conditions. However, the exact prevalence remains contentious as most of the research has focused on the HD population and neglected patients receiving PD and transplant patients.

Figure 13: Prevalence estimates of fatigue in ESRD (%), (313)



Tx = Transplant patients; HD = Haemodialysis; PD = Peritoneal dialysis; PAL = Palliative care; VAS = Visual Analogue Scale – Fatigue; BFI = Brief Fatigue Inventory; FAS = Fatigue Assess Scale; MOS SF-36 = Medical Outcomes Study SF-36.

3.5.1 Prevalence and Severity of Fatigue in ESRD

Overall, there is variation regarding the estimated prevalence of fatigue, ranging between 42% and 89% according to treatment modality and the instruments used to measure the presence of fatigue. A recent large investigation using a VAS reported that 81.5% of HD patients experienced fatigue (226). A similarly high prevalence of fatigue in the HD population (77.9%) is reported elsewhere (314). Others, however, report lower rates when using the SF36 vitality subscale (41.9%) (Figure 13) (315).

The severity and frequency of patients' fatigue also varies according to the instrument used (Table 18). Studies using the FSS report total sum severity scores between 31 and 47 (44, 316-318) and mean severity item scores between 5.15 and 6.14 (319, 320). The nine-item FSS total score ranges from a minimum of 9 to a maximum of 63, suggesting that the scores for renal patients indicate problematic levels of fatigue. Studies in the general population report significantly lower mean scores (M = 3.7 (321); M = 2.5 (322)). Similar findings have been reported using the MFI-20 (38, 323, 324).

Table 18: Severity of fatigue among renal patients, (313)

Study	Measure/cut-off	Population	Mean Severity (SD)	Scale Range	n
Akin et al.	VAS	HD	Fatigue subscale 72.1 (20.3) Energy subscale 23.9 (7.8)	13-130 5-50	325
Bonner et al.	FSS	CKD	47.7 (13.2)	9-63	28
Bonner et al.	FSS	Pre-Dx, HD, PD, Tx	Females 43.7 (14.6) Males 38.7 (13.3)	9-63	92
Bonner et al.	FSS	Pre-Dx, HD, PD	39.9 (14.5)	9-63	112
Chang et al.	Chalder Fatigue Scale	PD	5.8 (2.7)	0-14	64
Joshwa et al.	FSS	HD	31 (13.2)	9-63	47
Karadag et al.	FSS	HD	Females 6.14 (1.1) Males 5.30 (1.9)	1-7	73
McCann & Boore	MFI-20 VAS	HD	15.3 (2.7) 69.2 (25.3)	4-20 0-100	39
O'Sullivan & McCarthy	MFI-20	HD	12.6 (4.3)	4-20	46
Sajadi et al.	FSS	HD	5.2 (1.5)	1-4	56
Tsay et al.	PFS, VAS	HD	PFS = 6.0 (1.5) VAS = 57.7 (22.2)	3-10	106
Lobbedez et al.	MFI-20	HD, PD, controls	Dialysis: 14 (3) Controls 10.8 (4)	4-20	54

Tx = Transplant patients; HD = Haemodialysis; PD = Peritoneal dialysis; CKD = Chronic Kidney Disease; VAS = Visual Analogue Scale – Fatigue; FSS = Fatigue Severity Scale; MFI-20 = Multidimensional Fatigue Inventory, PFS = Piper Fatigue Scale. Mean severity data rounded to 1 d.p.

3.5.2 Fatigue in Haemodialysis

The literature regarding the experience of fatigue in HD patients indicates that fatigue impacts the physical and mental domains. Physical fatigue was described by patients as a constant lack of energy, which seemed worse on dialysis days. Fatigue is negatively correlated with physical functioning (38, 323), role limitations (38), activity levels (40), and mental and physical quality of life (41). It interferes with patients' abilities to manage their everyday activities (42, 43), which require more time to complete when patients are fatigued and cause patients to feel isolated from others and society. Some feel too fatigued to communicate with others and have difficulty maintaining close relationships (42).

Fatigue also negatively affects patients' abilities to remember and concentrate on conversations and on what is going on around them (43). Clearly, fatigue is frequently debilitating and hinders participation in even simple physical and mental activities for patients on dialysis.

3.5.3 Post-dialysis Fatigue (Post-dialysis Recovery Time)

Post-dialysis fatigue is a frequent complaint of haemodialysis patients. Patients who experience fatigue after dialysis require almost five hours of sleep to recover after their session and have more depression, insomnia, and body aches than those who do not experience post-dialysis fatigue (325).

Furthermore, patients with post dialysis fatigue experience limitations in their functional independence and participation in social activities on the day of dialysis. The symptom is not predicted by clinical measures such as nutrition, laboratory results, or the adequacy of dialysis (326). Research suggests that it may be part of a symptom complex that includes nausea, muscle cramps, and headache, which may be the result of the fluid shifts that occur during haemodialysis (327). It is possible that post dialysis fatigue is conceptually similar to the persistent fatigue that patients experience, though it differs in severity and timing. It is a common, often incapacitating, and may be improved with more frequent treatment (43, 325, 327). In addition, the relationship between recovery time (time needed for the patient to

recover) and fatigue is strongest immediately after dialysis and weakens progressively during the time between sessions. The time to recover from HD also shows a significant positive association with the total dialysis stress score, which encompasses an array of physical signs and symptoms that can arise during HD procedure (328).

3.5.4 Contributors to Fatigue in ESRD

In the dialysis population, physiological, behavioural, treatment-related, and individual characteristics may be associated with fatigue. Physiological aetiologies include anaemia, malnutrition, uraemia, dialysis inadequacy, hyperparathyroidism, coexisting chronic illnesses, sleep disorders, depression, and side effects of medications. Dietary and fluid restriction may also play a role. Physical inactivity has been associated with higher levels of fatigue. Socio-demographic factors, including age, sex, race, education, marital, and vocational status, may also play a role in the experience of fatigue in dialysis patients. It is also important to note that pro-inflammatory cytokines have emerged as potential mediators of fatigue, providing a common biological pathway for physiologic, behavioural, and treatment-related factors to cause fatigue in the dialysis population.

3.5.4.1 Demographic Factors

In general, patients who are older, female, and white/Caucasian may have higher levels of fatigue, but at times, the evidence is not clear (329). Some studies found no relation between fatigue and demographic variables such as age (323), gender (314), and education level (330). Others, though, found significant relationships between these and other demographic variables and fatigue. Most findings indicate that women report higher levels of fatigue than men (331). Others demonstrate that age is associated with higher fatigue levels among patients on dialysis (315). Patients receiving haemodialysis in their early sixties report significantly higher total fatigue levels than those in their thirties (330). In contrast, in other studies, age has been found to be negatively correlated with fatigue levels (315, 332). Some studies

suggest that being Caucasian and unemployed may be related to higher levels of fatigue (333). Others, though, found no significant differences in fatigue levels between the employed and unemployed (323, 334). It is possible that demographic variables such as these may help identify a group of patients who are more at risk for fatigue than others.

3.5.4.2 Psychosocial Factors

There are limited studies of the relationship between psychosocial variables and fatigue in the haemodialysis population, though depression, anxiety, and social support may all have a role. Three studies (314, 315, 335) found that fatigue was significantly correlated with depression in haemodialysis patients. Furthermore, not only depression but also a risk of suicide were correlated with fatigue (336).

Depression has been shown to be related to fatigue severity, both physical and mental fatigue (38, 314). Fatigue scores are significantly higher for haemodialysis patients who are depressed rather than those who are not depressed. Depression is a significant predictor of fatigue in this population (38, 330, 337). Similarly, mood disorder, which includes depression and anxiety, significantly predicts fatigue in this population (338). Anxiety has been shown to be significantly correlated with fatigue (38, 315, 336, 338), though not all studies agree (332). Social support is not related to fatigue in haemodialysis patients (327, 338), but this relationship has not been studied extensively.

3.5.4.3 Physiological Factors

Physiological variables have been investigated in relation to fatigue in patients on dialysis. It is difficult to determine which specific facet of human physiology is most culpable in the occurrence of fatigue. Indeed, it may be a combination of physiological factors that contribute to fatigue. Interdialytic weight gain, weight gain that occurs between dialysis sessions as a result of fluid accumulation, has been significantly correlated with fatigue in dialysis patients. There is a weak but significant correlation between fatigue and interdialytic weight gain fatigue

(beta=0.43, p<0.001 and beta=0.25, p<0.05, respectively) (314). This association indicates that weight gain may be one of the many contributors to fatigue in haemodialysis patients.

Serum chemistry and haematology measures for the most part do not seem to significantly contribute to fatigue in this population. There have been suggestions of a weak correlation between fatigue and anaemia (338), though, in cross-sectional analyses, most studies found that anaemia (38, 314, 331, 334, 335, 339), albumin levels (38, 330, 331, 334), blood urea nitrogen and creatinine levels (38, 314), calcium and phosphorus (38), potassium, and magnesium levels (335) were not related to fatigue. In contrast, fatigue increased with lower creatinine levels (due to lower muscle mass) and decreased significantly with higher albumin levels (315). The use of erythropoietin stimulating agents (ESA) to correct anaemia in dialysis patients has been shown to improve fatigue and HRQOL and I will expand on this in detail in section 3.7.3.

There is conflicting evidence about the relationship between dialysis vintage (number of months or years on dialysis treatment) and fatigue (40, 332). Suboptimal dialysis adequacy has been suspected as the source of various uremic symptoms including fatigue in patients on haemodialysis (340). Studies investigating Kt/V, a measurement of dialysis adequacy, have failed to confirm a relation between adequacy and fatigue in haemodialysis patients (330, 331, 335).

3.5.4.4 Inflammation

ESRD is an inflammatory state characterised by elevated circulating levels of pro-inflammatory cytokines (341-343).

Cytokines might contribute to fatigue by directly activating the central nervous system, hypothalamic pituitary, and adrenal axis or indirectly triggering multi-system deregulation due to chronic inflammation (344). For example, Interferon (IFN) produces neurasthenia, a neurological fatigue suggestive of frontal lobe changes manifesting as lack of motivation (345). Cytokines such as IL-1, IL-6, and TNF-α suppress erythropoiesis and have been hypothesised as contributing to anaemia and fatigue in cancer patients (346). Cytokines (IL-6, TNF), trigger hyper-responsiveness

of muscular ergoreceptors, which sense fatigue or the work performed by the muscle, and thus contribute to fatigue (347). Cytokine-mediated malnutrition and hypo-albuminemia may also contribute to fatigue (348).

Although the causes of elevated cytokines in HD patients are not fully understood, it has been suggested that these patients have overproduction of cytokines by peripheral blood mononuclear cells secondary to chronic activation by interaction with dialysis membranes (349, 350). Moreover, in this complex pathological condition, the possibility of intrinsic alterations of signalling pathways and immune defects cannot be excluded (351). IL-6, CRP, and TNF-α have been associated with mortality, decreased muscle strength, and vital exhaustion in the elderly and post-myocardial infarction patients (352-355). IL-6 also induces protein catabolism, lipolysis, and insulin resistance and has been shown to have a strong negative correlation with serum albumin in patients undergoing HD (349, 356).

A number of human studies have linked inflammatory cytokines to fatigue in both aging and chronic health conditions such as cancer and CFS (346, 348, 357). Interestingly, elevated levels of pro-inflammatory cytokines have been linked to an increase in energy expenditure, mortality, and lower functional status in HD patients (358-360). Higher levels of IL-6 have been associated with significantly higher levels of resting energy expenditure (359), which has been previously associated with higher mortality in HD and PD (344, 358-360).

3.5.4.5 Physical Activity

Dialysis patients have severe exercise limitation, which has been attributed to muscle atrophy and weakness, the presence of abnormal mitochondria, and impaired oxidative capacity (361). Muscle fatigue, defined as the reduction in force with repeated or sustained contractions, can lead to manifestations of myopathy. Contributors to excessive muscle fatigue in dialysis patients include poor oxidative metabolism, greater accumulation of metabolic by-products, central activation failure, and impaired neuromuscular propagation (362). Endurance training has been shown to increase muscle strength, power, peak work rate, VO_2 peak, and physical function (363). In addition, exercise rehabilitation programmes may have

morphological and metabolic benefits in the skeletal muscles and improve work capacity (364).

Physical inactivity is associated with higher levels of fatigue in ESRD patients (40). In addition, obesity, which has been described as a chronic inflammatory state, may also mediate alterations in levels of certain cytokines leading to fatigue (365). Acute exercise results in an inflammatory response (e.g. increases in white blood cell counts, IL-1, and C-reactive protein (CRP), whereas regular exercise has an anti-inflammatory effect and reduces the level of pro-inflammatory cytokines (366-368). However, the effect of physical activity on the immune system may be different in HD patients than in healthy adults (369). There is also evidence that muscle catabolism is increased in dialysis patients, which may be due to insulin resistance, acidosis. or inflammation. This may lead to muscular fatigue and further physical inactivity (43, 370).

3.5.4.6 Sleep

Sleep disorders have been hypothesised as associated with fatigue through two mechanisms: the disturbance of sleep resulting in daytime sleepiness and the separate underlying biological pathways associated with a variety of sleep disorders. Dialysis patients have high rates of sleep apnoea, insomnia, restless legs syndrome, and excessive daytime sleepiness (371, 372).

Impaired sleep initiation, maintenance, and adequacy are associated with significantly lower vitality in both HD and PD patients (38, 53, 373). Sleep apnoea has been associated with lower HRQOL in patients on HD, and those without sleep apnoea experience significantly better vitality, social functioning, and emotional and mental health (48). Other symptoms, such as restless legs, which is common in dialysis patients, can affect sleep quality and may also impact vitality. Symptoms of restless legs are significantly associated with lower physical and mental well-being, lower vitality, higher bodily pain, and lower sleep quality (53).

HD patients often suffer from nocturnal pruritus and difficulties finding a comfortable sleeping position, resulting in impaired sleep quality, which contributes to daytime sleepiness and fatigue (373).

The relationship of sleep disorders and increased levels of inflammatory cytokines may help explain the association of sleep disorders with fatigue in this population. Higher levels of Interleukin (IL)-18 were associated with poor sleep quality in HD patients (374). In healthy people, the administration of Tumour Necrosis Factor (TNF)-α and IL-1β increase the amount of non-rapid eye movement (NREM) sleep and decrease rapid eye movement (REM) sleep (375). IL-6 is associated with the amount and depth of sleep, and higher levels are associated with poor sleep (376, 377). IL-1α and TNF-α have also been associated with sleep disordered breathing in dialysis patients (378). In healthy people, elevated levels of TNF-α and IL-6 have been associated with circadian rhythm disruption and obstructive sleep apnoea (OSA) independent of obesity (376, 379, 380).

Poor sleep quality may be the result of a combination of physiological and psychological factors and presents a problem for many patients on dialysis (381). However, the extent to which poor sleep is related to fatigue in this population is unclear, though overall trouble with sleep is significantly correlated with general and mental fatigue (38). Intuitively, poor sleep is a likely cause of fatigue in the dialysis population, though research is lacking.

3.6 Fatigue Overlapping in Depression and Uraemia

Fatigue and depression are closely interrelated and depression may manifest as feelings of tiredness and lack of energy. Depression has also been shown to correlate strongly with overall symptom burden and severity, including fatigue in dialysis patients (382).

There are conceptual similarities between depression and fatigue. Fatigue, like depression, can be assessed as a single symptom (a uni-dimensional approach), a cluster of symptoms (a multi-dimensional approach), or as a clinical syndrome with a set of criteria for the diagnosis of fatigue such as CFS or cancer-related fatigue (279).

Symptoms of fatigue include physical (e.g. reduced activity, low energy, tiredness, decreased physical endurance, increased effort with physical tasks and with overcoming inactivity, general weakness, heaviness, slowness or sluggishness, non-

restorative sleep, and sleepiness); cognitive (e.g. decreased concentration, decreased attention, decreased mental endurance, and slowed thinking); and emotional dimensions (e.g. decreased motivation or initiative, decreased interest, feeling overwhelmed, feeling bored, aversion to effort, and feeling low).

Physical fatigue or loss of energy is included as a single item in the DSM-IV criteria for major depressive disorder. However, all of the dimensions of fatigue can be found in other criteria for MDD. For example, mental fatigue (e.g. difficulty concentrating) and emotional fatigue (e.g. anhedonia) are also associated with depression (383). The overlap in symptomatology makes it difficult to disentangle the complex relationship between depressive syndromes and fatigue syndromes in relation to chronic disease. Further complications in the assessment of fatigue are the presence of different subtypes of depression.

Atypical depression is of particular interest when considering fatigue because patients with this subtype are significantly more likely than patients with other forms of depression to report fatigue (384). Both community-based studies and studies of psychiatric outpatients have shown that approximately one-fifth to one-fourth of depressed individuals exhibit the atypical subtype (385, 386). There is emerging evidence that atypical depression is associated with endocrine abnormalities that differ from the classic melancholic depression. In many studies of the HPA axis, melancholic depression is associated with hypercortisolism, which is thought to be a result of elevation in hypothalamic corticotropin-releasing hormone (CRH). In contrast to a centrally activated HPA axis in melancholic depression, atypical depression may be associated with a pathological reduction of stress-system mediators and a deficiency in hypothalamic CRH. Hypo-activity of the core stress system components that promote arousal could contribute to the fatigue that is characteristic of atypical depression (387).

A twin study showed that fatigue during a severe major depressive episode is more likely to be reported by women than men (388). This evidence, along with the preponderance of women with the atypical subtype of depression, suggests that women are at greater risk of developing fatigue in depression. However, the reasons for the sex difference are unknown.

Fatigue is common in major depressive disorder (389), especially in the atypical subtype, and it is the depressive symptom that correlates most strongly with diminished functioning (390). It is also a common prodromal symptom in patients with their first major depressive episode (391), and it strongly predicts progression to a chronic course of depression (392).

There are several competing hypotheses in the literature about the temporal relationship of chronic fatigue and major depression and what the differences could mean. **Does chronic fatigue cause depression, or is it depression that causes the fatigue?** Or perhaps fatigue and depression are conditions that arise concurrently as a result of a common underlying pathophysiological process.

In a study of a national birth cohort, the causal relationship between psychiatric disorder and physical symptoms of fatigue seemed likely to operate in both directions. These findings further substantiate the idea that fatigue is neither purely predictive nor a consequence of psychiatric disturbance, but rather is aetiologically heterogeneous (393).

In the DSM-IV diagnosis of MDD, fatigue or loss of energy nearly every day is the A6 criterion – and is not considered a core symptom. Furthermore, fatigue with a distinct quality is used as the B3 criterion for an atypical feature specifier: leaden paralysis (heavy, leaden feelings in arms and legs). However, in the definition of depressive episode according to ICD-10 (66), reduced energy is described as a core feature besides depressed mood and loss of interest and enjoyment. Reduced energy is specified as leading to increased fatigability and diminished activity, with marked tiredness after only slight effort being common.

The different wordings of ‘fatigue’ in DSM-IV and ICD-10 reflect its complexity and heterogeneity. This is highlighted even more by the coverage of fatigue in different depression rating scales. The Hamilton Depression Rating Scale (HDRS) covers fatigue in two different items: item 7 (work and interests) and item 13 (general somatic symptoms) (86, 394). In the BDI-II (181) fatigue is described by item 15 (loss of energy) and item 20 (tiredness or fatigue). Item 7 of the MADRS (88)] describes lassitude as representing a difficulty getting started or slowness initiating and performing everyday activities: a construct covering both fatigue and

retardation. The HDRS, BDI-II, and MADRS not only differ in their coverage/wording of fatigue but also in the perspective of the observer (HDRS and MADRS being observer-rating scales, BDI-II being a self-rating scale). Energy and worry are the most important symptoms differentiating depressed medical patients from depressed psychiatric patients, while suicidal ideation and loss of interest are the most important symptoms differentiating depressed psychiatric patients from depressed medical patients (395).

The prevalence of fatigue and its relationship with major depression over a 13-year prospective follow-up study was 14.0% of individuals reporting unexplained fatigue for two weeks or more in their lifetimes, with an 11-fold greater risk of a lifetime diagnosis of major depression compared to non-fatigued participants. Baseline depression was predictive of both recurrent/chronic fatigue and incident fatigue. Participants with recurrent/chronic fatigue had a 28-fold greater risk of developing major depression than those without fatigue (301).

3.7 Management of Fatigue

3.7.1 Assessment and Treatment of the Cause

Fatigue is viewed by health professionals as something that cannot be changed as it is part of the disease process (38). Thus, fatigue is rarely specifically treated medically.

Patients with ESRD, who require maintenance haemodialysis often, reported symptoms of fatigue and a poor quality of life (325, 396). Yet, despite the high incidence of fatigue and its negative impact on life quality, few interventions have been developed, tested, and directed at managing this debilitating symptom in persons with ESRD. People with a chronic illness, especially ESRD, often feel helpless in dealing with their disease. This sense of helplessness or loss of control often occurs when medical science does not have a curative treatment to offer.

Because there is no widely accepted tool for screening fatigue in the ESRD population, healthcare providers should consider screening for a sense of fatigue and tiredness that has a substantial impact on patients' functional abilities. Given the high

rate of sleep disorders, practitioners should clarify if the patient is sleepy or drowsy rather than weak and lacking energy. If the patient reports that fatigue leads to functional impairment, providers should actively consider common causes such as worsening heart failure, CFS, hypothyroidism, liver disease, depression, sleep disorders, and autoimmune diseases as well as the kidney-disease-related factors outlined in this review.

Due to the complexity of fatigue, a multi-disciplinary approach to treatment should be adopted by nephrologists. In order to address the level of fatigue, this symptom first needs to be recognised and accurately measured by healthcare providers. All renal providers should receive training on identifying and addressing the issue of fatigue, which will help to identify patterns in the severity of fatigue in patients with ESRD.

A better understanding of the pathogenesis of fatigue, particularly the role of cytokines, may help in designing interventions aimed at reducing inflammation and fatigue. Management of factors such as anaemia and sleep disorders is fundamental.

Treatment of depression, anxiety, stress, substance abuse, obesity, and malnutrition may be helpful, although studies substantiating the role of these interventions are lacking.

Dialysis nurses may be able to assist patients understanding the importance of diet, exercise, sleep, and strategies to improve good practice. To provide holistic care, nurses should try first to understand their patients' unique experience and try to assist them in developing strategies to address their problems.

3.7.2 Non-pharmacological Approach

Non-pharmacological interventions targeting nutrition, sleep hygiene, stress management, and treatment of depression may potentially decrease fatigue.

An RCT of 106 HD patients who were randomly assigned into acupressure group, sham group, or control group showed that acupressure may help improve fatigue, depression, and sleep quality in dialysis patients (397).

Fatigue is an important outcome for daily dialysis trials since the frequency of dialysis may also affect fatigue in HD patients. Some studies demonstrate that, compared to conventional therapy, daily dialysis significantly improves perceived energy level, uremic symptoms, cognitive functioning, and overall HRQOL (339, 398, 399).

Exercise and yoga have also been studied as effective measures in improving fatigue (363, 400). Whether this is due to the direct effect of muscle strengthening or indirect effect on the cytokines (or both) is unknown.

Energy conservation strategies, such as those used for multiple sclerosis patients, may similarly improve fatigue in ESRD patients (401). Overall, the bulk of evidence of non-pharmacologic interventions in the ESRD population in reducing fatigue consists of small trials assessing the impact of rehabilitation, exercise, and more frequent haemodialysis (402).

'Energy management' is a promising method for fatigue management because it can be used to regulate energy and treat or prevent fatigue. There are two levels of energy management, including preserving energy and producing energy. For preserving energy, nurses must know how to teach patients to balance their rest and activities and use skills to save energy. Preserving energy is not enough for patients. Thus, nurses should provide strategies that can produce energy to help patients (403). The best way to create energy is regular aerobic exercise, which may actually improve energy levels. If the interventions can be provided, the participants' energy can be saved or increased in appropriate ways, and fatigue and its effects may be minimised (403).

Improving the social support for the patient with severe fatigue is crucial and helps the patient cope with the disabling symptoms. Fatigue and tiredness may extend to the caregiver, who may provide support for home dialysis or the care of a child with ESRD (172).Therefore, the care for patients with ESRD includes education for the family as well as addressing fatigue issues to the caregiver.

3.7.3 Pharmacological Approach

Medical treatment for fatigue in ESRD patients may involve routine supplement of erythropoietin to correct anaemia that may be related to the symptom of fatigue (404). The use of ESA to correct anaemia in dialysis patients has been shown to improve HRQOL, fatigue, exercise tolerance, and work capacity (405, 406). ESA therapy in patients with renal insufficiency and cancer revealed a consistently positive relationship between HRQOL and haematocrit levels, with the strongest effect on the energy/fatigue domains (407). These findings were confirmed by a meta-analysis of the impact of epoetin alfa in patients with chronic kidney disease (408).

In pre-dialysis CKD patients, the Correction of Haemoglobin Outcomes in Renal Insufficiency (CHOIR) and Cardiovascular Risk Reduction by Early Anaemia Treatment with Epoetin Beta (CREATE) studies compared the HRQOL in patients with higher versus lower target haemoglobin levels (409, 410). The CREATE study reported significantly improved fatigue symptoms in patients with higher haemoglobin, whereas the CHOIR study did not reveal any significant differences between the two groups (411).

The lack of association between anaemia and fatigue in recent studies may relate to the relatively higher targeted haemoglobin levels for the control groups in the post-erythropoietin era (412). Although anaemia, resulting from reduced erythropoietin production, has been cited as an important contributor to fatigue in both the dialysis population and other chronic conditions (413), the optimal haemoglobin target remains unclear and may vary among individuals depending on the severity of fatigue.

The treatment of uraemia by dialysis may also influence fatigue, as the mode and frequency of dialysis are associated with fatigue. The potential impact of dialysis modality was shown in the CHOICE study (414), comparing the HRQOL in conventional HD and PD patients. There was no significant difference in the vitality scores among HD and PD patients at the initiation of dialysis therapy; however, patients on PD experienced significantly lower vitality at one year (415). The stimuli for inflammatory response in PD patients include fluid overload, decreased cytokine

clearance, presence of uraemia modified proteins, presence of chronic infections, and metabolic disturbances including hyperglycaemia (416, 417).

Typically, fatigue and lack of energy improve with antidepressant treatment, although their improvement may be less rapid than other symptoms of MDD (418). Antidepressant-treated patients experience an improvement in energy symptoms as their overall depression improves.

Besides being a common symptom of MDD or a prodromal symptom, fatigue can also be a side effect of antidepressant treatment, although this happens more typically with sedating antidepressants. On the other hand, even activating agents may be associated with fatigue as a side effect; this has been generally thought to be the result of disruption of sleep architecture, with sleepiness and fatigue being the consequence of poor sleep quality and sleep deprivation (419). Fatigue may also be a residual symptom of MDD. Studies in patients on maintenance antidepressant therapy showed that complaints of physical tiredness were related primarily to residual depression (420). One of the best known and most frequently utilised approaches to the treatment of residual symptoms in MDD is to augment a serotonin selective reuptake inhibitor (SSRI) or a serotonin norepinephrine reuptake inhibitor (SNRI) with bupropion, an norepinephrine (NE) and dopamine (DA) reuptake inhibitor (421, 422). Bupropion can increase both DA and NE in the frontal cortex, as well as in other areas of the brain (383, 423, 424). Bupropion may be effective in improving energy and fatigue, as well as executive function (425).

There are little data suggesting that any particular antidepressant specifically addresses the effects on fatigue-related symptoms. Among the first-line antidepressant monotherapies, agents that increase NE, DA, or both, particularly in pathways associated with physical and mental fatigue, may be preferable for patients with prominent fatigue and lack of energy (426). Thus, the pharmacological profiles of venlafaxine, bupropion, fluoxetine, and sertraline suggest that, of the first-line antidepressants, these agents may be most likely to relieve symptoms of fatigue in depression, but this has never been adequately studied.

A retrospective analysis of seven double-blind, placebo-controlled trials of fluoxetine in depression demonstrated that fluoxetine caused significant reductions in the

HDRS retardation factor (item 1 (depressed mood), item 7 (work and activities), item 8 (retardation), item 14 (genital symptoms) compared to placebo (427).

When first-line antidepressant monotherapies are not effective in the treatment of fatigue, a novel strategy is to target the neurotransmitters in the circuits that hypothetically underlie this residual symptom with a variety of augmenting strategies (428). Augmenting agents in the past have classically included buspirone, thyroid hormone, and lithium, based largely upon empirical observations (429, 430). However, a new set of augmenting agents can now be added to this armamentarium as atomoxetine or, perhaps more commonly, psycho-stimulants or modafinil (431).

Pharmacological augmentation of antidepressant therapy has shown promise in the treatment of residual fatigue. Bupropion or atomoxetine, which enhance DA and NE in the cortical and subcortical areas of the brain, have been added to selective serotonergic antidepressants to improve residual fatigue (432, 433). Studies suggest that modafinil, which activates orexin-containing and histaminergic neurons in the hypothalamus and releases histamine in the hypothalamus, as well as dopamine, norepinephrine, and serotonin in the cortex, may relieve residual fatigue after treatment with antidepressants (434, 435). Modafinil, unlike central nervous stimulants, does not release dopamine and norepinephrine in the nucleus accumbens, which reduces its abuse potential. There is an advantage of modafinil over placebo in treating fatigue among partial responders to antidepressant treatment (436). There is no evidence of this pharmacological intervention in HD patients.

A better understanding of the prevalence and pathogenesis of fatigue in HD patients, particularly the role of cytokines, may help in designing interventions aimed at reducing inflammation and fatigue. Management of factors such as anaemia and sleep disorders is fundamental. Treatment of depression, anxiety, stress, substance abuse, obesity, and malnutrition may be helpful, although studies substantiating the role of these interventions are lacking. In the empirical chapters to follow, we will focus on the interaction between depression and fatigue.

3.8 Summary

Fatigue is a common complaint in the community and primary care as well as being associated with several medical and psychiatric illnesses and a key area of overlap in depression and ESRD. The literature regarding the prevalence of fatigue in haemodialysis patients is sparse. Physical fatigue was described by patients as a constant lack of energy, which seemed worse on dialysis days.

Fatigue is negatively correlated with physical functioning, role limitations, activity levels, and mental and physical quality of life. It impacts patients' abilities to manage their everyday activities, which leads them to feel isolated from others and society. Fatigue also negatively affects patients' abilities to remember and concentrate on conversations and what is going on around them.

The overlap in symptomatology makes it difficult to disentangle the complex comorbidities between depressive syndromes and fatigue syndromes both in depression and haemodialysis, hence, complicating the assessment and management of fatigue.

It is, therefore, very important to establish the relationships of depression and fatigue and their relationships with clinical, biochemical, and haematological parameters, and to explore the extent to which somatic symptoms of depression such as fatigue contribute to the diagnosis of depression in this chronic disease state. Understanding these issues will enhance opportunities to improve clinical outcomes and quality of life in the HD population.

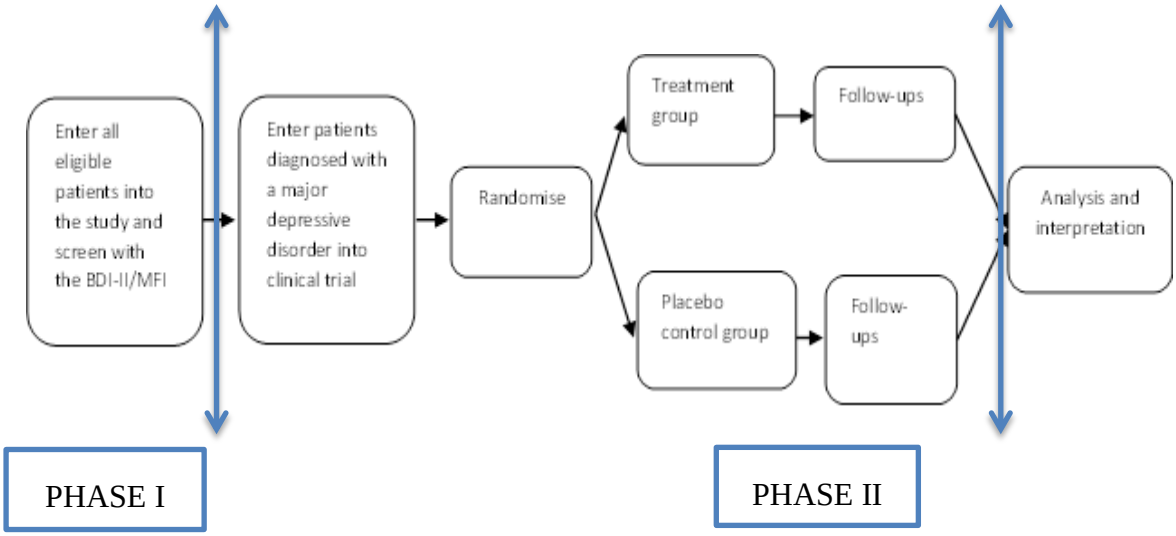
Chapter 4

Methods

4.1 Overview

In this chapter, I will explain the design and methods for the two distinct phases of the ASSertID (**A** **S**tudy of **S**ertraline **I**n **D**ialysis) study. The study comprised two phases, as shown in Figure 14. These were the prevalence of depression and fatigue in patients on HD (phase I) and the feasibility RCT of sertraline versus placebo in HD patients (phase II).

Figure 14: Schematic diagram of overall design



The study was funded by the National Institute for Health Research (NIHR) programme, Research for Patient Benefit (RfPB). The NIHR-RfPB is a Programme funding regionally derived applied research projects in health services and social care. The aim of the programme is to realise, through evidence, the huge potential for improving, expanding and strengthening the way that healthcare is delivered for patients, the public and the NHS.

The reference number was PB-PG-0110-21073, and Research Ethical Committee (REC) reference 12/LO/1554 and EudraCT reference 2012-000547-27. Copies of the approval letters are shown in the appendix 1.

4.1.1 My Role in the Studies

A large part of the design was already finalised when I started as a clinical research fellow and subsequently a PhD student; however, I will emphasise throughout this chapter my contribution and input into the design and methods of these studies.

During the initial months, I researched the literature on depression and its management in ESRD, as well as attending several renal outpatient/dialysis/transplant clinics to consolidate my knowledge in renal medicine. I became familiar with the protocol, contributed to final versions of the ASSertID protocol after the research ethics committee required a number of changes to be made before approval was granted. Once approvals and permissions were received, I worked with my colleagues on the set up of the paper CRF and the e-CRF, testing the e-CRF and making several amendments to the psychiatric assessment tools. I helped prepare information for training and educating non-psychiatric trained clinical staff on the recognition and management of depression for each site. I assisted with all the research site visits, prepared the sites for data collection, and familiarised myself with the different requirements, site policies, personnel, and operational procedures at each site.

I was involved in data collection, which included screening, diagnosing, and recruiting patients on dialysis with MDD into the trial phase. This involved careful assessment of patients and ongoing management of, for example, psychiatric or somatic adverse events. Finally, I contributed to the analysis and interpretation of the data and the dissemination of the findings from the research in the form of papers to peer-reviewed journals as well as conference poster and presentations. The main statistical plan and analysis, including RCT analysis, were undertaken by Dr David Wellsted. Sertraline plasma levels were done by Dr Alun Hutchings, of Cardiff Toxicology Laboratories, the Academic Centre, University Hospital Llandough.

In addition, I was keen to develop my own ideas stemming from the ASSertID study. From the literature review, it became clear that there is a vast range of overlapping symptoms of depression and ESRD, mainly the biological symptoms of depression, which could be due to psychological or physical factors, or both. The most common overlapping symptom was fatigue and tiredness. After discussion with my

supervisors, the decision was made to include a careful assessment of fatigue as a psychosomatic syndrome that spans depression and renal disease. I conducted a review of fatigue and fatigue rating scales and it became clear that there is minimal data on the prevalence of fatigue in ESRD. There was no data to help identify whether fatigue was due to the physical illness or secondary to depression, or both. This was an opportunity to contribute to the evidence base by collecting data on fatigue from newly recruited patients using validated fatigue assessment tools. An amendment was made to the study protocol, and IRAS and MHRA application forms were completed, submitted, and approved.

4.2 Prevalence of Depression and Fatigue Study

4.2.1 Aims

1- To establish the prevalence of depression in patients on dialysis.
2- To establish the relative effectiveness of screening tools for depression (PHQ-2, PHQ-9, and BDI-II) in this group of patients and compare the rating to a psychiatric diagnosis.
3- To establish the proportion of ESRD patients who scored positive on fatigue scales MFI and SF-36, and the energy/fatigue subscale.
4- To establish the relationship of depression and fatigue scores and their relationship to clinical, biochemical, and haematological parameters.
5- To establish whether there was a difference between drug and placebo on the measures of fatigue over the period of the study.

4.2.2 Design, Setting, and Sample

The prevalence study was an observational questionnaire survey of HD patients. We recruited from five renal centres in England within the following NHS Trusts:

1. East and North Herts NHS Trust
2. Southend University Hospital NHS Foundation Trust
3. University Hospitals Birmingham NHS Foundation Trust

4. Royal Free London NHS Foundation Trust
5. Basildon and Thurrock University Hospital NHS Foundation Trust

The chief investigator (CI) for the study was Prof. Ken Farrington, and principal investigators (PI) at each centre (see above), respectively, were Dr Enric Vilar, Dr Mike Almond, Dr Clara Day, Dr Andrew Davenport, and Dr Ian Barton.

Research nurses approached all HD patients who met the eligibility criteria, asking each patient to complete several questionnaires. Eligibility included patients with ESRD, receiving HD for at least three months, over 18 years of age, and with the ability to read and speak English fluently. Figure 14 shows the number of patients who received RRT at each of the five centres during 2013 (2).

Figure 15 Numbers of RRT in the five centres (1, 2)

Centre	*N*					Catchment population (millions)	2013 crude rate pmp	(95% CI)
	HD	PD	Dialysis	Transplant	RRT			
England								
B Heart	435	41	476	182	658	0.74	892	(823–960)
B QEH[a]	933	137	1,070	981	2,051	1.70	1,207	(1,155–1,259)
Basldn	160	30	190	80	270	0.42	651	(573–728)
Bradfd	202	30	232	288	520	0.65	798	(729–866)
Brightn	398	79	477	398	875	1.30	675	(630–719)
Bristol[a]	514	67	581	846	1,427	1.44	991	(940–1,043)
Camb[a]	380	25	405	793	1,198	1.16	1,035	(976–1,093)
Carlis	68	28	96	131	227	0.32	708	(616–800)
Carsh	762	122	884	604	1,488	1.91	778	(738–818)
Chelms	123	21	144	95	239	0.51	468	(409–528)
Colchr	115		115		115	0.30	384	(314–454)
Covnt[a,b]	383	86	469	471	940	0.89	1,054	(986–1,121)
Derby	217	85	302	170	472	0.70	672	(611–732)
Donc	163	35	198	61	259	0.41	632	(555–708)
Dorset	267	48	315	313	628	0.86	729	(672–786)
Dudley	175	56	231	81	312	0.44	706	(628–785)
Exeter[b]	410	73	483	413	896	1.09	823	(769–876)
Glouc	211	33	244	168	412	0.59	702	(634–769)
Hull	327	80	407	408	815	1.02	799	(744–854)
Ipswi	122	30	152	202	354	0.40	887	(795–980)
Kent	395	64	459	506	965	1.22	788	(738–838)
L Barts[a]	954	197	1,151	952	2,103	1.83	1,149	(1,100–1,198)
L Guys[a]	630	29	659	1,182	1,841	1.08	1,701	(1,623–1,779)
L Kings	498	105	603	362	965	1.17	824	(772–876)
L Rfree[a]	731	131	862	1,093	1,955	1.52	1,288	(1,231–1,345)
L St.G[a,b]	280	48	328	431	759	0.80	951	(884–1,019)
L West[a]	1,398	61	1,459	1,683	3,142	2.40	1,310	(1,264–1,356)
Leeds[a]	507	69	576	890	1,466	1.67	878	(833–923)
Leic[a]	905	152	1,057	1,015	2,072	2.44	851	(814–887)
Liv Ain	155	30	185	5	190	0.48	393	(337–448)
Liv Roy[a]	359	58	417	852	1,269	1.00	1,269	(1,199–1,339)
M RI[a]	522	83	605	1,259	1,864	1.53	1,217	(1,162–1,272)
Middlbr	351	14	365	471	836	1.00	833	(776–889)
Newc[a]	274	42	316	648	964	1.12	860	(806–914)
Norwch	330	40	370	322	692	0.79	880	(814–945)
Nottm[a]	371	83	454	621	1,075	1.09	988	(929–1,047)
Oxford[a]	435	99	534	1,031	1,565	1.69	926	(880–972)
Plymth[a]	134	37	171	332	503	0.47	1,071	(977–1,164)
Ports[a]	600	85	685	870	1,555	2.02	768	(730–807)
Prestn	547	56	603	487	1,090	1.49	730	(687–773)
Redng	282	76	358	373	731	0.91	803	(745–861)
Salford[b]	399	85	484	411	895	1.49	601	(561–640)
Sheff[a]	589	70	659	670	1,329	1.37	969	(917–1,021)
Shrew	187	32	219	123	342	0.50	683	(611–755)
Stevng[b]	464	40	504	254	758	1.20	630	(585–674)
Sthend	120	18	138	83	221	0.32	698	(606–790)
Stoke	311	87	398	328	726	0.89	816	(757–875)
Sund	197	11	208	215	423	0.62	684	(619–749)
Truro	151	24	175	202	377	0.41	913	(820–1,005)
Wirral	213	35	248	4	252	0.57	441	(386–495)
Wolve	301	82	383	180	563	0.67	842	(772–911)
York	140	27	167	242	409	0.49	831	(750–911)

4.2.3 Measures and Data Collected

The following data were collected directly from patients or their medical notes onto a study-specific designed case report form (CRF):

- Demographics (date of birth, gender, ethnicity, marital status, and social class/education).
- Information on the primary renal disease and date of starting renal replacement therapy. Previous transplants and dates, if there were any.
- Past history of depression or anxiety diagnosed by a doctor.
- Treatment for depression or anxiety by a GP or psychiatrist or any other involvement with psychology or psychiatry services.
- Social support – who they lived with.
- Questions on comorbid problems, including: heart disease, stroke, amputation of limbs, diabetes, cancer, liver disease, lung disease, and any other medical conditions such as rheumatoid arthritis.
- Clinical parameters, including: haemoglobin, serum albumin, calcium and phosphate, and Kt/V (most recent values).
- Estimated urine volume per day, dry weight, height, dialysis time, interdialytic weight gain, and number of missed and truncated treatment sessions in past month.
- Midweek pre- and post-dialysis blood pressure.
- Estimated recovery time from dialysis sessions.

In addition to the above data, the research nurses administered the BDI-II (180) and PHQ-9 (79) to screen for depressive symptoms and the vitality scale of the SF-36 energy/fatigue subscale (270) and MFI (272) for fatigue symptoms. These questionnaires were described in detail in Chapters 2 and 3, respectively.

Following the ASSertID steering group meeting (13/04/2015) after the completion of the study, it was agreed to collect additional data on CRP and survival from the five centres. A substantial amendment to ethics was submitted and approval granted on 24/04/2015 (Appendix 1; we obtained information about whether the patient was still receiving dialysis or had died, the date of death, and date of transplantation/transfer to a different centre). In two units (Royal Free and East and North Herts) information

about baseline CRP results was also collected. The data was collected by the local PI and supplied to us under the original patient identification (PID) number. The data allowed us to determine whether having a high depression score at screening has an impact on prognosis.

4.2.4 Procedures

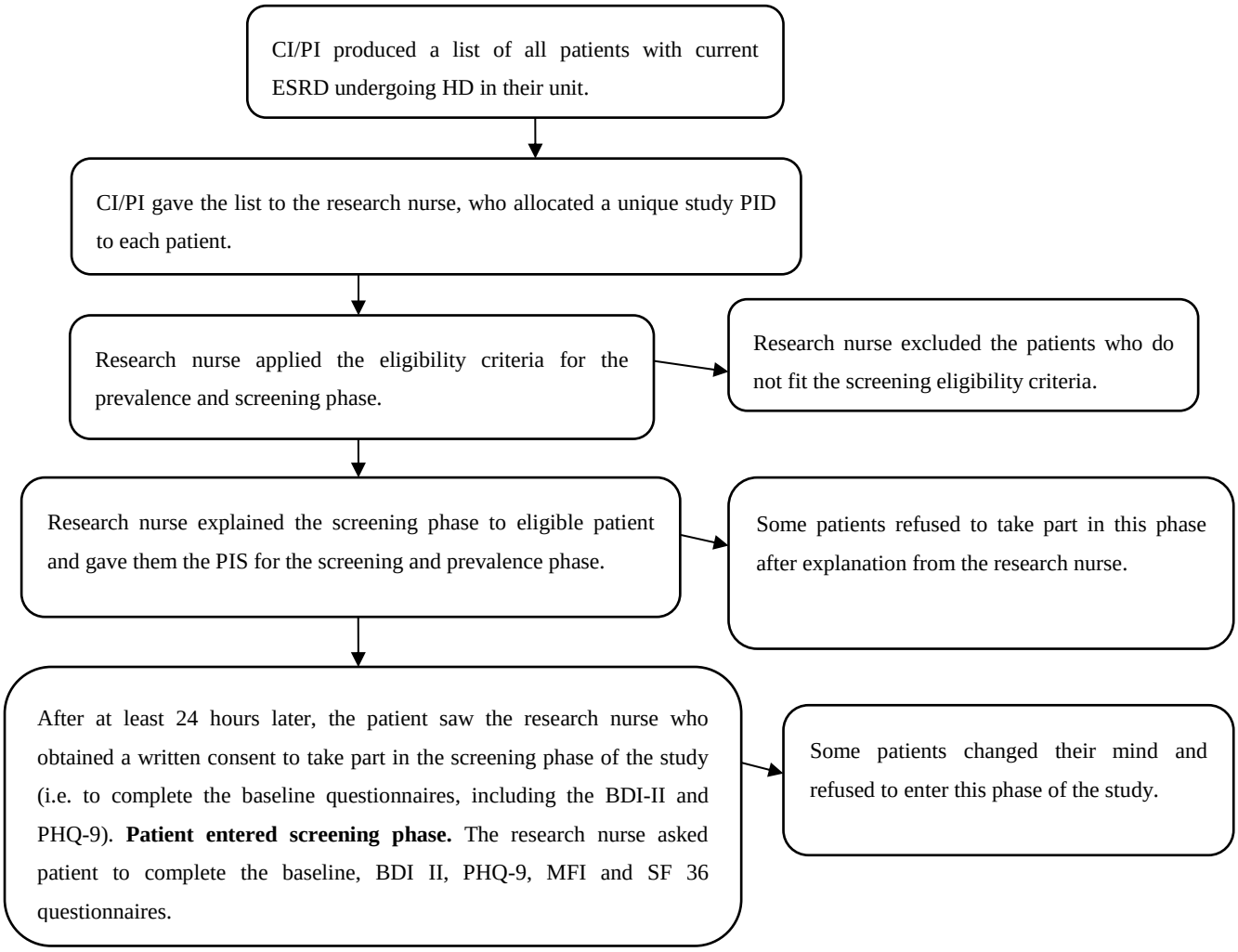
The CI/PIs at each renal centre drew up a list of all the ESRD patients aged 18 or above who were on HD in their units. They asked the research nurse or clinical studies officer to approach each patient about the prevalence and screening phase (Figure 16).

The research nurse:

1- Allocated a unique study patient identification number (PID) to each patient on the list. This number remained with the patient throughout the different stages of this study and was the unique identifier of each patient. It was used on all CRFs.
2- Excluded those patients who were unable to speak and read English, as well as receiving HD for less than three months, and recorded this on the paper CRF and database.
3- Approached all remaining patients and explained the purpose of the prevalence and screening phase. The research nurse gave each patient the Patient Information Sheet about the prevalence and screening phase, which was recorded in the CRFs. They gave each patient at least 24 hours and up to one week to think about the study before they asked the patient for written consent on the Informed Consent Form (ICF) [1]. If consent was obtained, the research nurse asked the patient a number of questions and gave the patient four standardised questionnaires to complete.

I played a role in the recruitment at the Royal Free units as well as screening patients. I recruited 70 patients from the four Royal Free satellite units and this included approaching the patients, providing the required information, answering any queries, and consenting the patients.

Figure 16 Phase I recruitment



4.3 The RCT

4.3.1 Aims

1- The main aim was to evaluate the feasibility of conducting a fully powered, double-blind, placebo-controlled RCT by measuring the number of ESRD patients who took part and completed the study as well as evaluating their outcomes. The safety and drug exposure of sertraline in ESRD patients was also assessed.

2- To establish the potential effectiveness of sertraline as a treatment for depression in this patient group. Was the drug tolerated well? Did it have an acceptable adverse effect profile? Were there indications that it was more effective than placebo in reducing depressive symptoms?

4.3.2 Design and Setting

This was multi-centre double blind feasibility RCT of sertraline versus placebo in patients with end-stage kidney disease receiving haemodialysis treatment who have MDD. The RCT was conducted in the same five renal centres listed in section 4.2.2. Patients were invited to participate for six months.

4.3.3 Intervention and Control

Patients were randomised to take sertraline plus usual care and additional psychiatric monitoring or placebo plus usual care and additional psychiatric monitoring for six months.

Sertraline is a licensed SSRI indicated for the treatment of major depressive episodes, prevention of recurrence of major depressive episodes, and other disorders including anxiety disorder. A recent meta-analysis recommended sertraline due to its favourable balance between efficacy and acceptability, and low acquisition cost (437). It has been found to be effective and to have fewer side effects (except for diarrhoea) than many other commonly prescribed antidepressants (438). Several studies found sertraline to be safe to administer to patients with cardiovascular

disease (246, 439) as it has the most robust safety profile for cardiac disease. It is hepatically cleared, and believed to require no dosage adjustment in ESRD (246).

The study placebo was microcrystalline cellulose and magnesium stearate. The sertraline and placebo tablets were sourced and prepared from the Royal Free Hospital Pharmacy Manufacturing Unit, who identically over-encapsulated the tablets.

Each medication bottle contained 37 capsules (50mg) of sertraline or placebo enough for one month supply at a dose of 50mg/day. This represents more than a month's supply to allow a window for any possible delays in follow-up assessments and dispensing of the medication. The bottles were labelled as ASSertID Study Medication with a tear-off portion that indicated if the bottle was treatment A or B. Sufficient numbers of bottles were shipped out to the main pharmacies at each research site.

Usual care consisted of standard care received from the multidisciplinary renal team, including doctors, nurses, dieticians, pharmacists, social workers, counsellors, and/or psychologists. Patients received centre-based haemodialysis three times weekly for around four hours each session. Dialysis and regular monitoring of physiological parameters before, during, and after each dialysis session was carried out by specialist nurses and support staff. These highly trained personnel were well placed to detect clinical as well as social and psychological problems and to initiate referral of patients for expert professional help from relevant members of the multidisciplinary team. Care also included management of renal-related problems, including hypertension, bone and metabolic problems, and anaemia, and management of extra-renal comorbidities, including diabetes, heart disease, and inter-current infections. In addition, there was social and psychological support with access to trained social workers, renal counsellors, and/or psychologists at some study centres.

4.3.4 Sample

4.3.4.1 Inclusion Criteria

The following patients were included in the study:

- Patients with a BDI-II of 16 or above, a cut-off found and validated by Chilcot et al. (177).
- Patients who, according to the CI/PIs, had a prognosis of more than one year.
- Further inclusion criteria included assessment by the research psychiatrist:
    - Patients who were diagnosed with a mild to moderate MDD according to a DSM-IV interview.
    - Patients who scored 18 or above on the MADRS.
    - Patients who had the mental capacity to understand the trial and were able to give consent.

4.3.4.2 Exclusion Criteria

Patients were excluded who:

- Were treated or had been treated for depression and/or anxiety with any antidepressant or formal psychological therapy or had been involved in a drug intervention study in the last three months.
- Were waiting a planned living donor transplant within the period of the trial.
- Had less than a year survival prognosis according to the CI/PIs
- Had a contraindication to sertraline.
- Had hepatic impairment (serum levels of alanine transaminase (ALT) more than twice the upper limit of normal), hepatitis B or C, HIV/AIDS, and/or Creutzfeldt-Jakob disease or elevated INR greater than 1.3.
- Were pregnant or of childbearing potential and not using adequate birth control.
- Were taking any of the following medications: MAOIs or pimozide triptans, antipsychotics, dopamine antagonists, tramadol, linezolid, or warfarin.
- Further exclusion criteria by the research psychiatrist assessment included:
    - A diagnosis of a severe MDD.

- Judged to be at any acute and moderate to severe risk of self-harm.
- Scored above 4 on item 10 on the MADRS or answered yes to question A3G on the MINI. These are questions related to suicide risk.

4.3.5 Recruitment into the Trial

The research nurses drew up a list of eligible patients for the psychiatric assessment interview, as shown in Figure 17, as well as a list of non-eligible patients but who scored 16 or above on the BDI-II. Then, the CI/PI reviewed all these patients and applied the relevant eligibility criteria for the psychiatric assessment interview and gave the research nurse a revised list of eligible and non-eligible patients.

The research nurse approached all the eligible and non-eligible patients. The research nurse told each patient that they had scored 16 or above on the BDI-II and that they could suffer from low mood. The research nurse gave the patient several options of further care. For the non-eligible, it included referral back to their nephrologist, or referral to their general practitioner. The nephrologist or GP would discuss with the patient whether or not they needed a further referral to a mental healthcare professional, for example, a counsellor working in the renal team. For the eligible patients, the options were the same, in addition to the option to join the trial outcome phase of this study.

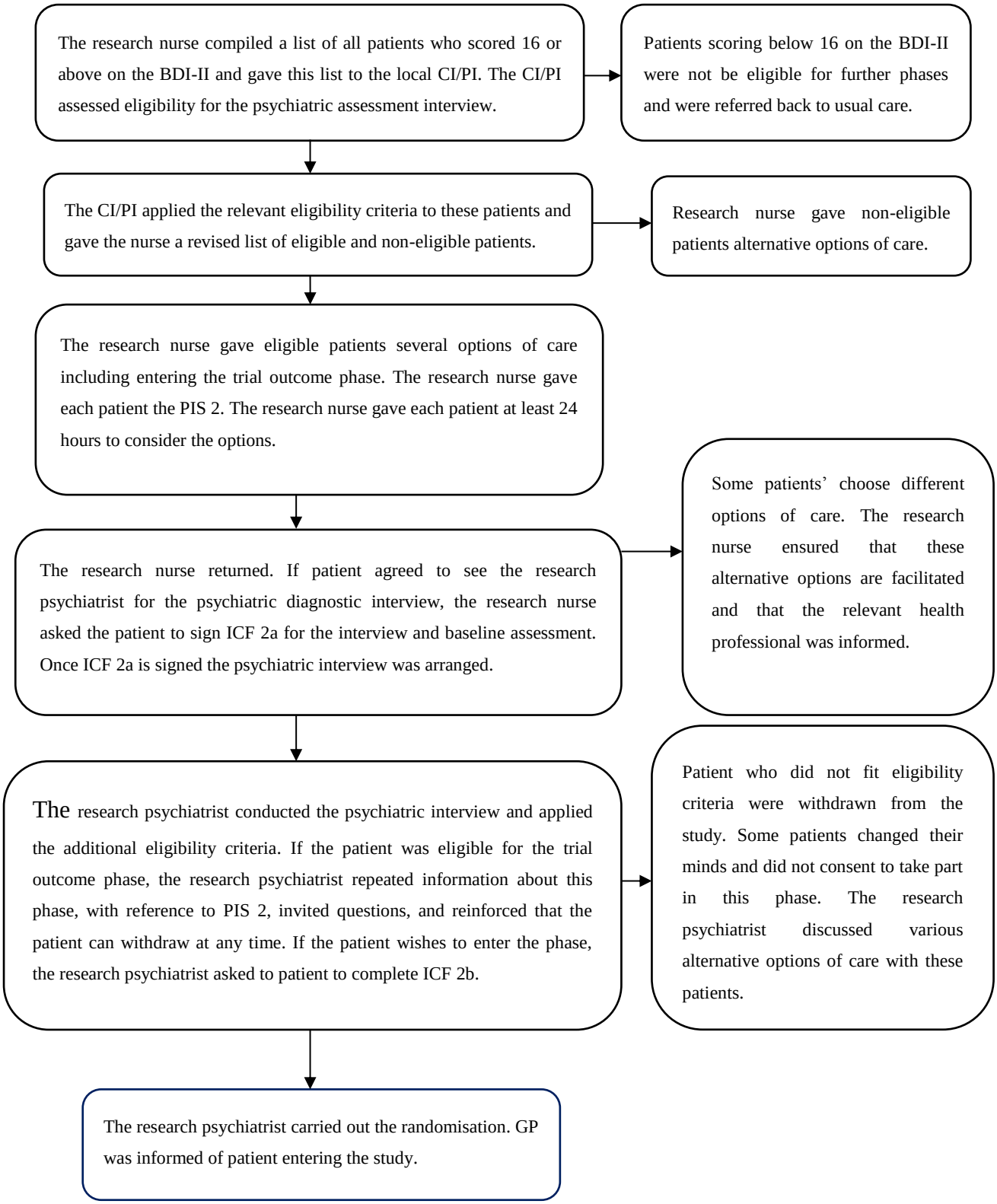
The research nurse explained the aims, methods, anticipated benefits, and potential hazards of the trial outcome phase. At least 24 hours and up to one week were given to each patient to decide which option they wished to take. If the patient decided to enter the trial, the research nurse repeated the information on the trial outcome phase and invited them to take part in the initial psychiatric interview and baseline assessment. The research nurse asked the patient to sign a study-specific ICF 2a to take part in the baseline assessment and psychiatric interview. If a patient decided not to enter the trial, the research nurse ensured that the alternative options of care were facilitated and the relevant healthcare professional was informed once verbal consent was given by the patient. Once the patient had signed the consent form to see the research psychiatrist and agreed to complete the baseline assessment, the research nurse arranged a mutually convenient time for the patient to see myself as the

research psychiatrist. At the same time, the research nurse asked the patient to complete the baseline questionnaires and collect relevant baseline information from the medical notes or computerised medical records. I completed this recruitment process instead of the research nurse for 12 patients at the Royal Free.

On completion of the psychiatric interview, the research psychiatrist applied the additional eligibility criteria. The research psychiatrist told the patient if they were eligible for the trial outcome phase. Patients who did not fulfil the additional eligibility criteria were thanked for taking part so far. The research psychiatrist gave each non-eligible patient a set of options for further care, which included referral back to their nephrologist, a referral to their GP, or a referral to the local Community Mental Health Team (CMHT). For patients who were diagnosed by the research psychiatrist with severe mental illness and at risk of self-harm, the research psychiatrist referred the patient to the local CMHT.

If the patient was eligible for the trial outcome phase, the research psychiatrist repeated the information on the aims, methods, anticipated benefits, and potential hazards of this phase. They referred to the PIS-2 that the research nurse gave them. As the patient had already received that information more than 24 hours prior to meeting the research psychiatrist, the research psychiatrist asked for written consent on the ICF 2b to take part in the trial outcome phase. The study-specific ICF 2b had to be signed by the patient and the research psychiatrist and dated. On receiving consent, the research psychiatrist performed the randomisation. Both the research psychiatrist and patient were blind to the allocation. The research psychiatrist was also responsible for preparing and sending a letter to the GP informing them that their patient had entered this study, and recorded this action on the CRF.

Figure 17: Phase II recruitment



Patients were randomised to either treatment A or treatment B. The Norwich CTU prepared the randomisation list. A block randomisation was used at each of the five centres. There were 50 codes for each centre. These codes were incorporated into a protected web-based randomisation programme prepared by Norwich CTU. Only the research psychiatrist had authorised access to the online randomisation programme. They were provided with an identification code and a password to access the randomisation programme. All the clinical team and research team were blind to study medication and only the data manager held the code.

The research psychiatrist entered the specific internet site, using their username and password, and entered the study PID, which included the centre code. The computer allocated the next consecutive randomised code. The computer sent an email to the relevant pharmacy to inform them that the patient (using the study PID) had been entered into the study and that they had been allocated to treatment A or treatment B. Only the pharmacist knew about the allocation of A or B. They tore off a small label that indicated that the bottle contained medication A or B, as described above in section 4.3.3.

Upon randomisation, the research psychiatrist gave the patient a study-specific Patient Carrying Card, which included the study title, study PID, date of birth, information about taking the medication, medications to be avoided, and the contact details of the CI or PI and out-of-hours contact details in cases of emergency.

The Norwich CTU held the data on the random allocation of each patient. They held the master file on their server and only the CI and PI had access to this file via a special login.

After randomisation, the research psychiatrist informed the trial manager (TM) of patients entering the study. The research psychiatrist sent a standard letter to the patient's GP informing them about the study and that their patient had entered this study.

Once randomisation had occurred, the pharmacy staff received an email from Norwich CTU. The email detailed the PID and the treatment allocation (A or B). The research nurse from the renal unit was responsible for presenting the study prescription with the PID to the local hospital pharmacy. The pharmacy staff checked

the PID with the email detailing the allocation to treatment. The pharmacist recorded the PID on the label of the study medication bottles. They tore off the label saying treatment A or B on the bottle and dispensed the correct study drug to the research nurse. The research nurse did not know if the patient was receiving drug A or B. The pharmacist recorded the details of dispensing in the pharmacy dispensing log, part of the study pharmacy file. The research nurse was also responsible for recording in the CRF that they had received the medication bottles and given them to the patient.

4.3.6.1 Emergency Unblinding

The study randomisation codes were intended to be broken only for valid medical and safety reasons. Blinding could be broken in a medical emergency when the knowledge of the blinded treatment was necessary, such as:

- Deterioration in mood involving suicidal thoughts or attempted suicide
- Suspected serotonin syndrome or neuroleptic malignant syndrome
- Cardiac arrhythmias or GI bleed
- Where a child in a participant's household accidentally took an investigational medicinal product (IMP)
- In an event of a suspected unexpected serious adverse reaction (SUSAR)

In addition, the randomisation code could be broken if:

- Requested by the Data Monitoring and Ethics Committee
- A patient in the study withdrew due to the offer of a transplant

All emergency unblinding was recorded in the CRFs. In practice, in the trial there was no need to invoke emergency unblinding.

4.3.7 Dispensing the Medication to the Patient

At baseline, the patient was prescribed 50mg of sertraline hydrochloride or placebo capsules, to be taken orally once a day in the morning for one month. The patient had another prescription for 50mg per day of the study medication for the second month. The research psychiatrist assessed each patient at two weeks to check for mental state

and tolerability of the drug in both groups. The research psychiatrist again assessed each patient at the two-month follow-up for tolerability, and if clinically indicated, the dose was titrated to 100mg per day if required. The research psychiatrist issued two prescriptions for either 50mg or 100mg per day, each for one month. At the four-month follow-up, the research psychiatrist repeated the assessment of mood and drug tolerability and issued two prescriptions of either 50mg or 100mg per day, each for one month. The dose was not further titrated. At the end of the six months, when the patient had their final assessment with the research psychiatrist and the research nurse, the patient was advised to taper their study drug (medicinal product or placebo). Patients on 100mg were advised to take 50mg for one week, then take 50mg on alternate days for one week, and then stop taking the study medication. Patients on 50mg were advised to take 50mg on alternate days for one week and then stop taking the study medication. At the end of the tapering period, the CI/PIs were responsible for ensuring the appropriate future management of the patient. They acted on the advice of the research psychiatrist who carried out the final study assessment and the patient wishes. Management options included prescribing sertraline at an initial dose of 50mg daily or continuing on no antidepressant medication. In either case, the patient's GP was informed and early review was arranged within 2-4 weeks within the multidisciplinary team. Patients were referred to the local CMHT if deemed appropriate on psychiatric advice.

The research psychiatrist and research nurse provided the patient with information about possible withdrawal symptoms, reassuring them that they were usually mild and temporary. Patients were told to contact the CI/PIs if they experienced continuous and unpleasant symptoms while stopping the medication or placebo. Any adverse events (AE) were recorded in the medical notes or computerised records and Adverse Event form in the CRF.

If a patient withdrew before the end of the intervention period, the same tapering plan was recommended as described above. The research nurse alerted the CI/PIs to assess the patient at the end of the tapering period to decide on alternative treatment options as outline above.

4.3.8 Assessment and Data Collection

- **Baseline assessment by the research nurse**

The research nurse collected the data on the patient's medical history specified below on the study-specific CRFs. Data was collected via the medical notes, from self-report questionnaires completed by the patient, as well as the research nurse who asked the patient directly or asked the nephrologist to provide the data.

- List of all drug treatments
- Description of the current dialysis treatment, including dialysis type (HD/HDF), dialysis session duration, and target Kt/V
- Achieved dialysis adequacy assessed using the last Kt/V recorded within the last month
- Dry weight
- Current interdialytic weight gain
- Mid-week pre- and post-dialysis blood pressure during the previous week
- Haematology blood results – Hb, white blood cell count, platelets
- Biochemistry blood results – urea/electrolytes and liver function tests, including bilirubin, alanine transaminase (ALT) and/or aspartate transaminase (AST), alkaline phosphate (ALP), bicarbonate, albumin, calcium, and phosphate

- **Psychiatric assessment**

The research psychiatrist formally assessed depression by interviewing patients with the:

- MINI version 6.0 (74) and the Folstein Mini Mental Status Exam (MMSE) (440). These were used by the psychiatrist to make a formal DSM-IV diagnosis of MDD.

In addition, the research psychiatrist administrated the following assessment:

- MADRS (88)
- Clinical Global Impression – Severity Scale (92)

The research psychiatrist assessed each patient clinically for suicidal risk. A score of greater than 4 on item 10 on the MADRS or yes to question A3G on the MINI excluded the patient from the study. The plan was for patients with a high suicide risk score to be referred by the research psychiatrist to the local acute services and they would inform the CI and/or PI who would contact the patient's GP. This happened only once during the course of the study.

The above questionnaires were described in detail in Chapter 2.

- **Subsequent assessments by the psychiatrist**

Two weeks after the first prescription had been given, the research psychiatrist saw each patient in person, administered the PHQ-9, and asked about the study medication. A mental state exam was performed and recorded in the clinical psychiatry study file. All actions taken were recorded in the CRF. With regard to medication, the psychiatrist asked the question, 'How have you managed with your medication so far?'. Any adverse events or action taken were recorded in the CRF. If question 9 (suicidality) on the PHQ-9 was answered positively (either 2 or 3), the research psychiatrist would perform a full psychiatric assessment. The patients would be withdrawn and unblinded if they were found to be at high risk of suicide. No incidences of this occurred during the study.

The research psychiatrist assessed each patient again after **two, four, and six** months in person to check their psychological status and, in particular, suicide risk. A mental state exam was performed by the research psychiatrist and recorded in the clinical psychiatry study file. Any action taken was recorded on the CRF. The research psychiatrist asked the patient to complete the self-reported measures MFI and SF-36 energy/fatigue subscale and administered the following assessment:

- MADRS (88)
- Clinical Global Impression – Severity Scale and Clinical Global Impression - Improvement Scale (92)

At the two- and four-month follow-ups, the research psychiatrist assessed the tolerability of the medication taken. Any adverse events or action taken were

recorded in the CRF. A decision was made on the basis of psychiatric state and tolerability of medication on whether or not to titrate the dose of the intervention from 50mg to 100mg at the two-month follow-up appointment. All data was recorded on study-specific CRFs.

- **Subsequent assessments by the research nurse**

The research nurse, together with the CI/PIs, recorded the following data on a monthly basis, including the final assessment at six months:

- PHQ-9 score
- Question, 'How are you getting on with your medication?'
- Compliance data – how many tablets were missed and the reasons
- Dry weight
- Changes to medication at the end of each month
- Change of the dialysis treatment over the last month, including dialysis type, time on dialysis, target Kt/V
- Achieved dialysis adequacy assessed using the last recorded Kt/V (measured monthly)
- Interdialytic weight gain
- Mid-week pre- and post-dialysis blood pressure in the last week of each month
- Last values of the month – haematology blood results: Hb, calcium, phosphate, and albumin
- ECG – conducted by the research nurse and interpreted by the CI/PIs at the two-, four-, and six-month follow-up dates

The research nurse recorded the above data on study-specific CRFs. They involved the CI/PIs to interpret the ECGs and other relevant tests. To minimise demand on the patients, all study assessments by the research nurse and CI/PIs were undertaken during routine clinic visits. The nurse formally assessed the patient's mood by using the PHQ-9 and asked the patient how they had got on with the study medication. If question 9 on the PHQ-9 was answered positively (either 2 or 3), then the P4

suicidality screener (441) was administered. The P4 screener asks about the '4 Ps': past suicide attempts, suicide plan, probability of completing suicide, and preventive factors. Patients were classified as minimal, lower, and higher risk based upon responses to these four items. If the patient was found to be at high risk of suicide according to the P4 screener, the research psychiatrist would be contacted. At the two-, four-, and six-month visits, the research psychiatrist would assess the patient in person that day. At the one-, three, and five-month visits, when a formal psychiatric assessment was not scheduled, the research psychiatrist would be contacted by the research nurse and they would both endeavour to see the patient on that day. If this was not possible, the research psychiatrist would review the patient with the research nurse on the phone and decide if the patient needed to be referred to the PI and referred urgently for assessment to the local mental health services. This happened with one patient during the course of the study. BDI-II was also completed at the final visits (month six). A summary of the collected data is shown in Table 19.

- **Adverse events**

All AEs were recorded in patient medical notes or computerised records and recorded on the CRFs. Deterioration of mood was monitored closely as a possible side effect from the study medication. SAEs were recorded on a study specific form. The sponsor was informed of each new SAE and a log of all SAEs was kept up to date.

- **Patient safety and drug exposure**

The research nurses took two blood samples (one pre- and one post-dialysis) during routine clinical sampling from each patient who had been on the study medication for three to five months to examine sertraline levels. Blood was taken into a plain or EDTA container and centrifuged on site.

The plasma samples were couriered overnight to the CI main research site and were frozen until the end of the study when the unblinding of the participants had occurred. The frozen plasma samples for the placebo group were discarded and only the frozen samples of the sertraline group were sent to the toxicology laboratory for analysis. The CI/PIs and the research nurses were responsible for recording that the samples had been taken in the medical notes/computerised notes and the CRFs.

Table 19: Summary of data collection

	Screening	Psychiatric interview	Entry to clinical trial	1-2 weeks	1 month	2 months	3 months	4 months	5 months	6 months
Informed Consent	X	X	X							
Inclusion/exclusion criteria fulfilled	X	X	X							
Demographics	X									
Comorbid conditions (self-report)	X									
Brief psychiatric history	X									
BDI-II	X									X
PHQ-9	X			X	X	X	X	X	X	X
MFI	X					X		X		X
SF-36 energy/fatigue	X					X		X		X

P4 suicidality screener				X	X		X		X	
Psychiatric assessment		X		X		X		X		X
Montgomery- Åsberg Depression Rating Scale		X				X		X		X
Mini International Neuropsychiatric Interview		X								
List of medications			X		X	X	X	X	X	X
Description of dialysis treatment			X		X	X	X	X	X	X
Mid-week pre- and post-dialysis blood pressure	X		X		X	X	X	X	X	X
Dry weight	X		X		X	X	X	X	X	X
Adherence to dialysis treatment	X		X		X	X	X	X	X	X
Interdialytic weight gain	X		X		X	X	X	X	X	X
Urine volume per 24 hours	X									

Dialysis adequacy Kt/V	X		X		X	X	X	X	X	X
Dialysis time	X		X		X	X	X	X	X	X
Full blood count	X		X		X	X	X	X	X	X
Electrocardiogram			X			X		X		X
IMP review					X	X	X	X	X	X
Drug compliance				X	X	X	X	X	X	X
Sertraline plasma blood test								X		
Baseline assessment of signs and symptoms			X							
Adverse events				X	X	X	X	X	X	X
Clinical Global Impression Severity Scale		X				X		X		X
Clinical Global Impression Improvement Scale						X		X		X

4.4 Original Sample Size Calculation and Amendments to the Studies

4.4.1 Sample Size

As a feasibility study, sample size was determined by the need to estimate the population variance of the outcome measures, and pragmatic considerations about potential recruitment. A sample size of 30 per arm (N=60) was selected allowing the population variance to be estimated with reasonable precision (1.2 x variance) (442), allowing reliable estimates to be derived for the outcome measures, and design of the planned full-scale trial. Previous studies suggested that 30% of patients would screen positive on the BDI-II (177), 50% of patients scoring ≥16 on the BDI-II would be subsequently diagnosed with MDD, and 50% would agree to be randomised. Given a target of 60 patients representing 7.5% of the screen sample, the target for screening was 800 patients, to be screened from four renal units with a population of 2,000 patients receiving dialysis (2).

During the screening phase, it was challenging to recruit the numbers due to the high prevalence of patients already taking antidepressants, an exclusion criterion to the study. Based on this finding the numbers were recalculated and an additional centre was added. Current research suggested that 33% of patients would screen positive on the BDI-II, of whom approximately 34% would be eligible, and 20% to 30% of those eligible would be diagnosed as depressed and agree to take part. This would give a recruitment rate of 3-4%. To meet a sample size of 25 to 30 patients, we had to screen approximately 700 patients (giving 24 to 32 patients). Hence, our revised target recruitment numbers for the first phase was approximately 700 patients. A sample of this magnitude enabled the proportion of positive screened patients to be estimated with a 95% confidence interval width of less than 8%.

4.4.2 Prevalence and Screening

The primary purpose of the prevalence and screening phase were to determine the proportion of patients who screened positive on the BDI-II. The secondary purpose was to assess the feasibility of using the PHQ-9 in clinical practice.

The analysis initially documented the proportions of patients meeting the (wide) inclusion criteria, and characterised those patients excluded from the study. The analysis also recorded the proportions of patients who refused to be screened, and the given reasons for refusal. In all cases, proportions were estimated with 95% confidence intervals assuming a normal distribution unless otherwise indicated.

The demographic and clinical characteristics of the patients identified for screening were described. Patients were subdivided into two groups, into a no depression group or a possible depression group, using the cut-off criteria for the BDI-II (a score ≥16). Comparisons between patients ≥16 or not were considered for each of the clinical and demographic parameters using appropriate paired comparisons (t-tests orχ2).

Finally, the analysis considered agreement between the BDI-II and the PHQ-9 to evaluate the extent to which the PHQ-9 can be used in place of the BDI-II for patients with ESRD. We used ROC analysis to define the best cut-off for the PHQ-9 in relation to the known performance of the BDI-II. Levels of agreement of these different cut-offs were examined.

4.4.1 Fatigue

The primary purpose of this element of the prevalence and screening phase was to determine the relationship of the fatigue scales (MFI and SF-36 energy/fatigue subscale) to depression and fatigue and their relationship to demographic, clinical, biochemical, and haematological parameters.

4.4.2 RCT

The study aimed to recruit 30 patients from the five centres, giving 15 patients in each arm. A sample size of 30 would provide estimates of the population variance to a precision of 1.2 times the sample variance, allowing reliable estimates to be derived for the outcome measures, and inform design of the planned full-scale trial (442).

Baseline characteristics for all patients randomised were evaluated (means, proportions, counts) for patients in the treatment and placebo arms. To meet the Consolidated Standards of Reporting Trials (CONSORT) reporting criteria, the flow of patients through recruitment to this phase of the study were recorded, and the numbers of patients falling into each group evaluated.

The primary analysis was descriptive, seeking to characterise the acceptability of the study to patients by estimating the proportions of patients who agreed to take part in this phase, or not, those withdrew from randomised treatment, and those who agreed to continue with the trial measures despite withdrawing from randomised treatment. The degree of adherence to the randomised treatment was evaluated in general terms to inform future trial design.

Lastly, the nature and number of the reported AEs were classified to examine the safety profile of the study drug.

The aim of the secondary analysis was to characterise the variability of the outcome measures at six months, and estimate the effect size of treatment versus placebo for each outcome. Using an ‘as treated’ sample, the effect size (Cohen’s d) was estimated for all the outcome measures. Analysis considered the influence of covariates on the outcome measures to determine the need for stratification in the larger RCT to follow. Additional analysis sought to characterise the effect of treatment centre on the observed effect (e.g. the intraclass correlation), to estimate bias introduced by missing data and non-completion, the extent to which somatic symptoms of depression such as fatigue contributed to the diagnosis of depression in this chronic disease state, and whether there was a difference between drug and placebo on the measures of fatigue over the period of the study.

The statistical packages used were SPSS version 23 for all routine analysis and STATA version 13.1 (Stata Corp LP) for the trial outcome phase. The primary analysis of the trial outcome phase was carried out mainly by Dr David Wellsted.

4.5 Protocol Amendments

The main protocol amendments were:

- Protocol 1.0, dated 17/4/12: Original Submission
- Protocol 2.0, dated 2/9/12: New application to ethics committee
- Protocol 3.0, dated 3/10/12: Further information to provisional opinion and changes had been requested by ethics
- Protocol 4.0, dated 18/1/13: Changes in safety or integrity of trial subjects, changes in conduct/management of trial, clarification to protocol
- Protocol 5.0, date 5/7/13: Added short patient information sheets, added two self-report questionnaires, clarification and version control of patient information sheets, consent forms, and GP letter
- Protocol 6.0, date 9/1/14: Added an additional research site, changes to the eligibility criteria for phase 3, the qualitative study, and a reduction in the sample size estimation
- Protocol 6.1, date 19/3/14: Version control of patient information sheets, consent forms, and GP letter and separate from protocol. Spelling mistake in SAE form
- Protocol 6.2, date 11/4/14: Updating the whole research protocol to mention that we had five sites, not four, i.e. replacing the word ‘four’ with ‘five’ when relating to sites
- Protocol 7.0, date 20/4/15: Collecting additional data on CRP and survival data, clarifying archiving, adding patient study card, and informing about end date

Relevant regulatory documents are found in appendix 1.

Chapter 5

Prevalence and Screening

Details of the design, setting, and measures were explained in full in the method chapter previously but will be reiterated briefly here. Patients over the age of 18 years who had receive treatment by HD for three months or more were approached. Patients who could not read and speak English were excluded. Consenting patients completed the BDI-II and PHQ-9 questionnaire during dialysis. Data relating to demographics, medical and psychiatric history, and dialysis treatment were also collected. Those with a BDI-II score ≥16, not on current treatment for depression (antidepressants or psychological therapies) in the past three months and without any pre-defined exclusion criteria, which included planned living-donor kidney transplant within the period of the trial, a prognosis of less than a year, several associated medical conditions and contraindicated medications, were approached to undergo a diagnostic interview by a psychiatrist using the MINI to confirm the presence of MDD. Following this, consenting patients diagnosed with mild to moderate MDD and with a score of 18 or above on the MADRS were randomised into the trial phase. Patients with severe depression or suicidal ideation were excluded and referred urgently to psychiatric services. Patients were also excluded who had evidence of cognitive impairment on the Folstein Mini mental status examination (MMSE). We sought written informed consent from patients at three separate points in the study, before screening, before interview by the study psychiatrist, and before randomisation to enter the trial.

5.1 Data Collection

Data were collected from electronic records and directly from patients. This included: age, gender, marital status, ethnicity, current living arrangements (alone, with partner, or family or friends), and educational attainment. The amount of time the patients had been receiving dialysis (vintage) was recorded to sessional adequacy (Kt/V), as well as routine clinical observations (blood pressure and dry weight) on

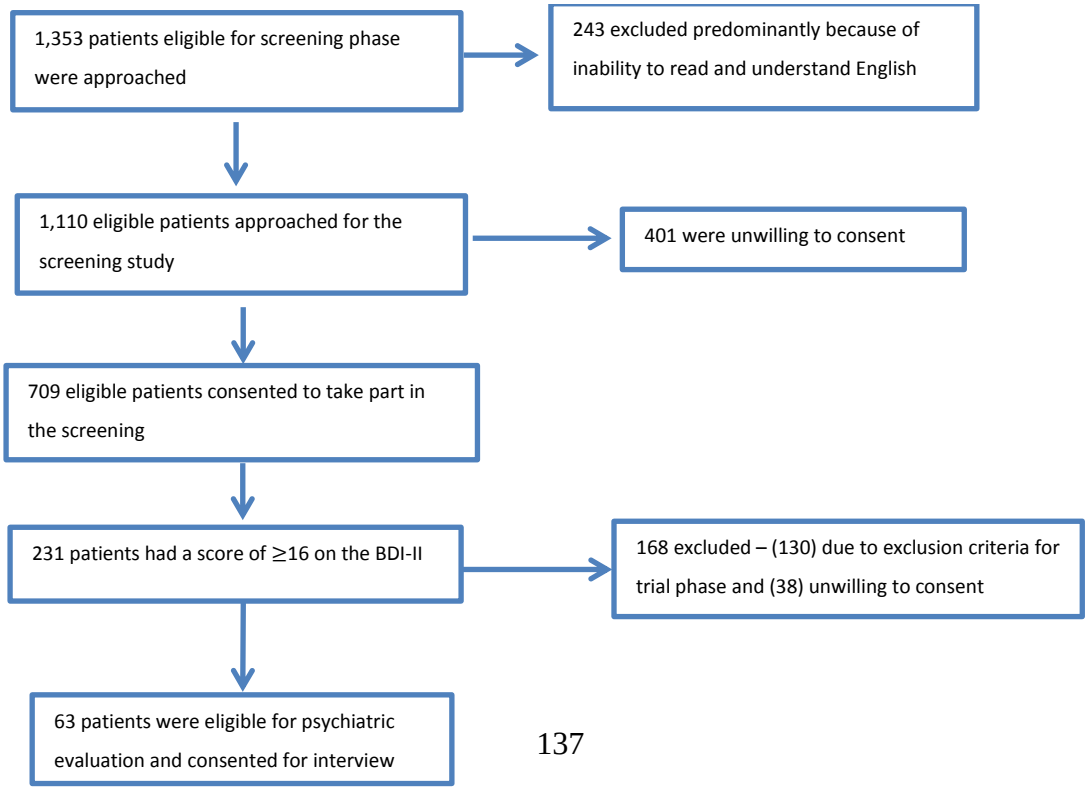
the day of completion of the questionnaire. The most recent biochemical and haematological data were collected from the electronic patient record including: blood haemoglobin and serum albumin, calcium, and phosphate. We collected information on history of depression and its management. Comorbidities were recorded as the presence or absence of: diabetes, heart disease, stroke, amputation, cancer, lung disease, and liver disease. Transplant history was recorded as never transplanted or transplanted and returned to dialysis. We also asked patients to self-report urine output as being less than one cup per day or greater than one cup per day and post-dialysis recovery time categorised as <1hr, 1-4hrs, 4-8hrs, 8-12hrs, or >12hrs.

5.2 Results

In this chapter, I will discuss the baseline results.

1,355 haemodialysis patients were approached at five renal centres, as shown in the CONSORT diagram in Figure 18.

Figure 18 Screening CONSORT



243 patients were excluded predominantly because of inability to read and understand English. 1,110 eligible patients were approached to enter the screening study, of which 401 were unwilling to consent. 709 eligible patients consented to take part in the screening. All were adults (>18 years) on haemodialysis for over three months. The mean age was 64 years (±16.4), and 449 were male (63.3%). 493 (69%) were white, 76 (10.6%) Asian, 55 (7.7%) black, 67 (9.4%) mixed race and others totalled 17 (2.4%). 364 (51%) were married or in a civil partnership. 211 (30%) were living alone. 291 (41%) patients had received formal educational qualifications beyond the age of 16. The mean dry weight was 75.5kg (±18.4), with a BMI of 26.9 (±7.9), and the median dialysis vintage was 4.4 years (IQR 5.2).

The commonest comorbidities recorded were: diabetes (33.5%), followed by heart disease (32%). Other comorbidities were: cancer, stroke, lung disease, liver disease, and amputation, as shown in Table 20. 25% had a past history of depression, 16% were receiving treatment for depression, including 11% on antidepressants in the last three months, and 5% undergoing psychological therapy in the last three months. 699 completed the BDI-II and the median score was 10 (IQR 14). 702 completed the PHQ-9 with a median score of 5 (IQR 8).

Table 20: Characteristics of screened cohort (n=709).

Values are recorded as mean ± SD or median (interquartile range)

Number	**709**
Age (years)	64 ± 16.4
Gender (% male)	63.3
Ethnicity (% white)	73
Weight (kg)	75.5 ± 18.4
BMI	26.9 ± 7.9
Pre-dialysis systolic BP (mmHg)	140 ± 27
Pre-dialysis diastolic BP (mmHg)	75 ± 17
Married/partner (%)	51
Single/living alone (%)	30
BDI-II	10 (14)
PHQ-9	5 (8)
Comorbidity (%)	
Diabetes	33
Heart disease	32
Cancer	11
Stroke	8
Dialysis parameters	
Vintage (years)	2.8 (4.9)
Kt/V	1.45 ± 0.35
Laboratory parameters	
Haemoglobin (mg/l)	112 ± 12.2
Albumin (g/l)	37 ± 4.4
Calcium (mmol/l)	2.26 ± 0.19
Phosphate (mmol/l)	1.60 ± 0.49

Past history of depression (%)	25
Treatment of depression in the last three months (%)	16
Antidepressants in last three months (%)	11
Psychological treatment last three months (%)	5

231 of these had a BDI-II score of ≥16. The main differences between the high BDI-II scorers and the 709 patients were that the high BDI-II scorers were of a younger age, at 59.5±16.5 vs 64.0 ±16.4 ($p<0.001$), and a higher prevalence of people lived alone, at 53.5% vs 30% ($p<0.001$). There was a higher prevalence of patients with a past history of depression, at 46% vs 25% ($p<0.001$), undergoing current treatment of antidepressants, at 20.4% vs 11% ($p=0.001$), and undergoing current psychological treatment, at 11% vs 3.8% ($p<0.001$).

Of those 231 patients, 168 patients were excluded from consideration for the trial phase due to the exclusion criteria (Table 21) and/or unwillingness to consent. 39 patients were not considered for the trial phase because of current antidepressant treatment, 12 because of current psychological therapy, and 17 were receiving both of these treatments. Other reasons for ineligibility were medical and other psychiatric problems (34), other contraindicated medications (17), and miscellaneous other reasons (11), including participation in other interventional studies and inadequate birth control. 38 patients declined to consent to take part in the psychiatric interview. 63 patients were eligible for and consented to psychiatric interview.

Table 21: Exclusion criteria

Medical reasons	Hepatic impairment
	Hepatitis B and C
	HIV/AIDS
	Creutzfeldt-Jakob disease
	Pregnancy or childbearing potential and not using adequate birth control
	Psychiatric conditions, including substance dependency, psychosis, personality disorder, and dementia or panic disorder, with the exception of other anxiety disorders
Contraindicating medications	Monoamine oxidase inhibitors (MAOIs)
	Pimozide
	Triptans
	Antipsychotics
	Dopamine antagonists
	Tramadol
	Linezolid
	Warfarin

5.3 Characteristics of Screened Patients with Elevated BDI-II (≥16)

231 (32.5%) of patients scored ≥16 on the BDI-II and 467 patients scored below this cut-off. The characteristics of these two groups are compared in Table 22. There were major differences in the median BDI-II score (25 [IQR 13] vs 6 [IQR 15]: p<001) and the PHQ-9 score (13 [IQR 8] vs 3.5 [IQR 4]: p<001) between the groups.

Other major differences were that the patients with high BDI-II scores were younger (59.5 ±16.5 vs 66.4±17.5: p<001), less likely to be married or have a stable partner (46.5% vs 54.3: p=0.053), more likely to have been on dialysis for longer – i.e. to have a higher dialysis vintage (3.6 [IQR 5] vs 2.5 [IQR 4.8] years: p=0.004), more likely to have a past history of depression (46% vs 15%: p<0.001), more likely to have had previous treatment with antidepressants (35% vs 12%: p<0.001), anti-depressant treatment in the last three months (21% vs 6%: p<0.001), and psychological treatments in the last three months (11% vs 1%: p<001).

There were no differences in comorbidity (diabetes, heart disease, cancer, and stroke), ethnicity, body weight, blood pressure, haemoglobin, albumin, calcium, phosphorus, Kt/V, or maximum educational attainment. However, anuria was more prevalent in patients with a BDI-II ≥16 than in those with lower scores (53% vs 41%: p=0.003). In addition, anuric patients had higher BDI-II scores than those passing urine (11 [IQR 16] vs 9 [IQR 14]): p=0.001). PHQ-9 scores were also higher (6 [IQR 10] vs 4 [IQR 7]: p<0.001). Among patients who screened positive on BDI-II, those on antidepressants had higher BDI-II scores than those not receiving these agents (30 [IQR 17] vs 24 [IQR 11]; p=0.008). In logistic regression analysis (controlled for ethnicity, living with partner or not, haemoglobin, serum albumin, sessional Kt/V, dialysis vintage, and comorbidities, including diabetes, heart disease, and stroke), significant predictors of high depressive symptom scores (BDI-II≥16) were age (odds ratio 0.973: p<0.001), anuria (odds ratio 1.712; p=0.002), past history of depression (odds ratio 4.686; <0.001), and having cancer (odds ratio 1.923; p=0.033). However, the model predicted only 20% of the variation (Nagelkerke R square 0.203).

The median BDI-II score was higher in those patients with high BDI-II who were taking antidepressants (or had taken them in the previous three months) than in those not taking these agents (30 [IQR 17] vs 24 [IQR 11]; p=0.008).

Table 22: Characteristic differences of patients with high BDI-II (≥16: n=231) and low BDI-II (<16; n=467)

Values are recorded as mean ± SD or median (interquartile range)

	High BDI	**Low BDI**	**P value**
Number	231	467	
Age (years)	59.5 ± 16.5	66.4 ± 17.5	<001
Gender (% male)	66	63	NS
Ethnicity (% white)	68	70	NS
Weight (kg)	76 ± 19	75 ± 18.1	NS
Pre-dialysis systolic BP (mmHg)	144 ± 27	142 ± 24	NS
Pre-dialysis diastolic BP (mmHg)	74 ± 18	72 ± 15	NS
Anuria (% <1 cupful of urine/day)	53	41	0.003
Marital status (%)			
Married/partner	46.5	54.3	0.053
Single/living alone	30	30	NS
BDI-II	25 (13)	6 (15)	<001
PHQ-9	13 (8)	3.5 (4)	<001
Comorbidity (%)			
Diabetes	33	32	NS
Heart disease	33	31	NS
Cancer	11	11	NS
Stroke	9.1	7.5	NS
Dialysis parameters			

Vintage (IQR) years	3.6 (5)	2.5 (4.8)	0.004
Kt/V	1.45 ± 0.35	1.45 ± 0.31	NS
Laboratory parameters			
Haemoglobin (mg/l)	111 ± 13	112 ± 12	NS
Albumin (g/l)	38 ± 5	37 ± 4	NS
Calcium (mmol/l)	2.26 ± 0.19	2.27 ± 0.19	NS
Phosphate (mmol/l)	1.62 ± 0.55	1.60 ± 0.47	NS
Past history of depression (%)	46	15	<001
Treatment of depression (%)	35	12	<001
Anti-depressants in last three months (%)	21	6	<001
Psychological treatment last three months (%)	11	1	<001

5.3.1 Relationship of BDI-II ≥16 with Previous Failed Transplantation

The median BDI-II score was higher in those who had previously received a transplant compared to those who had not: (13.5 [IQR 20] vs 10 (IQR 13]: p=0.022). 45.6% of those previously transplanted had a BDI-II of ≥16 compared to 30.8% of those never transplanted (p=0.002). There was a significant difference between the BDI-II score in relation to the number of previous transplants (0, 1, and 2). The median BDI-II scores were 10 (IQR 13), 13 (IQR 22), and 15 (IQR 20) (p=0.02), respectively. Fifty percent of those who had two previous transplants had a BDI-II score of ≥16, compared with 44.8% with one transplant and 30.8% of those never transplanted (p=0.002). However, adding the presence of transplantation to the logistic regression model, described above in 5.3, did not improve the model.

5.3.2 Relationship of BDI-II ≥16 with Post-dialysis Recovery Times

Post-dialysis recovery is a frequent complaint of haemodialysis patients after dialysis sessions. Post-recovery duration was collected using patients' self-reports and divided in to five groups, and is presented in Table 23 below.

Table 23: Post-dialysis recovery time groups

	Frequency	%	Median BDI-II (IQR)	Median PHQ-9 (IQR)
< 1 hour	169	23.8	6 (9)	2.25 (6)
1-4 hours	190	26.8	10.25 (14)	5 (8)
4-8 hours	107	15.1	11.5 (15)	6 (9)
8-12 hours	76	10.7	12 (17)	6.75 (10)
> 12 hours	159	22.4	12 (17)	6.88 (10)

The median BDI-II and PHQ-9 scores were closely related to recovery time ($p<0.001$ in both cases by the Kruskal Wallis test. The biggest difference was between those who recovered within one hour and the rest. In patients with prolonged recovery times (>1 hour), the median BDI-II score was significantly higher than in those with faster recoveries (12 [IQR 15] vs 6 [IQR 9]: $p<001$). The PHQ-9 was also higher (6 [IQR 9] vs 2.25 [IQR 6]; $p<0.001$). More had a history of depression in the prolonged recovery group (29.5% vs 10.7%; $p< 0.001$), more had taken antidepressants (22.7% vs 10.1%; $p<0.001$), and more had significant depressive symptoms – BDI-II ≥16 (38.7% vs 15.5%; $p< 0.001$). Women were more prevalent in those with prolonged recovery than in those who recovered more quickly (36.8% vs 27.2%; $p =0.003$). Patients with prolonged recovery times were more likely to be anuric (47.4% vs 36.9%; $p=0.02$) than those recovering more quickly, and less likely to be living with a partner (48.7% vs 61.5%; $p=0.005$). There was also a significant centre effect with the proportion of subjects reporting long recovery varying from 71.3% to 93.8% among the five centres ($p=0.047$). There was no relation to age,

ethnicity, or comorbidity (diabetes, heart disease, cancer, stroke, and amputation), dialysis vintage, haemoglobin, serum albumin, Kt/V, pre- or post-dialysis systolic pressure, or weight.

The best logistic regression model of recovery time >1 hour, in Table 24, showed that gender, past history of depression, and BDI-II score were significant independent predictors. Centre and Living with Partner approached significance though the model and explained only 15% of the variation (Nagelkerke R square = 0.152).

Table 24: Logistic regression model of predictors of prolonged post-dialysis recovery (>1 hour)

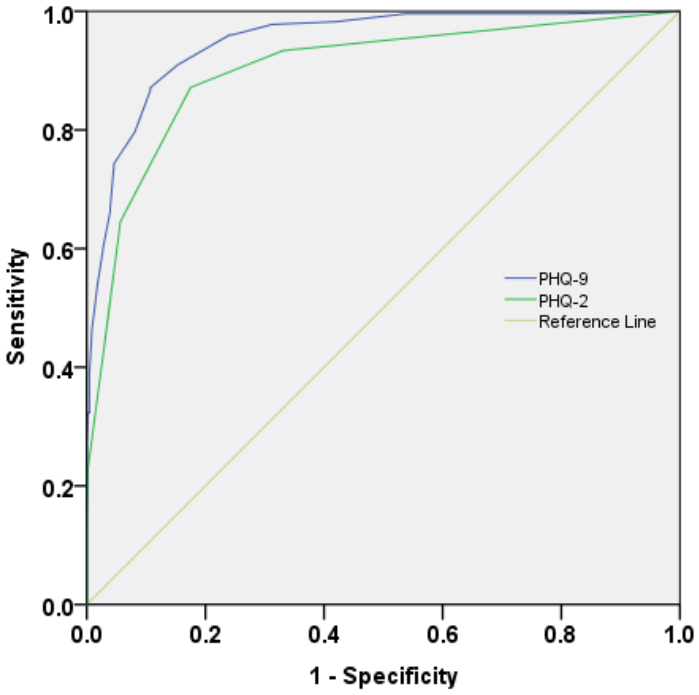
	B	SE	p-value	Exp (B)
Gender (Female)	.450	.207	.030	1.569
Centre	.132	.075	.077	1.141
Past history of depression	.723	.285	.011	2.060
BDI-II score	.060	.012	.000	1.061
Living with partner	-.342	.194	.078	.711
Constant	-.058	.317	.856	.944

5.4 Comparison of BDI-II, PHQ-9, and PHQ-2

We compared screening cut-off values for the PHQ-9 and PHQ-2 with that of the BDI-II in the HD population. We compared the two measures against the validated cut-off point on the BDI-II of ≥16, using Receiver Operating Characteristics (ROC) analysis (Figure 19).

The median scores for BDI-II, PHQ-9, and PHQ-2 were 9 (IQR 13), 5 (IQR 7), and 1 (IQR 2), respectively. Using the BDI-II cut-off ≥16, the area under the curve in the ROC analysis (Figure 19) for PHQ-9 was 0.946 and for PHQ-2 was 0.902 (both p>0.001).

Figure 19: ROC curve relating PHQ-9 and PHQ-2 to BDI-II ≥16



The optimal cut-off point for PHQ-9 in this context was ≥8 and for PHQ-2 was≥2 (sensitivity 87%, 87%, specificity 89%, 83%, respectively). The PHQ-9 ≥10 was more specific but less sensitive and with a lower negative predictive value (Table 25).

Table 25: Comparison between cut-off points of PHQ according to the BDI-II ≥16

	PHQ-9 ≥8	PHQ-9 ≥10	PHQ-2 ≥2
% population identified	36%	28%	40%
Sensitivity	87%	75%	87%
Specificity	89%	95%	83%
Positive predictive value	80%	89%	71%
Negative predictive value	93%	88%	92%
κ values	0.743	0.730	0.678
p-value	<0.001	<0.001	<0.001

The proportion of patients with PHQ-9 ≥8 was 36%, with PHQ-9 ≥10 at 28%, and PHQ-2 ≥ 2 at 40%. Levels of agreement of PHQ-9 ≥8, PHQ-9 ≥10, and PHQ-2 ≥2 with BDI-II ≥16 were substantial (κ = 0.743, 0.730, and 0.678, respectively) (Table 25).

5.5 Characteristics of Patients Eligible for Psychiatric Assessment

63 patients were eligible for psychiatric assessment and consented to take part in the interview. One was found to have cognitive impairment at diagnostic interview and was not considered in the subsequent analysis. The demographic and clinical characteristics of the remaining 62 are shown in Table 26. 37 (58.7%) had a diagnosis of major depressive episode (MDE) according to the MINI. The differences between those diagnosed with MDE and those with no MDE are

presented in Table 26. Patients with no MDE tended to be older, but not significantly. A greater proportion of patients with MDE were divorced or separated (22% vs 0%; p=0.02). In addition, those with MDE had higher scores on the BDI-II and PHQ-9 questionnaires. There were no other significant differences between the groups. Both these parameters (BDI-II and PHQ-9) were significant independent predictors of a diagnosis of MDE in logistic regression analysis (controlled for age, gender, ethnicity, and past history of depression). An increase of one point on the BDI-II score increased the likelihood of a diagnosis of MDE by 20% (p=0.002). The odds ratio and significance of the predictive power of being divorced or separated was indeterminate. The model explained 47% of the variance.

In the ROC analysis, there was a significant relationship between BDI-II scores and the MINI diagnosis of MDD (C-statistic 0.788; p< 0.001). The relationship of MDD with PHQ-9 was weaker (C-statistic 0.690; p=0.012). The best cut-off point for predicting MINI diagnosis for MDD in this population was PHQ-9 $\geq$10 (κ=0.444; p<0.001). In comparison, the level of agreement for PHQ-9 $\geq$8 was 0.252 (p= 0.013).

Table 26: Characteristic differences between patients with and without diagnosis of depression by MINI.

P-value refers to significance of difference between those with and without MDE

	All	MDE	No MDE	P value
Number	62	37	25	
Age (years)	61.4 ± 15.0	59.4 ± 13.9	64.1 ± 16.1	NS
Gender (% male)	73	73	72	NS
Ethnicity (% white)	60	57	64	NS
Weight (kg)	76 ± 18	75 ± 16	77 ± 21	NS
Pre-dialysis systolic BP (mmHg)	146 ± 25	148 ± 25	145 ± 26	NS
Pre-dialysis diastolic BP (mmHg)	76 ± 18	75 ± 18	77 ± 18	NS
Anuria	55	57	52	NS
Marital status (%)				
Married/partner	52	49	58	NS
Single	23	19	29	NS
Divorced/Separated	13	22	0	0.02

Widowed	12	11	13	NS
Depression screening				
BDI-II	25 (11)	30 (14)	21 (7)	0.001
PHQ-9	13 (7)	13 (7)	11 (6)	0.011
PHQ-2	3 (2)	3 (3)	3 (2)	NS
BDI-II ≥16 (%)	100	100	100	-
PHQ-9 ≥8 (%)	86	92	72	0.013
PHQ-9 ≥10 (%)	75	92	52	<0.001
PHQ-2 ≥2 (%)	90	92	88	NS
Dialysis parameters				
Vintage (IQR)	2.9 (4.7)	2.9 (3.3)	3.0 (5.5)	NS
Kt/V	1.50±0.35	1.46±0.25	1.57±0.45	NS
Comorbidity (%)				

Diabetes	37	43	28	NS
Heart disease	60	46	32	NS
Cancer	14	8	24	NS
Stroke	6	11	0	NS
Amputation	3	5	0	NS
Laboratory parameters				
Haemoglobin (g/l)	114 ± 12	114 ± 12	114 ± 11	NS
Albumin (g/l)	39 ± 5	39 ± 4	39 ± 5	NS
Calcium (mmol/l)	2.26 ± 0.17	2.26 ± 0.16	2.27 ± 0.19	NS
Phosphate (mmol/l)	1.56 ± 0.47	1.56 ± 0.54	1.57 ± 0.37	NS
Past history of depression (%)	29	35	20	NS
Previous antidepressants (%)	13	16	8	NS
Current treatment of depression (%)	0	0	0	NS

5.6 Discussion

Our results confirmed that many patients on HD suffer from depression. A high proportion (32.5%) screened positive on the BDI-II using the cut-off ≥16, which corresponds with previous literature (173), and 36% had a PHQ-9 of ≥8. Indeed, people with CKD identify improving psychosocial aspects of living with their illness among their most important research priorities (59, 172). Our study showed that 46% of those screening positive for depression had a past history of depression. This is considered to be the largest screening multi-centre study to date. It is noteworthy that, in the general population, the point prevalence of depression has been reported to be 5-9% in women and 2-3% in men, and the lifetime prevalence of depression in the general population is 21.3% among women and 12.7% among men (443). This study demonstrated that the prevalence of depression is much higher in the HD population, which may in part be due to the presence of overlapping somatic symptoms related to uraemia (444).

One of the major findings was the high prevalence of HD patients receiving treatment for their depression either by antidepressants or psychological therapy, despite the lack of evidence for the efficacy of antidepressants in this setting. The only previous report in the literature citing the use of antidepressants in this setting is that of Lopes et al. (228). We demonstrated in our study that antidepressants are commonly prescribed in this population. It was notable that 24% of patients with a high BDI-II score were currently taking antidepressants and 12.5% were receiving psychological therapies (7% were receiving both). Positively screened BDI-II patients receiving antidepressants had higher BDI-II scores than their untreated counterparts, questioning the role of antidepressants in this population. These factors raised questions regarding the prescribing practices and efficacy of these agents in this population. As a result of these findings, it was decided to gain further ethical approval for a further study to explore the progression of depressive symptoms in this group of patients, that is, HD patients on antidepressants. This will be fully covered in a subsequent chapter.

There were no differences in comorbidities: heart disease, stroke, amputation, lung disease, cancer, and liver disease (the latter two are not shown in the table due to

very small numbers) and this differed from previous literature (220, 228), which found that patients with depression identified by physicians were more likely to have comorbid conditions. However, in multivariable analysis, the presence of cancer was associated with a high BDI-II. Similarly, we found no relationship between high BDI-II scores and haemoglobin levels and this also differed from past literature (445). This may be due to extensive use of erythropoietin (EPO) in our population, which may have limited the variation in haemoglobin levels and reduced some of the somatic symptoms often associated with depression.

We were unable to find an association between depression and body weight, albumin, calcium, and phosphorus, which was similar to previous studies (162, 224). However, a Korean group showed negative correlations between BDI scores and these parameters (446). Similar findings regarding albumin levels were obtained by Lacovides et al. (447) in a disparate group of 82 European ESRD patients treated with HD and PD. Friend et al. (448), in a study of HD patients, showed that depression preceded a decrease in serum albumin concentration. The reasons for these disparities remain unclear, but may be because of differences in ethnicity, gender, or age compositions of the study populations, and cultural and socioeconomic factors. Treatment conditions and nutritional differences may also play a role.

There was no relationship between dialysis vintage and BDI-II scores in our study, which accords with previous studies (162). However, there are studies that showed differences between mean levels of BDI-II scores in incident and prevalent HD populations (449) and others that found a trend for greater prevalence of depression in patients treated for ESRD for more than one year (220). Chilcot et al. (450) found that higher levels of depression were associated with a poorer understanding of illness, coherence to treatment, perceptions that kidney failure has severe consequences, and a more recurring timeline. In addition, beliefs that treatment-controlled kidney failure decreased over time in patients with increasing depression symptoms.

The number of studies on the psychosocial condition of patients with renal graft failure and patients on the transplantation waiting list are limited, though there are indications that, upon returning to HD after graft rejection, patients are prone to

develop severe depression (451). Other studies have found that depression is a prevalent and problematic comorbidity and predicts poor outcomes, including graft survival in transplant patients in general (452). Patients with longer functional graft duration had lower levels of depression, whereas early transplant failure patients tend to be depressed due to unfulfilled high expectations. In addition, patients who had been on dialysis longer before their graft loss were less likely to be depressed, perhaps due to having a longer period of adaptation to dialysis challenges/restrictions. Patients awaiting a cadaveric donor have been reported to have a greater risk of anxiety and more severe depressive disorders than patients with an available living-related donor (453). We also found higher BDI-II scores in patients who had previous transplants – the higher the number of previous transplants, the higher the BDI-II score.

Marital status and social support have been associated with depression in studies of patients in the presence and absence of renal disease (24, 162, 258, 454); we found that there was a trend towards a lower proportion of patients married or with a partner among those with high BDI-II scores.

We also found that anuric patients (<1cup of urine/day) had higher BDI-II scores than those passing more urine, and were more likely to have a BDI ≥16, which was similar to previous literature. This may be due to patients' perception of kidney loss and subsequent low mood being heightened by low urine volumes and loss of the social elements afforded by drinking. Both may increase depressive vulnerability (455).

There is only a weak association of depressive symptoms with post-dialysis recovery time and this is likely to be mediated by the somatic element of the BDI-II score, to which the symptom of fatigue is a major contributing factor. This will be discussed in detail in Chapter 7.

Our findings also suggest that PHQ-9 and PHQ-2 are acceptable screening tools compared to the BDI-II in dialysis patients, with cut-off points of ≥8 in PHQ-9 and ≥2 in PHQ-2 approximating the BDI-II cut-off of ≥16. There is perhaps some conflict between this finding and previous literature (175), which validated the BDI-II and PHQ-9 against the Structured Clinical Interview for Diagnostic and Statistical

Manual of Mental Disorders, fourth edition. The optimal BDI-II and PHQ-9 cut-off values for depressive disorders combined were ≥16 and ≥10, respectively. However, we did find that the strongest predictor of the MINI diagnosis in patients with high depressive symptoms (BDI-II ≥16) was a PHQ-9 of ≥10.

It may be possible to reconcile these findings. The BDI-II score reflects both the somatic and cognitive aspects of depression. Hence, the BDI-II scores are inflated in HD patients due to an overlap of depressive symptoms and those of uraemia. This is partially compensated by use of a higher cut-off in the HD group (≥16) than in the general population. Nevertheless, a high proportion of those with BDI-II ≥16 do not have MDD on formal interview. Use of a lower cut-off in the PHQ-9 scale (≥8 vs ≥10) in screening also inflates the number of screen-positive patients, to a level comparable to those identified by the BDI-II ≥16 cut-off. However, in the general HD population, the PHQ-9 ≥10 cut-off is superior at identifying those with diagnosed MDD (175), a group that excludes those patients whose depressive symptom scores showed inflated somatic symptom overlap. The same seems to hold true in the selected group of HD patients we studied, i.e. those already identified with high BDI-II scores (≥16).

5.7 Effectiveness of Screening Methodology in Identifying Potential Trial Participants

The main purpose of the screening phase was to identify HD patients with depression suitable to enter the RCT. In spite of approaching 1,353, only 37 were ultimately deemed suitable to be randomised, and only 30 agreed. The main reasons for dropping out were:

- Inability to speak and understand English; this excluded 243 patients from being considered for screening
- Refusal to consent for screening; this excluded 401 patients
- Of the patients who screened positive with high depressive symptoms with the BDI-II, exclusions included:

- Current treatment for depression either by antidepressants, psychological therapy, or both [68]
- Medical and other psychiatric problems [34]
- Contraindicated medications [17]
- Declined to consent for trial [38]

The screening process was very robust. It might be questioned if it was too robust. Opportunities that may have increased the number of patients suitable for the RCT were:

- Using validated-translated versions of the screening tools to enable inclusion of more non-English speaking patients; this would require translated versions with multiple languages, none of which are currently available.
- Giving the opportunities for patients who were already on antidepressants to be considered for the RCT after a washout period; this approach has a number of risks, including worsening of depressive symptoms for some patients and increased complexity of the RCT. Using patients receiving psychological therapy might have similar complexities. It may also be possible to conduct an RCT of stopping antidepressants in a selected group of patients. Each of these possibilities is associated with difficult ethical issues, which may complicate regulatory approval.
- Relaxed criteria concerning other medical/medications exclusions. It would be difficult to justify using patients with limited prognosis and other major conditions. It would be difficult to justify simultaneous treatment with agents cautioned or contraindicated with pharmacopeia.
- Encouraging patients to consent to participate in the study may have been improved by a more consistent approach across the participating units. The consent rate for the screening phase was 709/1110 (64.5%) of those eligible. The consent rate for the psychiatric interview was 63/101 (62.4%) and the consent for the RCT was 30/34 (88.2%). The four who refused consent for the RCT preferred the offer of definitive antidepressant treatment rather than entering into the study and having a 50% chance of receiving the active drug.

- From a general perspective, therefore, these consent data seem very reasonable. There may be some scope to increase the consent rate, but it may be difficult to increase in reality.

Considering all of these recruitment challenges, screening seems to be reasonably successful.

5.8 Concluding Remarks

The prevalence of depressive symptoms is high in HD patients. Antidepressant therapy is common, despite little evidence of efficacy in HD patients and a high potential for adverse effects. This was an important clinical finding, which also had ramifications for our feasibility RCT study – limiting identification of recruitable subjects.

In addition to the planned feasibility study of the efficacy of sertraline in depressed HD patients, and as a result of these findings, a further study was designed and ethically approved to follow up a cohort of those HD patients on antidepressants to examine the natural history of this phenomenon. This will be described in Chapter 8.

The predictors of high depressive symptoms (BDI-II ≥16) were younger age, anuria, past history of depression, and the presence of cancer. Previous failed transplantation was also associated with high depressive symptoms.

BDI-II scores were also predictive of post-dialysis recovery time.

PHQ-9 ≥8 is the best cut-off of the PHQ-9 test to detect patients with BDI-II ≥16.

PHQ-9 ≥10 is the best cut-off to detect patients with MDD in a cohort with high depressive symptoms (BDI-II ≥16).

Longitudinal studies and studies correlating depressive symptoms with psychiatric diagnoses are urgently needed in ESRD patients.

Depressive affect rather than a pychiatric illness may be an important risk factor for ESRD patients, and may be amenable to treatment, with ramifications beyond mere changes in affect.

Chapter 6

The RCT

6.1 Introduction

We conducted a multicentre, double-blind, placebo-controlled, feasibility randomised trial of sertraline in HD patients with mild to moderate MDD. The main purpose of the study was to evaluate the feasibility of conducting a fully powered double-blind, placebo-controlled RCT, by measuring the number of ESRD patients who took part and completed the study, as well as evaluating their outcomes.

We wished to establish the potential effectiveness of sertraline as a treatment for depression in patients on HD. We also wished to establish whether the drug was well tolerated, whether it had an acceptable adverse effect profile, and whether there were indications that it was more effective than placebo in reducing depressive symptoms, in particular, fatigue. The safety and drug exposure of sertraline was also assessed.

6.2 Brief Methodology

Full details of the design, setting, outcomes, and statistical analysis are documented in Chapter 4. In brief, patients over the age of 18 who had been receiving treatment by HD for three months or more were approached. Those who could not read and speak English were excluded. Consenting patients completed the BDI-II questionnaire. Demographics, medical and psychiatric history, and dialysis treatment data were also collected. Those scoring ≥16 on the BDI-II, not on treatment for depression (antidepressants or psychological therapies) currently or in the past three months, and without any pre-defined exclusion criteria, including planned living-donor kidney transplant within the period of the trial, a prognosis of less than a year, several associated medical conditions and contraindicated medications, were approached to undergo diagnostic interview by a psychiatrist using the MINI to confirm the presence of MDD. Following this, consenting patients diagnosed with mild-moderate MDD and with a score of 18 or above on the MADRS were randomised into the trial phase. We planned to exclude patients with severe

depression and active suicidal ideation from the study and refer them urgently to psychiatric services. We also planned to exclude patients who had evidence of cognitive impairment on MMSE (440). We required written informed consent from patients at three separate points during the study, before screening, before interview by the study psychiatrist, and before randomisation to enter the trial.

6.3 Results

Screening and recruitment into the study took place between 1 April 2013 and 30 April 2015. The CONSORT flow diagram for the study is shown in Figure 20 . We approached 1,353 patients in five UK renal units, to enter the screening phase. 243 were excluded mainly due to lack of proficiency in English. Of the remaining 1,110 patients, 709 (64%) consented to screening. On screening, 231 patients (32.6%) had a BDI-II score of 16 or above. 168 of these were excluded from consideration for the trial phase – 39 were not considered because of current antidepressants treatment, 12 because of current psychological therapy, and 17 were receiving both these treatments. Other reasons for exclusion were medical and other psychiatric problems (34), other contraindicated medications (17), and miscellaneous other reasons (11), including participation in other interventional studies and inadequate birth control. 38 patients declined to consent to take part in the psychiatric interview (see Chapter 5).

Sixty-three of those eligible for the trial phase consented to be seen by the study psychiatrist for diagnostic interview. Thirty-seven of these (58.7%) were diagnosed with MDD. However, three had recently started antidepressants, one had severe cardiac disease, one had severe cognitive impairment, one was diagnosed with substance misuse, and another preferred to be seen by their primary care physician. The remaining 30 consented to enter the RCT. On unblinding, it was apparent that 15 had been randomised to the sertraline and 15 to the placebo group.

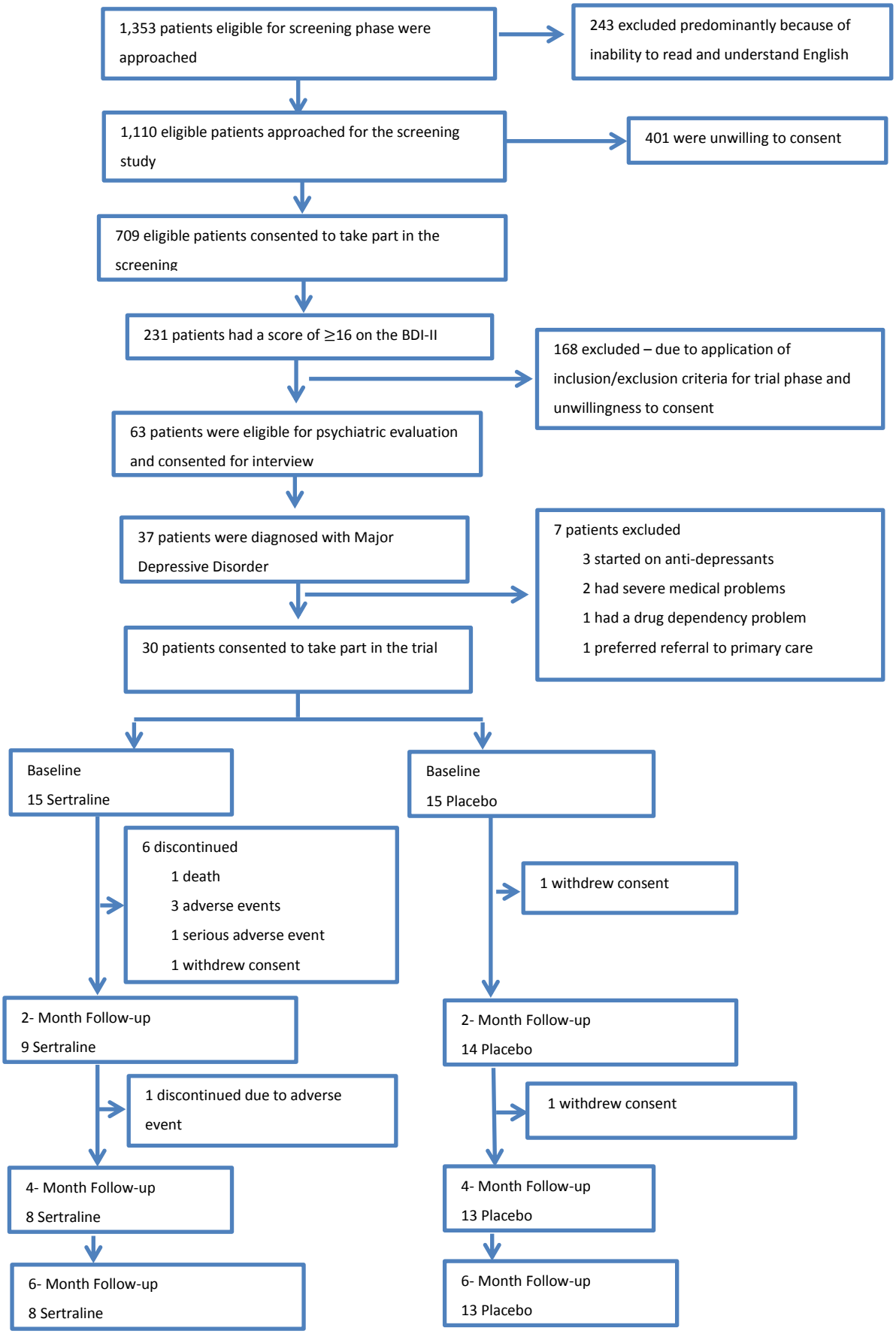
The baseline characteristics of the patients randomised in these groups are shown in Table 27. All characteristics were similar in these groups, except that patients in the sertraline group were on average five years older (61.7 ± 13.2 vs 56.4 ± 14.4 years; p=0.15). The sample was predominately men (77%). For the whole study sample, the mean age was 59.0 ± 13.8; 60% were white, 20% Asian, and 20% other ethnicities.

Fifty percent were married or living in a civil partnership, and 33% lived alone. Over 80% had at least one comorbidity, with diabetes and heart disease the most common. Thirty-three percent had a past history of depression and 17% had previously used antidepressants.

Table 27: Baseline characteristics

	Sertraline **n=15**	**Placebo** **n=15**
Age (years)	61.7 (13.2)	56.4 (14.4)
Male	11 (73%)	12 (80%)
Ethnicity	White 10 (67%) Asian 2 (13%) Black 2 (13%) Mixed 1 (7%)	White 8 (53%) Asian 4 (27%) Mixed 3 (20%)
Living conditions	Alone 5 (33%) With partner 5 (33%) With family 5 (33%)	Alone 5 (33%) With partner 6 (40%) With family 4 (27%)
Dialysis vintage (years)	3.1 (5.1)	3.3 (5.4)
Diabetes	6 (40%)	7 (47%)
History of depression	5 (33%)	5 (33%)
Haemoglobin (g/L)	118 (19)	117 (14)
Urea (mmol/L)	16.0 (6.3)	15.7 (7.6)
Creatinine (umol/L)	707 (285)	664 (315)
Kt/V (Last value at month 1)	1.43 (0.36)	1.47 (.21)
Pre-dialysis BP (mmHg)	148/77	147/84

Figure 20 Study CONSORT diagram



6.4 Comparison between Sertraline and Placebo Groups

Twenty-one patients completed the trial (70%) at the six-month follow-up. There were eight (53%) in the sertraline group and 13 (87%) in the placebo group ($\chi 2=3.97$: p=0.046). In the sertraline group, six withdrew within the first two months. One of them took no tablets as they were concerned about side effects. Three patients experienced adverse effects (one withdrew after three days because of nausea, another after 12 days with headaches and dizziness, and a third due to insomnia after 23 days). One patient died following cardiac arrest having taken one tablet. The sixth was admitted for a prolonged hospital stay with leg ulcers shortly after randomisation and was subsequently withdrawn without having taken any study medication. A further patient withdrew after three months because of sweating and palpitations. In the placebo group, one withdrew after baseline assessment because of concern about taking extra medication, and another decided against continuing after three months with no reported reason. There were no significant differences in safety data, including ECG, haemoglobin, and liver function tests between groups during the course of the study.

The number of drop-outs due to adverse or severe adverse events was greater in the sertraline group (33% vs 0%; p =0.042). Patients who withdrew were older (70 vs 54 years: p=0.001) and had lower baseline haemoglobin levels (109 vs 121 g/L: p=0.04). There were no other differences between those who withdrew and those who remained in the study.

6.5 Comparison between BDI-II and MADRS scores in sertraline and placebo groups

There was a significant fall in the BDI-II from baseline to month 6 (29.1 ± 8.4 to 17.3 ± 12.4: p<0.001) and in the MADRS scores (24.9 ± 4.3 to 10.7 ± 5.2: p<0.001), with similar significant falls in both sertraline and placebo groups (Figure 21 and Table 28). The mean change in the MADRS score over the six months of the study was -14.5 (CI -20.2 to -8.8) in the sertraline group and -14.9 (CI -18.4 to -11.5) in the placebo group. Changes in BDI-II were similar at -15.7 (CI -24.3 to -7.1) in the

sertraline group and -13.0 (CI -19.6 to -6.4) in those on placebo. There were no statistically reliable differences between the groups. For the MADRS score there were no differences between the groups at any other time point with respect to change from baseline values. The maximum difference occurred at two months, at which stage, nine patients remained on sertraline and 14 on placebo (MADRS scores 13.9 ± 5.7 and 15.8 ± 4.8 respectively, difference 1.89 [CI -2.7 to 6.5]: p=0.20) (Table 28 and Figure 21). The effect size at this time point was estimated at 0.37 using Cocks et al.'s approach (442).

Eighteen patients experienced adverse events and/or serious adverse events (SAEs), nine in each randomised group. Infections (8) and nausea (4) were the most commonly reported adverse events. With regard to the SAEs, there was one death that was possibly related to the study medication, as mentioned above, six SAEs that were unlikely to be related, and six SAEs that were not related to the study medication. In none of these events was emergency unblinding needed. For neither was urgent referral to psychiatric services necessary during the course of the study. There was one patient who was retrospectievely was found to be on Tramadol (started by GP), which was a relative contraindication with sertraline; in view of the fact that she had experienced satisfactory pain relief on this agent without developing side effects, we decided to continue this medication and continue her in the trial.

Figure 21: MADRS score over six months

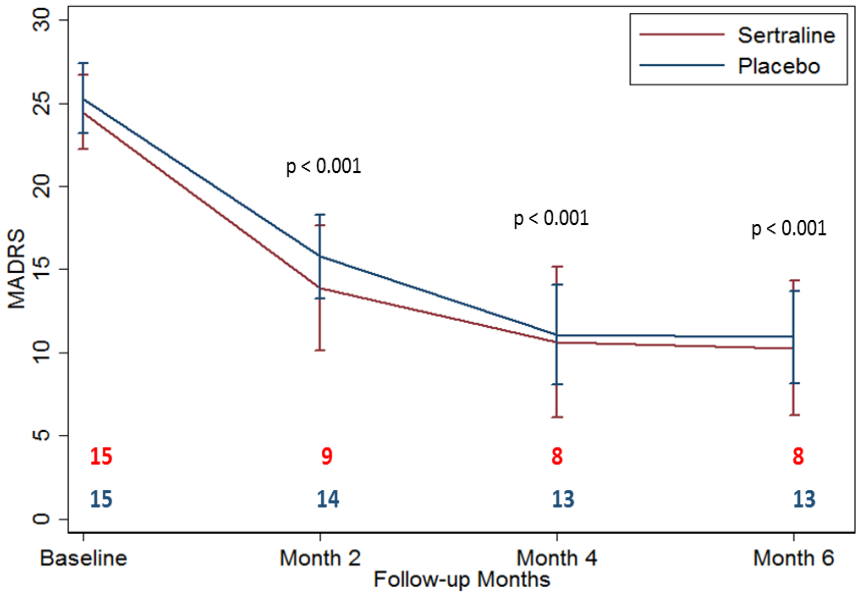


Table 28: Comparison between the MADRS score in sertraline and placebo groups

		Sertraline	Placebo	Treatment effect
MADRS	Baseline	24.5 (4.5) n=15	25.3 (4.2) n=15	
	2 months	13.9 (5.8) n=9	15.8 (4.8) n=14	-1.9 (-6.5, 2.7)
	4 months	10.6 (6.6) n=8	11.1 (5.5) n=13	-0.45 (-6.0, 5.1)
	6 months	10.3 (5.8) n=8	10.9 (5.1) n=13	-0.67 (-5.7, 4.4)
	Change from baseline			
	To 2 months	-10.4 (-16.4, -4.4)	-8.9 (-13.3, -6.4)	
	To 4 months	-14.1 (-19.6, -8.6)	-14.8 (-18.1, -11.4)	
	To 6 months	-14.5 (-20.2, -8.8)	-14.9 (-18.4, -11.5)	

Mean (and standard deviation) values for the MADRS score at two, four, and six months for the sertraline and placebo groups. The treatment effect is estimated as the difference between the observed outcome scores (with 95% confidence intervals) for the sertraline and placebo groups. As the difference between the groups was effectively 0 at six months, no adjusted differences have been estimated. The change in the MADRS score from baseline to two, four, and six months (with 95% confidence intervals) is provided in the 2nd half of the table.

6.6 Medication Adherence and Safety

Mean medication adherence among those who completed the study, estimated by a count of returned tablets, was 88% (range 46 – 100%). In only one patient was adherence to the study medication less than 75% (it was 46%). Pre- and post-dialysis sertraline levels were analysed after unblinding at the end of the study and the process was previously explained in Chapter 4. Five of the eight patients, all taking 100mg daily, had similar pre- and post-dialysis levels (32 ± 12 ug/l vs 34 ± 18 ug/l). In two others, both taking 50mg daily, levels were <10 ug/l. One had been 46% and the other 94% adherent on tablet counts. Levels were unmeasurable in one patient due to an interfering compound, possibly verapamil.

6.7 Discussion

This feasibility study is the largest trial of an antidepressant in HD patients to date. We recruited 30 patients and 21 (70%) patients completed the six-month study.

Recruitment to the trial, however, was constrained. The final number of 30 patients was well below the original planned sample size, which was 60. Just over 70% of the screend patients with BDI-II ≥16 were non-eligible or were unwilling to consent to psychiatric interview. 29% were already taking anti-depressants or receiving psychological therapies, which were exclusion criteria. Some patients seemed reluctant to take additional medication because of already high pill burdens.

Our results confirmed that a high proportion of patients on HD (32.3%) screened positive on the BDI-II and suffered from significant depression. 46% had a past history of depression, and 25% were currently taking antidepressants or receiving psychological therapies. We also confirmed that sertraline is not removed substantially in the haemodialysis procedure and adherence to the medication also seemed to have been adequate.

Eighteen patients, nine in each randomised group, experienced adverse events, with infections and nausea the most commonly reported. With regard to the SAEs, there was one death that was possibly related to the study medication, six SAEs that were unlikely to be related, and six SAEs that were not related to the study medication.

Depression scores for both BDI-II and MADRS improved significantly in the sertraline and placebo groups over six months. There was no significant difference between the groups. There was a suggestion that the rate of decrease in the MADRS scores over two months tended to be greater in those on sertraline, though this may relate to the higher drop-out rate in this group.

The significant improvement in depression over six months could be due to a strong placebo effect, to the effect of study participation (Hawthorne effect) (456), or perhaps related to the natural history of MDD in this context. There is also a possibility that sertraline may cause harm, related to adverse effects. The only death occurred was in this group.

Our main study limitation was the small sample size. RCT recruitment was difficult and constrained by exclusion of an unexpectedly high number of patients already receiving treatment for depression. These exclusions not only limited recruitment but also may have inadvertently introduced a selection bias in our sample. The clinical outcomes we have described need to be interpreted with great caution due to the study design and the small sample size.

6.8 Concluding Remarks

Our study raises concerns about the benefits and risks of antidepressant treatment in patients on HD, a highly comorbid group with a huge pill burden and with high prevalence of depression. Identifying effective treatments is a major clinical need, hence the need for a definitive study.

We recommend that the design of such a study should enable inclusion, rather than exclusion, of patients currently taking antidepressants. This would require a washout period, in cases that have been judged to be appropriate on clinical grounds.

To evaluate the potential advantage for sertraline over placebo at two months, assuming alpha=0.05 and 1-beta=0.90 with a one-sided test, the required sample size would be 135 patients per study arm. If such a study included patients already on depression treatment, 3,600 HD patients would need to be screened to achieve this recruitment target. A shorter follow-up period of two to three months could be sufficient as recovery may be more rapid on the active drug and most drop-outs appear to occur in this timescale. The definitive trial could be powered based on our effect size at two months, with a required sample size of 270 patients randomised to two study arms. Given the high degree of symptom overlap between depression and advanced kidney disease, depression should be diagnosed by psychiatric interview, rather than questionnaires. It must be recognised that the basis of this power calculation is speculative given the small differences found between the sertraline and placebo effects.

Current UK guidelines for treating depression in patients with chronic physical illness, issued by NICE, advocate pharmacological therapy for patients with MDD (457). We strongly agree with the European Renal Best Practice Group recommendations that 'The evidence on the effectiveness of antidepressants versus placebo in patients with CKD stages 3-5, and with DSM-IV-defined depression is insufficient, and in view of the high prevalence, a well-designed RCT is greatly needed' (230), and with the recent Cochrane review (458): 'Despite the high prevalence of depression in dialysis patients and the relative priority that patients place on effective treatments, evidence for antidepressant medication in the dialysis setting is sparse and data are generally inconclusive. The relative benefits and harms of antidepressant therapy in dialysis patients are poorly known and large randomised studies of antidepressants versus placebo are required'.

We believe it is highly recommended to conduct a large randomised placebo-controlled trial of antidepressants in this group of patients due to uncertainty about the efficacy and safety of antidepressants, and in consideration of the large numbers of haemodialysis patients currently taking these agents. We also recognise the potential difficulties of undertaking such a study.

Chapter 7

Fatigue

7.1 Aims

1- Establish the proportion of ESRD patients who scored positive on fatigue scales MFI and SF-36 energy/fatigue subscale.

2- Establish the relationship between depression and fatigue scores and their relationship to clinical, biochemical, and haematological parameters.

3- Explore the extent to which somatic symptoms of depression such as fatigue contribute to the diagnosis of depression in this chronic disease state.

4- Establish whether there is a difference between drug and placebo on the measures of fatigue over the period of the study.

7.2 Brief Overview of Methodology

As part of the screening phase of the ASSertID study, patients over the age of 18 years who had been receiving treatment by HD for three months or more were approached. Patients who could not read and speak English were excluded. Consenting patients completed the MFI and SF-36 energy/fatigue subscale questionnaires at bedside during dialysis. These questionnaires are described in detail in the introductory fatigue chapter 3, section 3.3. Data relating to demographics, medical and psychiatric history, and dialysis treatment were also collected.

7.3 Data Collection

Data was collected from electronic records and directly from patients on age, gender, marital status, ethnicity, current living arrangements (alone, with partner or family, or friends), and educational attainment. The duration (vintage) of dialysis time was recorded, in addition to dialysis adequacy (Kt/V) and routine clinical observations on

the day of completion of the questionnaire (blood pressure and dry weight). The most recent biochemical and haematological data were collected from the electronic patient record – haemoglobin, albumin, calcium, and phosphate. Details of patients' transplant history were recorded as never transplanted or transplanted and returned to dialysis. We also asked to self-report urine output as being less than one cup per day or greater than one cup per day and post-dialysis recovery was categorised as <1hr, 1-4hrs, 4-8hrs, 8-12hrs, or >12hrs. C reactive protein (CRP) was measured in a smaller subgroup.

7.4 Results

Ethical approval for the fatigue study was granted after the start of recruitment to the ASSertID screening study. An amendment to the ASSertID study to include the fatigue questionnaire was approved (Appendix 1). Hence, of the 709 eligible patients who entered the screening phase of the ASSertID study, 464 candidates completed both fatigue questionnaires.

7.4.1 Characteristics of the Whole Cohort

The characteristics of this cohort (464) were as follows: the mean age was 64 years (± 16.6); 306 were male (65%); 291 (62%) were white and all others, including Asian, black, and mixed race, totalled 176 (38%); 235 (51%) were married or in a civil partnership; 231 (49%) were living alone; 186 (40%) patients had received formal educational qualifications beyond age 16; dry weight was 76.5kg (± 19); and dialysis vintage was 4.1 years (IQR 5.2). Comorbidities were recorded and were highly prevalent in diabetes (35.5%), followed by heart disease (30%), cancer, stroke, lung disease, liver disease, and amputation. Blood pressure and the most recent biochemical and haematological data are shown in Table 29.

Table 29: Cohort characteristics (n=464)

Age (years)	64 ± 16
Gender (% male)	65
Ethnicity (% white)	62
Weight (kg)	76.5 ± 19
Pre-dialysis systolic BP (mmHg)	140 ± 25
Pre-dialysis diastolic BP (mmHg)	71 ± 16
Marital status (%)	
Married/partner	51
Single	49
Depression (%)	
Past history	24
Antidepressants	18
Psychological therapy	4
BDI-II	10 (11.4)
PHQ-9	5(6.2)
Comorbidity (%)	
Diabetes	35.5
Heart disease	30
Cancer	10
Stroke	8
Lung disease	6
Amputation	6
Dialysis parameters	
Vintage (IQR) years	4.1 (5.2)
Kt/V	1.5 ± 0.32
Laboratory parameters	
Haemoglobin (g/l)	112 ± 12.6
Albumin (g/l)	37.4 ± 4.7
Calcium (mmol/l)	2.23 ± 0.18
Phosphate (mmol/l)	1.60 ± 0.5

Median MFI score for general fatigue (GF), physical fatigue (PF), mental fatigue (MF), reduced activity (RA), and reduced motivation (RM) were: 13 (IQR 6), 15 (IQR 6), 9 (IQR 6), 13 (IQR 6), and 13 (IQR 6), respectively. The mean SF-36 energy/fatigue subscale score was 48.1 ± 23.9.

7.4.2 Predictors of Fatigue

7.4.2.1 Clinical Factors

There was an inverse correlation between GF and age (rho=-0.132; p=0.004) and a positive correlation with weight (rho=0.121: p=0.009). PF did not correlate with age but did correlate positively with weight (rho=0.169: p<0.001). MF did not correlate

with age or weight. There were no differences in relation to gender or ethnicity with respect to any of the fatigue subdomains.

There were no correlations with haemoglobin, albumin, calcium, phosphate, Kt/V, and systolic or diastolic blood pressure with any of the fatigue domains.

GF and PF were higher in patients with heart disease (14 (IQR 6) vs 13 (IQR 6): p=0.014 and 16 (IQR 6) vs 15 (IQR 7): p=0.002, respectively). Likewise, GF and PF were higher in patients with diabetes (14 (IQR 5) vs 13 (IQR 6); p=0.013 and 16 (IQR 6) vs 15 (IQR 6); p<0.001, respectively). There were no differences with respect to stroke, amputation, and cancer. There were no differences in MF scores with respect to any of these conditions. In a smaller group of patients (n=114), the PF score was higher in those with a CRP>5mg/l (15 (IQR 6) vs 14 (IQR 7): p=0.010). There were no differences with respect to either GF or MF.

Overall, GF was weakly related to age (but negatively), weight, heart disease, and diabetes. PF was similarly related to weight, heart disease, and diabetes, but also to high CRP. There were no associations of MF.

7.4.2.2 Depression Screening Scores

There were very strong correlations between the BDI-II, PHQ-9, and PHQ-2 scores and all MFI subdomains (GF, PF, and MF) (Table 30). The best correlations were between GF with BDI-II and PHQ-9 (rho=0.607 and rho=0.606: p< 0.001 in both cases).

Table 30: Correlation between BDI-II, PHQ-9, PHQ-2, and MFI

		BDI-II	PHQ-9	PHQ-2
General fatigue	Rho	.607**	.606**	.484**
	p-value	.000	.000	.000
Physical fatigue	Rho	.524**	.529**	.467**
	p-value	.000	.000	.000
Mental fatigue	Rho	.588**	.584**	.508**
	p-value	.000	.000	.000

7.4.3 Distribution of MFI in Patients with High BDI (≥16)

We compared the distribution of fatigue subdomains in the whole cohort and in patients with BDI-II ≥16 (high) and those with lower scores (normal), focusing on the general, physical, and mental fatigue subdomains, as shown in the graphs below. There were no differences in the median values of reduced motivation and reduced activities between those with high and normal BDI-II scores. These domains have been omitted from the remainder of the analysis.

Figure 22 Distribution of MFI subdomain scores

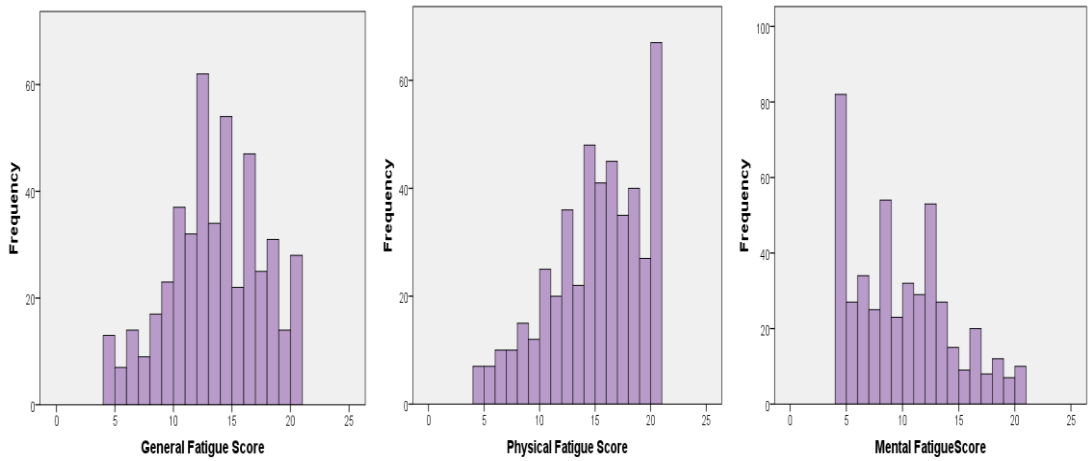
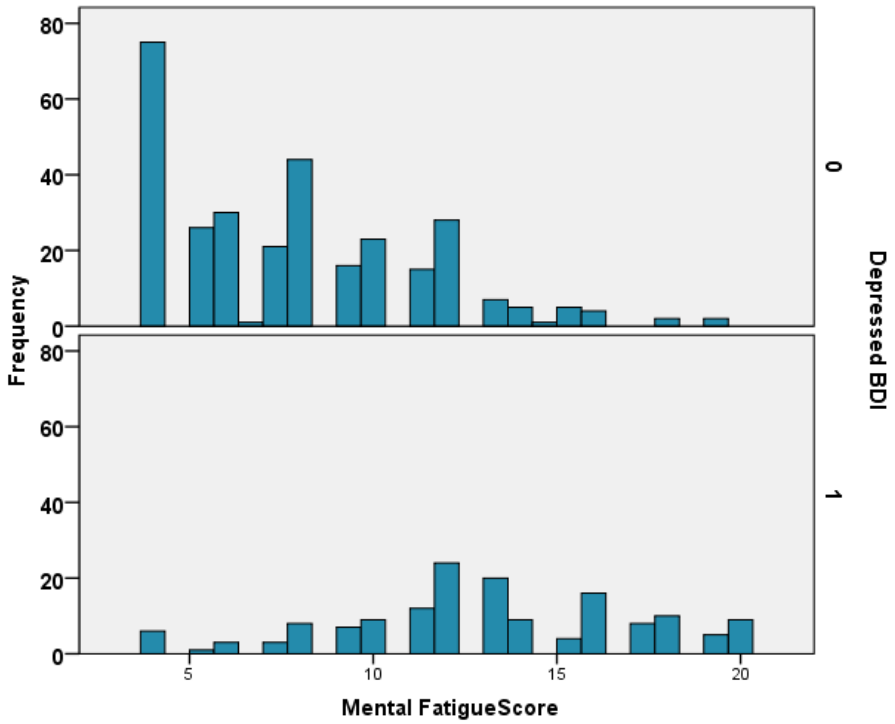


Figure 22 shows the distribution of MFI subdomains (GF, PF, and MF) in the whole cohort. The GF score was approximately normally distributed, and PF and MF scores were not. There was a negative skew in the PF score and a positive skew in the MF score.

Figure 23: Mental fatigue distribution in patients with high and normal BDI-II (1 = high)



With MF, there was a positive skew distribution in patients with a normal BDI-II compared to a relatively normal distribution in those with high BDI-II scores, as shown in Figure 23 above. This contrasts with the situation for PF. In this setting, patients with high BDI-II scores have a marked negatively skewed distribution of PF scores, as shown in Figure 24. The distribution in patients with normal BDI-II scores was more normal. There was a similar distribution in GF scores, as shown in Figure 25.

Figure 24: Physical fatigue distribution in patients with high and normal BDI-II scores (1 = high)

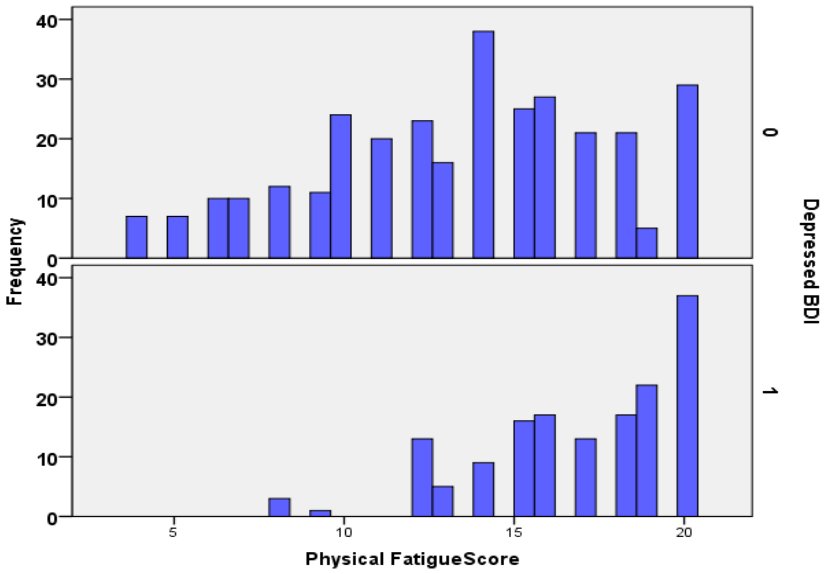
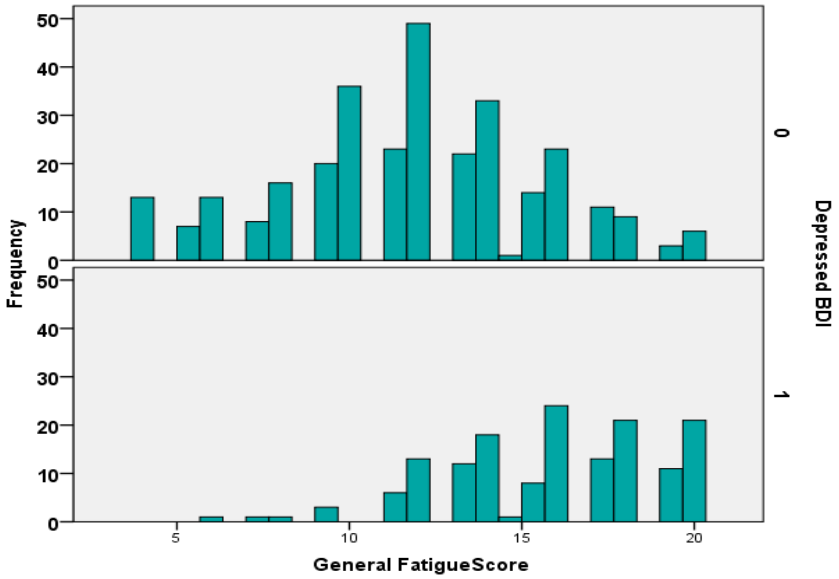


Figure 25: General fatigue distribution in patients with high and normal BDI-II scores (1 = high)



7.4.4 Relationship between BDI-II, PHQ, and MFI (GF, PF, MF) SF-36

GF, PF, and MF scores were all higher in patients with a BDI-II ≥ 16 compared to those with lower BDI-II scores. The same was true for patients with PHQ-9 ≥ 8 compared to those with lower scores (Table 31).

Table 31: Comparison between BDI-II, PHQ-9, and fatigue

	BDI-II <16	BDI-II ≥ 16	p-value	PHQ-9 <8	PHQ-9 ≥ 8	p-value
MFI						
GF	12 (IQR5)	16 (IQR4)	<0.001	12 (IQR5)	16 (IQR5)	<0.001
PF	14 (IQR6)	17 (IQR4)	<0.001	14 (IQR6)	17 (IQR5)	<0.001
MF	7 (IQR6)	13 (IQR5)	<0.001	7 (IQR6)	12 (IQR6)	<0.001
SF-36	57.2 ± 20.5	30.5 ± 20.5	<0.001	57.4 ± 20.1	32.1 ± 22.7	<0.001

7.4.5 Fatigue Scores as Predictors of High Depressive Symptoms

7.4.5.1 BDI-II ≥16

We first explored general factors predicting high BDI-II scores (≥16) in this group of patients, including factors likely on clinical grounds to have an influence. Factors considered were: age, gender, ethnicity, marital status, comorbidities, including heart disease, stroke, amputation, diabetes, and cancer, dialysis vintage, anuria, and past history of depression (Table 32).

Table 32: Baseline predictors of BDI-II ≥16 in logistic regression model

n=464	B	SE	P value	Odds ratio
Age (years)	-.026	.006	.000	.975
Gender (male)	.332	.201	.098	1.394
Ethnicity (non-white)	-.086	.216	.691	.918
Married/partner	.091	.193	.636	1.096
Heart disease	.210	.208	.313	1.234
Stroke	.316	.343	.357	1.372
Amputation	-.229	.544	.674	.796
Diabetes	.002	.215	.993	1.002
Cancer	.673	.302	.026	1.960
Dialysis vintage (years)	-.001	.002	.644	.999
Anuria	.568	.199	.004	1.764
Past history of depression	1.579	.207	.000	4.848
Constant	-.104	.457	.820	.901

The best logistic regression model of BDI-II ≥16, including the factors above, was highly significant ($p<0.001$) but explained only 19.9% of variation. Age, cancer, anuria, and past history of depression were significant predictors, and gender approached significance (Table 32). We then in turn added the fatigue subdomain scores to a model containing these significant predictors. Because of the high correlation between fatigue subdomains, we built individual models for each subdomain. The best model included MF. The model explained 48% of the variation in BDI-II ≥16. Significant predictors in this model were age and past history of

depression (Table 33). Cancer, gender, and anuria were not significant in this model, suggesting their effects in the previous model (Table 33) may have been mediated by fatigue. The models including GF and PF explained 41.5% and 34.7% of the variation, respectively.

Table 33: Logistic regression of predictors of BDI-II ≥16 including baseline factors and mental fatigue score

n=464	B	SE	P value	Odds ratio
Age (years)	-.025	.008	.002	.975
Gender (male)	.399	.281	.156	1.491
Cancer	.230	.461	.617	1.259
Anuria	.345	.259	.184	1.412
Past history of depression	1.168	.292	.000	3.216
Mental fatigue score	.337	.036	.000	1.400
Constant	-3.332	.665	.000	.036

In a smaller group of patients with available CRP measurements we built an additional model using the same factors and including CRP >5mg/l. The best model included in this factor explained 50% of variation in BDI-II ≥16 (Table 34). Significant predictors in this model were: age, past history of depression, MF, and CRP >5mg/l. Similarly to the previous model, cancer, gender, and anuria were not significant in this model, suggesting their effects in the original model (Table 33) may have been mediated by fatigue. Models including GF and PF explained 42.2% and 35.2% of the variation, respectively.

Table 34: Logistic regression of predictors of BDI-II ≥16 including baseline factors and mental fatigue score and high CRP

n=114	B	SE	P value	Odds ratio
Age (years)	-.025	.008	.001	.975
Gender (male)	.405	.284	.153	1.500
Cancer	.220	.459	.632	1.246
Anuria	.280	.263	.287	1.324
Past history of depression	1.226	.298	.000	3.408
Mental fatigue score	.342	.037	.000	1.408
CPR >5mg/l	-.784	.296	.008	.457
Constant	-2.768	.691	.000	.063

7.4.5.2 PHQ-9 ≥8

We first explored general factors predicting high PHQ-9 (≥8) in this group of patients, including factors likely on clinical grounds to have an influence. Factors considered were: age, gender, ethnicity, marital status, vintage, comorbidities, including heart disease, stroke, amputation, diabetes, and cancer, anuria, and past history of depression (Table 35).

Patients with PHQ-9 ≥8 were younger (60 ± 16 vs 66 ± 16.4), with greater anuria (53%), and with a past history of depression (44%). There were no differences in gender, ethnicity, dialysis vintage, comorbidities (heart disease, stroke, amputation of limb, and diabetes), and marital status.

Table 35: Predictors of fatigue scores with PHQ-9 ≥8

n=464	B	SE	P value	Odds ratio
Age (years)	-.021	.006	.000	.979
Gender (male)	-.025	.189	.893	.975
Ethnicity (non-white)	-.423	.206	.040	.655
Married/partner	.056	.185	.762	1.058
Dialysis vintage	.000	.002	.838	1.000
Heart disease	.284	.199	.153	1.328
Stroke	.082	.338	.808	1.086
Amputation of limbs	.558	.507	.271	1.747
Diabetes	.238	.203	.240	1.269
Cancer	.735	.292	.012	2.086
Anuria	.682	.190	.000	1.978
Past history of depression	1.310	.202	.000	3.706
Constant	.100	.443	.822	1.105

The best logistic regression model of PHQ-9 ≥8 including these factors was highly significant ($p<0.001$) but explained only 19% of variation. Age, ethnicity, cancer, anuria, and past history of depression were significant predictors.

We then in turn added the fatigue subdomain scores to a model containing these significant predictors. Because of the high correlation between fatigue subdomains we built individual models for each subdomain. The best model included MF. The model explained 42.3% of the variation in PHQ-9 ≥8. Significant predictors in this model were: age, past history of depression, and MF (Table 36). Cancer was not significant in this model and ethnicity and anuria were less significant than in the

previous model (Table 35). This suggests the effects of these parameters on PHQ-9 ≥8 were mediated by fatigue. The models including GF and PF explained 38.7% and 34.2%, respectively.

Table 36: Logistic regression for predictors of PHQ-9 ≥8 including MF score

n=464	B	SE	P value	Odds ratio
Age (years)	-.020	.007	.007	.980
Ethnicity (non-white)	-.426	.255	.095	.653
Cancer	.081	.428	.849	1.085
Anuria	.414	.241	.085	1.512
Past history of depression	.814	.283	.004	2.257
Mental fatigue score	.298	.033	.000	1.347
Constant	-2.427	.575	.000	.088

In a smaller group of patients with available CRP measurements we built an additional model using the same factors and including CRP >5mg/l. The best model included in this factor explained 43% of variation in PHQ-9 ≥8 (Table 37). Significant predictors in this model were: age, past history of depression, and MF. CRP >5mg/l tended towards significance. The difference between its predictive power for BDI-II ≥16 is likely to be due to there being more somatic domains in the BDI-II score.

Table 37: Logistic regression of predictors of PHQ-9 ≥8 including MF score and high CRP (>5 mg/l)

n=114	B	SE	P value	Odds ratio
Age (years)	-.021	.008	.006	.980
Ethnicity (non-white)	-.394	.257	.125	.674
Cancer	.072	.426	.867	1.074
Anuria	.375	.242	.122	1.455
Past history of depression	.832	.285	.004	2.298
Mental fatigue score	.302	.033	.000	1.352
CPR > 5mg/l	.513	.275	.063	1.670
Constant	-2.567	.583	.000	.077

7.4.6 Comparison between MINI diagnosis and MFI

Out of the cohort of 464, 45 patients had a psychiatric interview. 28 had a diagnosis of MDD with the MINI. The only MFI subdomain that approached being significantly higher in patients with a diagnosis of MDD than in patients without was MF (Table 38).

Table 38: Relationship between MINI diagnosis and MFI subdomain scores

	MINI	N	Median	IQR	P value
General fatigue	**No MDD**	17	15	5	NS
	MDD	28	16	6	
Physical fatigue	**No MDD**	17	16	5	NS
	MDD	28	18	4	
Mental fatigue	**No MDD**	17	12	7	0.085
	MDD	28	13	4	

7.4.7 Relationship between MFI and Post dialysis recovery time

In this group of 464 patients, post-dialysis recovery time was distributed into five groups as follows: <1hr (24%), 1-4hrs (27%), 4-8hrs (15%), 8-12hrs (11%), and >12hrs (23%).

MFI subdomain scores differed in relation to dialysis recovery time. The biggest difference was between patients who recovered quickly (<1hr) and patients with all other categories of recovery time. This is represented in Table 39.

Table 39: Median values of GF, PF, and MF by post-dialysis recovery time.

P values represent differences in median values by the Kruskal Wallis test

	<1hr	1-4 hrs	4-8 hrs	8-12 hrs	>12 hrs	p value
GF	10 (IQR6)	13 (IQR5)	14 (IQR6)	15 (IQR5)	14 (IQR5)	<0.001
PF	13 (IQR6)	15 (IQR6)	14 (IQR7)	16 (IQR5)	17 (IQR5)	<0.001
MF	8 (IQR7)	10 (IQR7)	8 (IQR7)	8 (IQR7)	10 (IQR5)	<0.002

We have previously found (Chapter 5) that centre, gender, past history of depression, living with partner, and BDI-II score were significant independent predictors of prolonged recovery time (>1 hrs).

We built logistic regression models to predict prolonged recovery time (>1hr) including the above factors and in turn adding MFI subdomains (GF, PF, and MF). The best model (model 1), controlled for centre, gender, and living with partner, was that including GF, which was highly predictive of prolonged recovery time. Past history of depression was also significant in this model. The BDI-II score was not significant. The model explained 25.2% of the variation (Table 40).

In the model of the same baseline factors including PF (model 2), both past history of depression and BDI-II score were predictive of prolonged recovery time. The PF score was highly predictive. However, the model explained only 17.8% of the variation (Table 40).

In the model using the same baseline factors and MF (model 3), past history of depression and BDI-II score were also predictive of prolonged recovery time, while MF was not. However, the model explained only 15.5% of the variation (Table 40).

This implies that post-dialysis recovery has both physical and mental components in relation to fatigue and that the physical component plays the greater role.

Table 40: Logistic regression models of predictors of prolonged recovery time

	B	SE	P value	Odds ratio
All models controlled for centre, gender, living with partner				
Model 1. Nagelkerke R-square 0.252				
Past history of depression	.820	.401	.041	2.270
BDI-II score	.014	.0167	.401	1.014
General fatigue score	.224	.041	.000	1.251
Model 2. Nagelkerke R-square 0.178				
Past history of depression	.876	.390	.025	2.402
BDI-II score	.045	.017	.007	1.406
Physical fatigue score	.087	.032	.006	1.091
Model 3. Nagelkerke R-square 0.155				
Past history of depression	.939	.387	.015	2.558
BDI-II score	.062	.018	.001	1.064
Mental fatigue score	.015	.037	.680	1.020

7.4.8 Fatigue and Survival Prediction

A number of Cox models were built to model survival in this cohort of 464 patients. The baseline model (Table 41) included those parameters pragmatically chosen as being likely to influence survival. In subsequent models, we added in turn each MFI subdomain. GF and MF were not significant in the model; however, PF was a highly significant predictor of mortality (HR 1.097: p=0.008). This implies that for every additional point increase on the PF subdomain scale, there is a 10% increase in

mortality risk. A further set of models were produced adding depression screening parameters to the baseline model, including MFI subdomains. None of these parameters (BDI-II score, BDI-II ≥16, PHQ-9 score, PHQ-9 ≥8, and PHQ-9 ≥10) predicted mortality in these models.

Table 41: Baseline Cox regression model predicting survival (n=464)

	B	SE	P value	Hazard ratio
Age (years)	.032	.010	.001	1.032
Gender (male)	.075	.251	.764	1.078
Ethnicity (white)	.608	.301	.043	1.837
Heart disease	.463	.230	.044	1.588
Stroke	-.095	.429	.825	.909
Amputation	.841	.472	.075	2.318
Diabetes	.645	.255	.011	1.907
Cancer	-.432	.436	.322	.649
Anuria	.442	.248	.074	1.556
Kt/V	-.641	.392	.103	.527
Albumin (g/l)	-.110	.027	.000	.896

7.5 Effect of Treatment with Sertraline and Placebo on the Measures of Fatigue during the Trial Phase

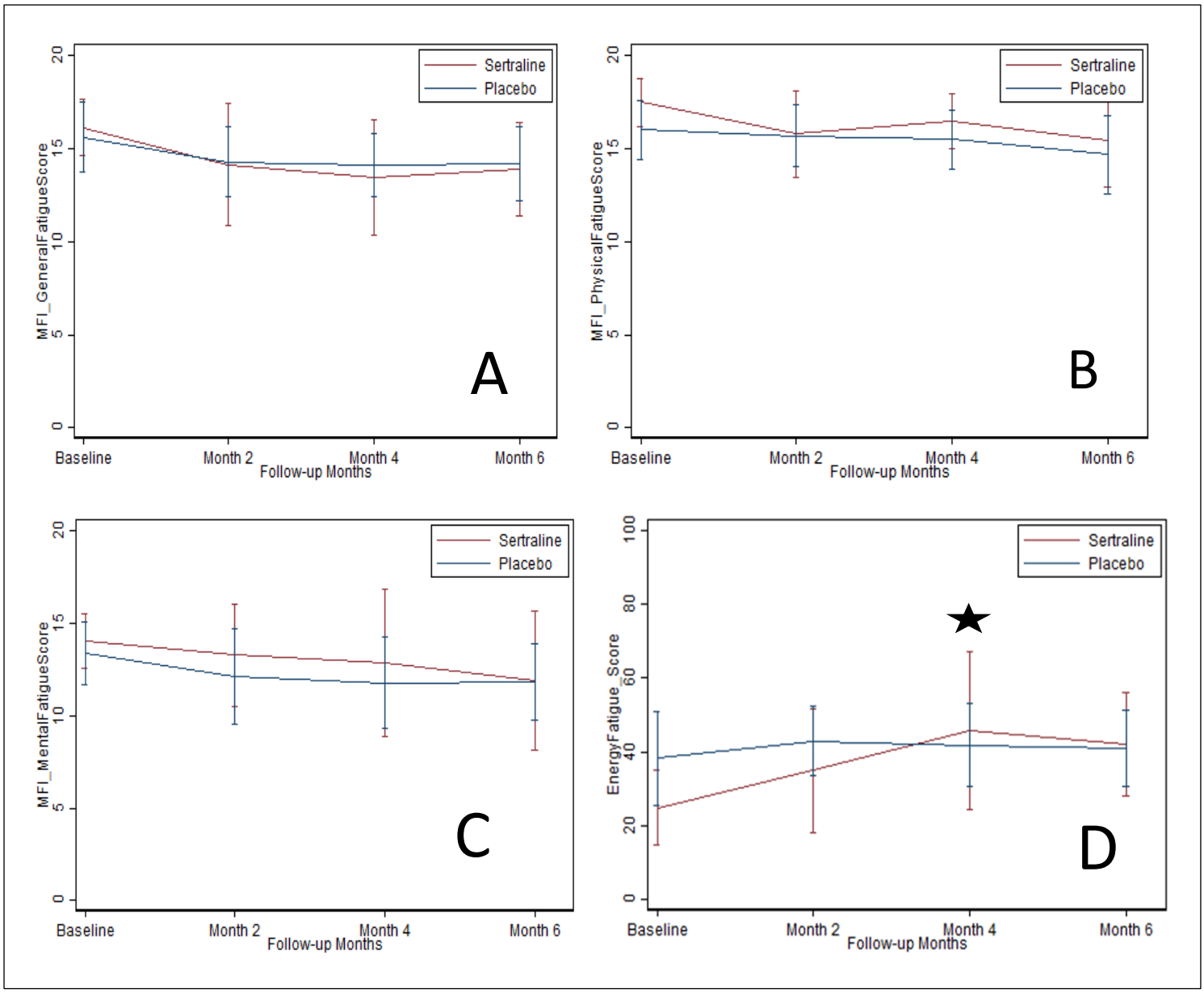
The collection of the fatigue data only commenced some way into the screening study, so the numbers of patients in the trial phase of the study with baseline fatigue scores was 23 compared with 30 for the depression scores (see Chapters 5 and 6). The numbers in each treatment group were: sertraline: 11 at baseline, eight at two months, seven at four months, and seven at six months; and placebo: 12 at baseline, 11 at two months, 11 at three months, and 10 at six months.

The changes in fatigue scores during the trial phase are shown in Figure 26. There were no significant changes in any of the MFI subdomains – general, physical, and mental (panels A-C in Figure 26). However, in the energy/fatigue subdomain of the SF-36 there was a significant increase in the score – representing improvement – between baseline and four months in the sertraline group, but no change in the placebo group. This is represented in panel D in Figure 26 and also in Table 42, which compares mean differences in this score between baseline and two, four, and six months in the sertraline and placebo groups.

Table 42: SF-36 score difference at two, four, and six months (sertraline vs placebo)

	Sertraline	**Placebo**	**p-value**
2 months	-15.6 ± 29.8 n=8	-4.6 ± 24.5 n=11	NS
4 months	-24.3 ± 32.3 n=7	-3.3 ± 15.7 n=11	0.04
6 months	-20.7 ± 27.3 n=7	-6.5 ± 20.4 n=10	NS

Figure 26 MFI (GF, PF, and MF) SF-36 over six months



★ Significant change between baseline and months 4: P=0.04

7.6 Discussion

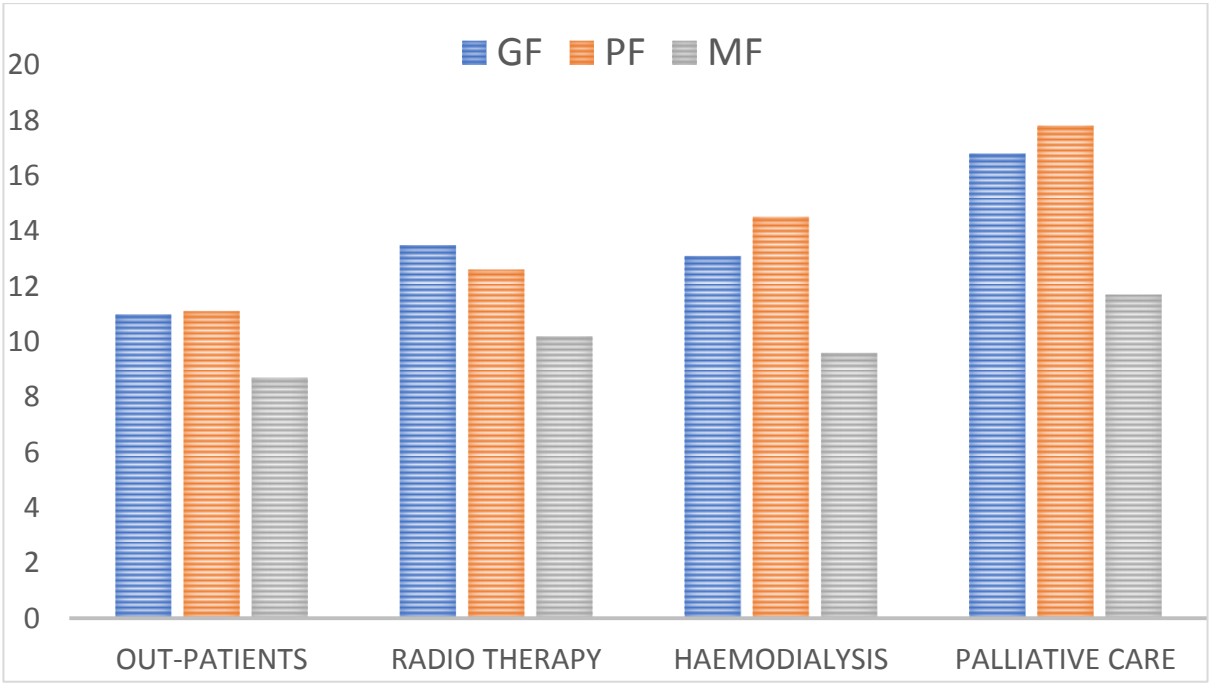
Fatigue is a psychosomatic syndrome that is also common in chronic disease, and a key area of overlap with depression in patients receiving HD. Previous studies suggested that the point prevalence of fatigue in end-stage renal disease ranges from 42% to 89% according to the treatment modality and assessment instruments (226). It was not possible in our study to establish the proportion/prevalence of fatigue in HD by using the MFI because there is no validated cut-off point.

Fatigue levels in this HD population are strikingly high in all domains – general, mental, and physical – are similar to those found in oncology patients. Hagelin et al. (459) looked at fatigue using the MFI scale in different groups of oncology patients (outpatient, radio therapy, and palliative care). We compared fatigue levels in these oncology patients with those in our HD patients. Mean fatigue levels in the general and physical domains were similar in HD and those receiving radiotherapy, though scores in the mental domain were slightly lower (Table 43 and Figure 27).

Table 43: Comparison between GF, PF, and MF in oncology and HD patients (mean, SD)

MFI	Outpatients		HD		Radiotherapy		Palliative care	
	m	sd	m	sd	m	sd	m	sd
GF	11.0	4.7	13.1	4.0	13.5	5.1	16.8	3.7
PF	11.1	5.1	14.5	4.1	12.6	5.0	17.8	3.2
MF	8.7	3.8	9.6	4.4	10.2	4.5	11.7	4.3

Figure 27 Comparison between GF, PF, and MF in oncology and HD patients



Females tended to have higher scores on the GF subdomain than males. This corresponds with previous literature (331), although the previous study reports related to total fatigue score rather than different fatigue domains. There were no gender differences in the PF and MF subdomains and no ethnicity differences in any subdomain corresponding with previous literature (314).

Previous studies have demonstrated that increasing age and weight were associated with higher fatigue levels among patients on dialysis (315, 330). Contrary to this, though levels of GF and PF were higher with increasing weight, we found a weak inverse correlation between GF and age. The reasons for this are unclear. MF did not correlate with either age or weight. Similar to previous studies, we found no relationship between any fatigue subdomain and routine biochemical, haematological, and haemodynamic parameters, nor with dialysis adequacy (38, 314, 331, 334). However, the presence of comorbidity was associated with fatigue. GF and PF were higher in patients with heart disease (334) and diabetes, but not in those with stroke, amputation, and cancer. The PF score also was higher in those with inflammation (CRP >5mg/l). None of these conditions affected MF scores.

Previous studies found that fatigue was significantly correlated with depression in haemodialysis patients (314, 335, 460). Our studies confirm this. There were very strong correlations between BDI-II and PHQ-9 scores and all MFI subdomains (GF, PF, and MF). The best correlation was between GF with BDI-II and PHQ-9. These correlations are unlikely to solely represent artefacts from overlapping item content between the MFI and BDI-II as only two or perhaps three out of a total 21 BDI-II items measure fatigue symptoms and only one item in the PHQ-9. This suggests that the symptom of fatigue may be a true consequence of low mood.

Fatigue scores in all subdomains (GF, PF, and MF) were also greater in patients with BDI-II ≥16 than those with lower scores. The best predictor of high depression symptoms (BDI-II ≥16) was MF compared to GF and PF. There were similar findings in relation to PHQ-9 ≥8. There was also a trend to higher MF, but not GF and PF, scores in patients with a MINI diagnosis of MDD compared with those with no MDD. Taken together, these findings imply that high depressive symptoms, and indeed the diagnosis of MDD, relate more strongly to cognitive rather than somatic factors.

However, the relationship between fatigue and depression is undoubtedly very complex. Depression may manifest as feelings of fatigue, tiredness, and lack of energy. Depression has also been shown to correlate strongly with overall symptom burden and severity, including fatigue, in dialysis patients (382). In keeping with this was the difference in distributions of MF and both GF and PF in patients with BDI-II ≥16. MF is normally distributed in these patients, while both GF and PF show a highly skewed distribution with many patients having very high GF and PF scores. These differences in distribution suggest that both PF and MF are major contributants to high depressive symptom scores.

Throughout the RCT study we found very little difference between fatigue scores in those sertraline and placebo groups. In fact, there was little change in scores in either group throughout the study. The only significant change was an improvement in the energy/fatigue subdomain scores of the SF-36 between basline and three months. Whether this represents a genuine treatment effect, a chance finding, or perhaps an effect of the higher drop-out rate in the sertraline group, is not known. The dissociation between the changes in depression scores (BDI-II and MADRS – see Chapter 6) and fatigue scores during the trial phase is striking and suggests that the change in depression scores during the study was more related to changes in cognitive than somatic components. There are a number of caveats. Sertraline might not be the drug of chocice in improving fatigue symtoms, especially in HD patients. Previous research has suggested that

monotherapeutic antidepressant agents that increase NE, DA, or both, particularly in pathways associated with physical and mental fatigue, may be preferable for patients in whom symptoms of fatigue and lack of energy are prominent (426). Fatigue can also be a side effect of antidepressant treatment, although this happens more typically with sedating antidepressants, and sertraline does not belong to this group. However, even activating agents may be associated with fatigue as a side effect resulting from disruption of sleep architecture, with sleepiness and fatigue being the consequence of poor sleep quality and sleep deprivation (419).

Fatigue may also be a residual symptom of MDD. Pharmacological augmentation of antidepressant therapy has shown promise in the treatment of residual fatigue (432, 435). Studies in patients on maintenance antidepressant therapy showed that complaints of physical tiredness were related primarily to residual depression (420). The approch to target this is to augment a SSRI with bupropion, an NE and DA reuptake inhibitor (421, 422). Bupropion can increase both DA and NE in the frontal cortex, as well as in other areas of the brain (423, 424). Bupropion may be effective in improving energy and fatigue, as well as executive function (425).

Our study showed that there was a significant difference between all MFI subdomain scores and dialysis recovery time. The biggest differences were between patients who recovered promptly (<1hr) and those who took longer. It seems that both physical and mental components of post-dialysis fatigue with the physical component play the greatest role. These factors seem to take precedence in predicting post-dialysis recovery time over others, including demographic factors, comorbidity, laboratory parameters, and dialysis adequacy, as has been previously described (326).

We also found that PF was highly predictive of mortality. There was no impact of any parameters related to depressive symptomatology on the prediction of mortality in these models. This suggests that the previously reported effects of depression on mortality (461) may be mediated by PF.

We have thus addressed all the aims of the study, except that we have not defined the prevalence of fatigue in our haemodialysis cohort. This is because there is no validated cut-off point for the MFI. Neither was it possible to establish whether there was a difference between sertraline and placebo on the measures of fatigue over the period of the study due to the small numbers recruited.

7.7 Concluding Remarks

Fatigue is a common and burdensome consequence of advanced kidney disease and is associated with depression symptoms, past history of depression, longer dialysis recovery, and higher mortality. Inflammation also appears to be associated with greater fatigue.

Depression scores are strongly associated with all fatigue subscales – general, mental, and physical. This emphasises the strong overlap of depressive symptoms and fatigue in this population, which complicates the diagnosis of depression, its management, as well as the management of fatigue. Though the relationship is complex, the mental component of fatigue seems to have a closer relationship to depression than the physical component, while the physical component seems to be a stronger predictor of post-dialysis recovery and mortality.

There was a slight improvement in the energy/fatigue subscale of the SF-36 on sertraline but little or no effect in relation to any of the MFI subscales. The dissociation between changes in depression scores and changes in fatigue scores during the RCT adds to the complexity of the relationship between fatigue and depression. This suggests that the improvements in depression scores during the RCT were mediated by elements not related to fatigue. Other interpretations include the possibility that sertraline is not the drug of choice for alleviating the symptom of fatigue in the context of depression in haemodialysis patients. Fatigue may even feature as a side effect of sertraline.

Further work in this area should focus on better defining physical and mental components of fatigue. Since fatigue is the major overlapping symptom of uraemia and depression, this might facilitate the diagnosis of depression in this condition. It might also guide the search for interventions aimed at managing fatigue in its own right.

Chapter 8

Progression of Depressive Symptoms in HD Patients on Antidepressants

8.1 Introduction

During screening in the ASSertID study, one of the major findings was that a large proportion (about 30%) of the HD cohort was already on antidepressant medication. Most of these patients appeared to have ongoing depressive symptoms but had been excluded from the interventional phase of the study because current antidepressant therapy was one of the exclusion criteria. It was felt to be important to follow up this cohort of patients taking antidepressants to ascertain the natural history of this phenomenon. Hence, a further study was devised to follow up these patients 6-15 months following their initial screening. We planned to repeat baseline screening tests, and to carry out a full clinical and psychiatric history, including a formal diagnostic interview to determine whether patients had major depressive disorder. Beliefs about antidepressant medication and adherence to this therapy would be ascertained using validated questionnaires.

The study was sponsored by East and North Herts NHS Trust, REC reference number 14/EE/0143. Copies of the approval letters are shown in the appendix 1.

8.2 Aims and Objectives

8.2.1 Primary Aim

To determine the prevalence of diagnosed MDD according to the MINI in this cohort of HD patients who had been taking antidepressant therapy at the ASSertID screening interview.

8.2.2 Secondary Aims

1) To describe the changes in depressive symptoms in these patients 6-15 months following initial screening, according to the BDI-II and PHQ-9 screening instruments.
2) To describe the relationship between scores in the MFI and diagnosed depression by the MINI.

3) To describe the use of antidepressant therapy (type, dosage) during the 6-15 months following the ASSertID screening interview.

4) To examine patient beliefs and attitudes about and adherence to antidepressant treatment according to the MARS (462), the Beliefs about Medicines Questionnaire – specific to antidepressants (BMQ) (463) (please see the questionnaires for details).

5) To describe the setting in which antidepressant medication was initiated (primary care, nephrology, psychiatry), and estimate the degree to which subsequent management was consonant with relevant NICE guidelines (150).

8.3 Questionnaires

8.3.1 Medication Adherence Rating Scale (MARS)

The Medication Adherence Rating Scale (MARS) was developed from Morisky et al.'s (464) Medication Adherence Questionnaire (MAQ). The MARS is a quick, non-intrusive measure of medication adherence. It is a ten-item self-report measure of medication adherence in psychosis. It evaluates both attitudes about medications and actual medication-taking behaviour. Compliance is considered if there is a No response for questions 1-6 and 9-10, and a Yes response for questions 7 and 8. Scoring requires some interpretation: a Yes response does not necessarily indicate a positive attitude or behaviour. Items in the MARS about attitude to medication may be informative to clinicians identifying barriers to adherence in individual cases, but do not appear to be valuable in predicting adherence behaviour over a large sample. The MARS total score reproduced the expected relationships of higher adherence with more insight into the need for medication, and higher adherence with less psychopathology. Its reliability is adequate, but validity appears only moderate/weak. The internal consistency of the MARS was moderate (alpha=0.60), but lower than the value produced by Thompson et al. (465) during the original development of the scale (alpha=0.75). This may not represent a weakness of the scale, however, as there are reasons to expect a reduced alpha value for scales with the format of the MARS, notably the binary response choice, a small number of items, and scale multidimensionality.

8.3.2 Beliefs about Medicines Questionnaire (BMQ)

The BMQ was validated for use in the chronic illness groups studied (466). The BMQ comprises two sections: BMQ-Specific, which assesses representations of medication prescribed for personal use, and the BMQ-General, which assesses beliefs about medicines in general. The test items were derived from themes identified in published studies and from interviews with chronically ill patients. The Principal Component Analysis (PCA) of the test items resulted in a logically coherent, 18-item, four-factor structure that was stable across various illness groups. The BMQ-Specific comprises two five-item factors assessing beliefs about the necessity of prescribed medication (Specific-Necessity) and concerns about prescribed medication based on beliefs about the danger of dependence and long-term toxicity and the disruptive effects of medication (Specific-Concerns). The BMQ-General comprises two four-item factors assessing beliefs that medicines are harmful, addictive poisons that should not be taken continuously (General-Horn) and that medicine are overused by doctors (General-Overuse). The two sections of the BMQ can be used in combination or separately.

The BMQ-Specific comprises two five-item scales assessing patients' beliefs about the necessity of prescribed medication for controlling their illness and their concerns about the potential adverse consequences of taking it. Examples of items from the necessity scale include: 'My health, at present, depends on my medicines' and 'My medicines protect me from becoming worse'. Examples of items from the concerns scale include: 'I sometimes worry about the long-term effects of my medicines' and 'I sometimes worry about becoming too dependent on my medicines'.

In assigning the scores to medication beliefs, participants indicate their degree of agreement with each individual statement about medicines on a five-point Likert scale, ranging from 1 (strongly disagree) to 5 (strongly agree). Scores obtained for the individual items within each scale are summed to give a scale score. The total scores for the necessity and concerns scales range from 5 to 25. Therefore, it is possible to differentiate between patients on the basis of their beliefs about the necessity of their medication and their concerns about taking it. Scores can be interpreted in two ways: as a continuous scale in which higher scores indicate stronger beliefs in the concepts represented by the scale, or by dichotomising at the scale midpoint. The latter method is a convenient way of categorising respondents according to the strength of their views about medication. However, the continuous scale is used in statistical analyses as this provides richer information that is lost when the scale is dichotomised (467). Beliefs about medicines were related to reported adherence: higher necessity scores correlated with higher reported adherence (r=50.21,

n=5324, p<0.01) and higher concerns correlated with lower reported adherence (r=50.33, n=5324, p<0.01).

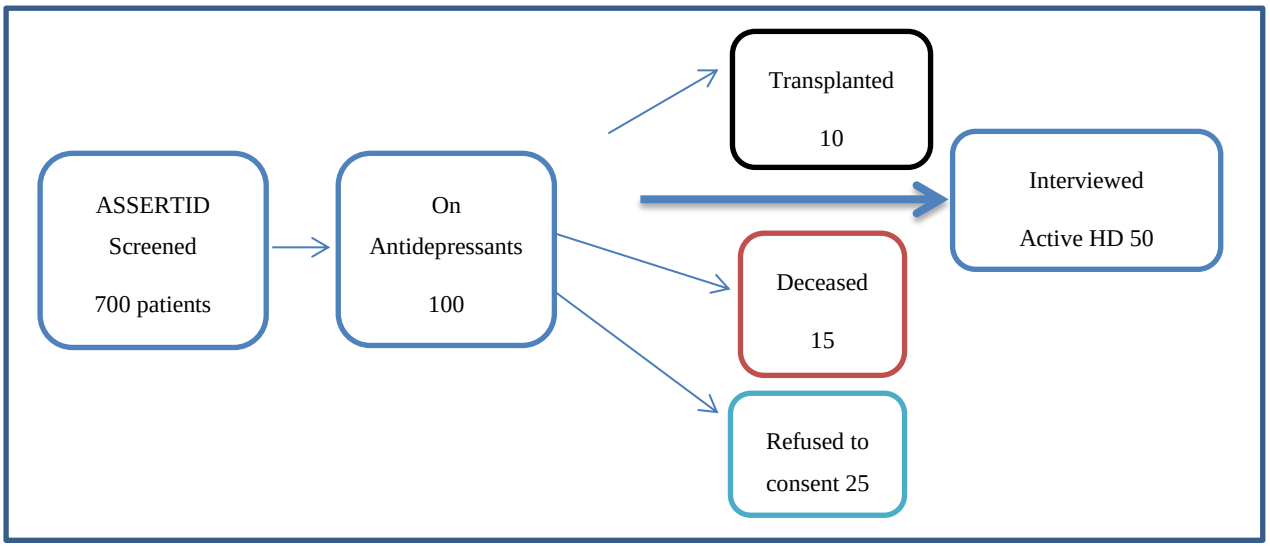
8.4 Design and Setting

The study combined prospective and retrospective observations of a cohort of ESRD patients who were initially screened for the ASSertID study. It was carried out at the renal centres at the following NHS Trusts: Lister Hospital Stevenage, University Hospitals Birmingham, Royal Free Hospital London, Southend University Hospital, and Basildon and Thurrock University Hospitals.

8.4.1 Sample

We aimed to study those patients who were taking antidepressant medication at the ASSertID screening interview. At approximately 6-15 months following that initial screening, we re-approached members of this group and invited them to take part in this further study; anticipated numbers were as shown in Figure 28. The numbers were anticipated from the primary analysis of the data and the decision about the study, and ethical approval was granted before the end of the ASSertID study.

Figure 28 Study diagram (anticipated numbers)



8.4.2 Inclusion Criteria

- Patients who were screened by BDI-II, PHQ-9, and/or MFI in the ASSertID study and were taking an antidepressant at the time of the screening interview.

8.4.3 Exclusion Criteria

- Patients who had other known psychiatric comorbidity, including substance dependency, psychosis, personality disorder, dementia, or panic disorder, with the exception of other anxiety disorders (e.g. Generalised Anxiety Disorder or Obsessive Compulsive Disorder).
- Patients who lacked the mental capacity to consent to participate.
- Patients who refused to consent to their GP being informed of the outcome of psychiatric assessment.

8.5 Procedures

8.5.1 Identification of the Participant

Patients were identified from the ASSertID database, the eligibility criteria were applied, and a suitability list was compiled. We used the same Patient Identification Number as the ASSertID study to enable us to isolate this data.

8.5.2 Approach to Participants

Patients were approached by the research psychiatrist during one of their routine dialysis sessions and asked if they were interested in taking part in a follow-up study to the ASSertID study. They were provided with a participant information sheet. The study psychiatrist explained the study to the patient and went through the participant information leaflet. He emphasised the intention to use some of the data from the previous ASSertID project in the new study. In addition, he explained that new data was collected as outlined above, which entailed seeing the research psychiatrist again and possibly a qualitative researcher. The research psychiatrist gave each patient an opportunity to ask questions and explained that they were under no obligation to enter the study. The research psychiatrist reinforced that the patient could withdraw at any time during the study, without having to give a reason. If the patient expressed an interest in participating, a follow-up appointment with the study psychiatrist was arranged at a mutually convenient time. The research psychiatrist gave the patient his contact details and it was made clear to the patient that they were perfectly free to change their mind about attending the appointment at any time.

8.5.3 Informed Consent and Interview with the Study Psychiatrist

At the follow-up appointment, the research psychiatrist repeated the information in the participant information leaflet and gave further opportunity for questions. He asked for written consent. Once written consent was received, the research psychiatrist carried out the medical and psychiatric assessment as well as administering the BDI-II, PHQ-9, MFI, MARS, and BMQ.

8.5.4 Data from the ASSERTID Study

We retrieved data from the ASSertID screening phase onto a study-specific case report form. Additional data was collected, including a diagnostic interview.

The following information was retrieved from the ASSertID database:

- BDI-II, MFI, and PHQ-9
- Demographics (date of birth, gender, ethnicity, marital status, and social class/education)
- Information on the primary renal disease, date of starting renal replacement therapy, and previous transplants and dates
- Past history and treatment of depression or anxiety diagnosed by GP or psychiatrist, or any other involvement with psychology or psychiatry services
- Social support – who they lived with
- Questions on comorbid problems, including: heart disease, stroke, amputation of limbs, diabetes, cancer, liver disease, lung disease, and any other medical conditions such as rheumatoid arthritis
- Haemoglobin, urea and electrolytes, serum albumin, calcium and phosphate, and Kt/V (most recent values)
- Estimated urine volume per day, dry weight, and height

8.5.5 New Data Collection

The research psychiatrist used hospital medical records (paper and computerised) to collect the following new data, repeating all the ASSertID screening data collection, including the administration of the BDI-II, PHQ-9, and MFI. That was in addition to:

- Full medical and psychiatric history
- Assessment including the MINI to identify the diagnosis of MDD
- Data on hospital admissions, change in comorbidities, medication, and blood results
- History of any psychotropic medications and primary prescriber
- Changes in clinical and social events, medication, and any additional psychological or psychiatric treatment that had taken place since screening
- Antidepressant adherence and beliefs using MARS and BMQ

8.5.6 Study Power

A pragmatic approach had to be taken for sampling in this study, since recruitment was planned to be opportunistic. It was planned to approach the whole cohort of patients who were taking antidepressants in the screening phase of the ASSertID study for consent to take part in this study. Anticipated numbers are showed in Figure 28.

8.5.7 Analysis

The following analysis was carried out:

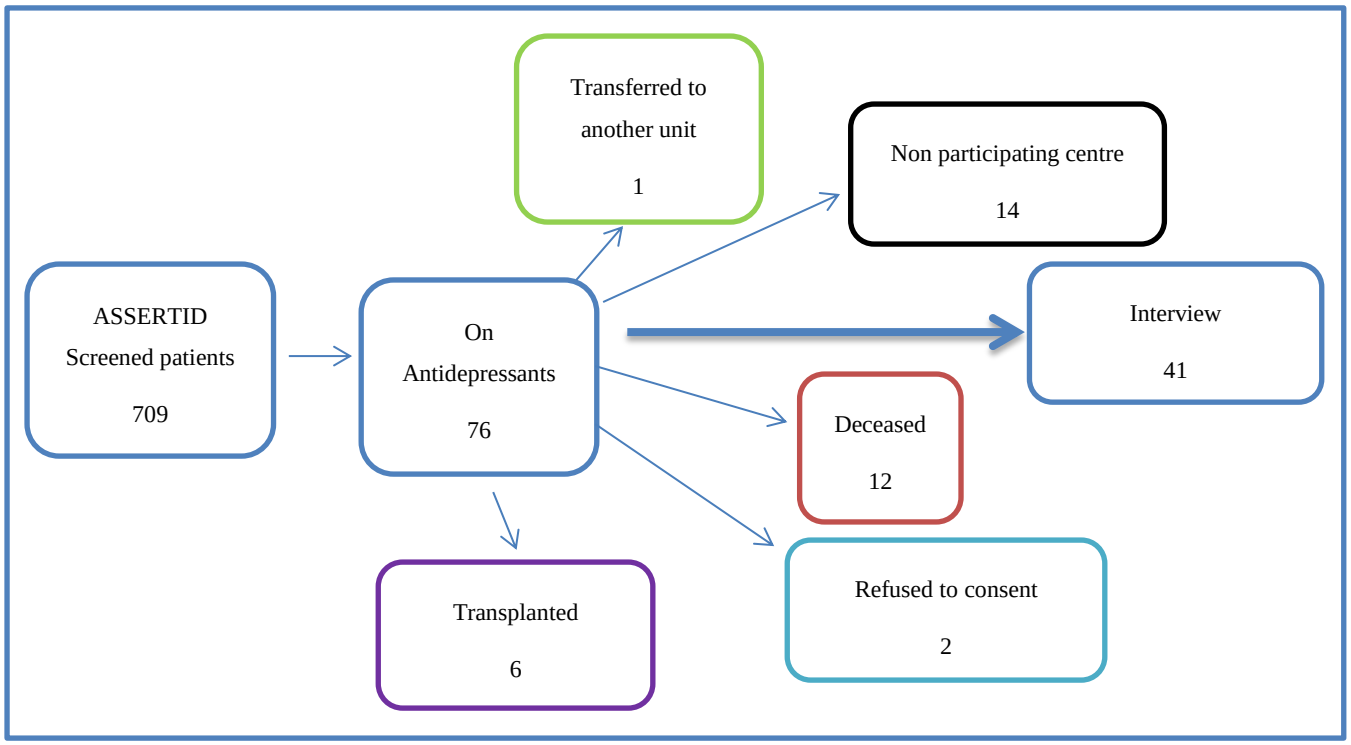
- The cohort was characterised in terms of the screening data and the additional data collected on the patients' history, using descriptive statistics.
- Change in the measured outcomes (BDI-II, PHQ9, and MFI) during follow-up assessed by paired t test or Wilcoxon signed rank test as appropriate.
- The relationship between the outcome of the psychiatric interview (i.e. currently depressed, recurrently depressed, past depression, and no depression) with:
    - Baseline and follow-up BDI, PHQ9, and MFI scores
    - Changes in these scores from baseline to follow-up
    - Findings in relation to beliefs about (BMQ) and adherence to antidepressant medication (MARS)

Assessment was carried out using ANOVA, t-tests, or the Mann-Witney test, as appropriate. Logistic regression analysis was carried out to determine predictors of current depression.

- We also examined whether patient beliefs (and other factors such as age, gender, length of time on antidepressants) predicted adherence, and whether adherence levels were related to changes in depression symptom scores
- The setting in which the antidepressant therapy was commenced (primary care, nephrology, psychiatry), and the degree to which subsequent management was consonant with relevant NICE guidelines was analysed descriptively.

Analyses were carried out using SPSS version 23.

Figure 29 Study design actual numbers



8.6 Results

41 patients were followed up a mean of 14±5 months following screening (Figure 29). 76 patients out of 709 screened were taking antidepressants at the time of screening. At the time of follow-up, six had been transplanted, one had been transferred to a renal unit in another trust, 12 had died, and two refused consent. We could not follow-up any of the patients at one non-participating centre [14] for logistics reasons. The demographic and clinical characteristics of these 41 patients are shown in Tables 44 and 45. Ten different antidepressant agents were being taken (Table 46), the most common being Citalopram (39%). The primary prescribers were as follows: GP 68%, nephrologist 22%, and psychiatrics 10%. There had been no review of antidepressant medication during follow-up in 16 patients (39%). Fourteen (34%) patients had their doses reviewed. A change in medications had occurred in 11 patients (27%). Most of these changes were instigated by the GPs. A significant proportion of patients (24%) were taking doses that might be considered sub-therapeutic or agents contraindicated or cautioned against in HD patients, e.g. dothiepin and Citalopram.

Table 44 Baseline parameters

Age (years)	**62 ± 16**
Gender (% male)	63
Ethnicity (% white)	73
Weight (kg)	81 ± 23
Pre-dialysis systolic BP (mmHg)	140 ± 27
Pre-dialysis diastolic BP (mmHg)	75 ± 17
Marital status (%)	
Married/partner	49
Single	27
Divorced/separated	12
Widowed	12
Depression (%)	
Antidepressants	100
Psychological therapy	32
Previous ECT	2
BDI-II	26 (IQR 19)
PHQ-9	12 (IQR 9)
Comorbidity (%)	
Diabetes	42
Heart disease	37
Cancer	22
Amputation	5
Dialysis parameters	
Vintage (IQR) years	3.5 (4.7)
Kt/V	1.33 ± 0.31
Laboratory parameters	

Haemoglobin (g/l)	110 ± 13
Albumin (g/l)	39 ± 4.2
Calcium (mmol/l)	2.26 ± 0.26
Phosphate (mmol/l)	1.50 ± 0.48

Table 45 Follow-up parameters (n=41)

Mean follow-up (month)	**14 ± 5**
Events	
Life/social event (%)	20 (49%)
Clinical event (%)	19 (46%)
Depression screening	
BDI-II	21 (IQR 17)
PHQ-9	10.5 (IQR 10)
MFI scale	
General fatigue	9 (8.5)
Physical fatigue	10 (7)
Mental fatigue	8 (9)
Reduced activity	8 (9.5)
Reduced motivation	10 (7.5)
MINI diagnosis	
Current MDE	8 (20%)
Recurrent MDE	7 (17%)
Past MDE	20 (48%)
No MDE	6 (15%)
Primary prescriber	
GP	28 (68%)
Nephrologist	9 (22%)

Psychiatrist	4 (10%)
Medication review	
Antidepressant agents used	10
Dose change	14 (34%)
Medication change	11 (27%)
None	16 (39%)

Table 46 Name, frequency of prescription, and dose of used antidepressant

Antidepressant	Number of patients	Dose range
Citalopram	16 (39%)	10mg (2), 20mg (10), 30mg (3), 40mg (1)
Fluoxetine	9 (22%)	20mg (8), 40mg (1)
Sertraline	6 (15%)	50mg
Mirtazapine	2 (5%)	30mg
Venlafaxine	2 (5%)	225mg (1), 75mg (1)
Escitalopram	2 (5%)	10mg (1), 15mg (2)
Paroxetine	1 (2%)	10mg
Dothiepin	1 (2%)	100mg
Nortriptyline	1 (2%)	40mg
Duloxetine	1 (2%)	60mg

8.6.1 Comparison of Baseline and Follow-up Values

There were no significant differences between baseline and follow-up with respect to weight, pre-dialysis blood pressure, Kt/V, haemoglobin, albumin, and calcium and phosphate. Twenty patients had life events and 19 had clinical events during follow-up (Table 47). Fourteen of these patients had both life and clinical events.

Table 47 Descriptions of life and clinical events

Life event/patient	Clinical event/patient
Death of wife	Knee replacement
Father died	2 x hospital admissions – cardiac events
Wife diagnosed with brain tumour	Failure of kidney transplant
Dog died, **daughter hysterectomy**	Hip replacement
Divorce	Failure of kidney transplant
Wife diagnosed with dementia	Nephrectomy
Lost job – financial constrains	Angioplasty
Mother died	Prolonged admission in isolation ward
Wife had affair	Failure of fistula
Death of two dialysis friends	Multiple hospital admissions (11) with epilepsy
Neighbour died, sister relocated	Melanoma becoming worse
Family breakdown	Urology operation in hospital over Christmas
Stressful family event	HD changed to PD
Reduced family support	Cardiac event – Boxing Day
Death of wife	Psoriasis deteriorating
Death of grandchildren	Removal of transplanted kidney
Daughter developed breast cancer	Memory clinic?? Dementia
Husband died	Amputation
Son migrated	Fracture R arm (operation) Hip replacement
Divorce	

There was a significant reduction in BDII-II score over the course of the study (26 (IQR 19) to 21 (IQR 17): p=0.015). The change in the PHQ-9 score was not significant (12 (IQR 9) to 10.5 (IQR 10): p=0.091).

At screening, 30 patients had a BDI-II score ≥16, indicating high depressive symptoms. Of these, 22 remained with high depressive symptoms at follow-up while eight improved (BDI-II <16 at follow-up). Those who improved had lower BDI-II scores (23 (IQR 13) vs 32 (IQR 15): p= 0.006) at baseline, lower dialysis vintage (3.7 (IQR 3.10) vs 5.9 (IQR 4.2) years: p=0.035), and fewer were anuric (13% vs 55%: p=0.04). Age, gender, ethnicity, marital status, comorbidity, haematological and biochemical profile, and clinical events during follow-up did not differ.

Of the 11 with BDI-II <16 at baseline, five had increased their BDI-II score to ≥16 at follow-up. These tended to be younger, 61 ± 12 vs 68 ± 21 years, to have higher dialysis vintage (3.9 (14.6) vs 2.4 (IQR 1.4)) and higher baseline BDI-II score (10 (IQR 8) vs 7.5 (IQR 7)), though none of these changes was statistically significant. No differences in comorbid load were apparent. However, baseline serum albumin tended to be lower in those who deteriorated (32.6 ± 5.1 v 38.8 ± 1.6: p=0.051) and more patients in this group had experienced clinical events, including below-knee amputation and stroke during follow-up (80% vs 17%: p=0.036). There was also a tendency for patients who were married/partnered to be less likely to have depressive symptoms in relation to BDI-II (17% vs 80%: p= 0.036).

Although 27 of 41 patients (66%) either deteriorated or failed to improve during follow-up, only 11 changes in antidepressant prescription (27%) were made during that time.

8.6.2 Comparison of Patients with High and Low Depressive Symptoms at Follow-up

At follow-up, 27 patients had a BDI-II score ≥16. These patients were younger, but not significantly, than those with lower BDI-II scores. There were no other differences with respect to demographic, clinical, or biochemical parameters, except that those with high BDI-II scores tended to have experienced more clinical events during follow-up (Table 48). There were, however, significant differences between the median values of the all MFI domains in patients with high BDI-II scores than those with lower scores (Table 48). Patients with a high follow-up BDI-II score also had a significantly lower necessity score on the BMQ questionnaire. The best logistic regression model (Table 49) showed that general fatigue (p=0.038: odds ratio 1.25) was an

independent predictor of high BDI-II, as were clinical events during follow-up (p=0.028: odds ratio = 11.33), and log of dialysis vintage (p=0.026: odds ratio=48.72). Necessity score (p=0.110: odds ratio = 0.76) approached significance, while age and gender were not significant in this model. The model predicted 58% of the variation (Nagelkerke R square 0.579).

Table 48 Comparison of depressed (BDI-II ≥16) and non-depressed (BDI-II <16) at follow-up

	Depressed	Non-depressed	p-value
Numbers	27	14	
Age (years)	60 ± 15	67 ± 18	NS
% Male	56	79	NS
% Married/partner	41	64	NS
% Clinical events	58	29	0.079
% Life events	54	43	NS
% Heart disease	37	36	NS
% Diabetes	44	36	NS
% Cancer	26	14	NS
Dialysis vintage (years)	5.7 (4.7)	2.9 (2.3)	0.005
General fatigue	10 (8)	6 (5)	0.013
Physical fatigue	10 (7)	9 (5)	0.008
Mental fatigue	9 (8)	3 (6)	0.017
BDI-II (baseline)	28 (17)	17 (18)	0.002
PHQ-9 (baseline)	14.5 (7)	7.5 (8)	0.005
BMQ necessity score	12.2 ± 3	14.5 ± 2.8	0.022
BMQ concerns score	12.7 ± 2.8	13.3 ± 2.5	NS
MARS score	7.9 ± 1.5	8.6 ± 1.1	NS

Table 49 Logistic regression model of predictors of high BDI-II ≥16 at follow-up

	B	SE	p-value	Odds ratio
Clinical events	2.427	1.105	.028	11.33
BMQ necessity score	-.281	.175	.110	.76
Log dialysis vintage	3.886	1.751	.026	48.72
General fatigue score	.222	.107	.038	1.25
Constant	-5.196	4.001	.194	.006

8.6.3 Comparisons between BDI-II, PHQ-9, and PHQ-2 Scores in MINI Diagnostic Groups

There were no differences between patients subsequently diagnosed on the MINI with current, recurrent, past, and no depression with respect to any baseline parameter (Table 50). However, there were significant differences with respect to follow-up BDI-II, PHQ-9, and PHQ-2 scores, which tended to be higher in those with current or recurrent depression, though there were no overall differences on Kruskal-Wallis analysis (Table 50). There were no differences between these groups with respect to age, gender, marital status, the presence of comorbidities, clinical or life event, any measured biochemical parameter, MFI scores, beliefs about antidepressant medications (BMQ) scores, or adherence to (MARS) antidepressant medication scores (Table 50). A change of prescription during follow-up occurred in only four patients (27%) with current or recurrent MDD.

8.6.4 Comparison of Depressed and Non-depressed Groups at Follow-up

Fifteen patients had MDD (eight current and seven recurrent). Table 51 compares these patients with those 26 who were not depressed at follow-up (20 past depressed plus six never depressed). All 15 patients with current or recurrent MDE at follow-up were among the 27 whose BDI-II scores deteriorated or did not improve (56%). BDI-II, PHQ-9, and PHQ-2 scores were significantly higher in patients with MDD compared to those without. The only other differences

between these groups was a tendency for depressed patients to have a higher likelihood of having diabetes, and to have experienced one or more clinical events during follow-up (Table 51), though neither of these reached statistical significance. There were no differences with respect to MFI fatigue scores, BMQ scores, or MARS scores (Table 51).

Depression symptom scores were the only significant predictors of MDD in logistic regression analysis; for example, a model of BDI-II scores explained 35% of the variation (Nagelkerke R square = 0.350). PHQ-9 and PHQ-2 scores were also predictive, explaining 24% and 25%, respectively, of the variation.

Table 50 Differences between MINI diagnosis categories at baseline and follow-up

	MDD (MINI Diagnosis)				
	Current	Recurrent	Past	Never	
Number	8	7	20	6	
Baseline					
Age (years)	63 ± 11	58 ± 20	60 ± 17	73 ± 12	NS
% Male	75	43	65	67	NS
% Married/partner	63	29	45	67	NS
% Heart disease	63	29	30	33	NS
% Diabetes	63	57	25	50	NS
% Cancer	38	14	15	33	NS
Dialysis vintage (months)	5.2 (6.2)	5.7 (5.7)	4.3 (4.9)	3.1 (2.2)	NS
BDI-II baseline	32 (17)	18 (16)	26.5 (14)	14.5 (27)	NS
PHQ-9 baseline	12 (6)	9 (10)	12 (9)	7.5 (16)	NS
PHQ-2 baseline	3 (1)	2 (4)	3 (2)	1.5 (3.5)	NS
Follow-up					
% Clinical events	63	71	40	20	NS
% Life events	50	71	40	60	NS
General fatigue	9 (9)	9 (10)	11 (10)	6.5 (5)	NS

Physical fatigue	10 (10)	10 (7)	11 (8)	9 (4)	NS
Mental fatigue	9 (3)	8 (8)	8.5 (13)	3.5 (5)	NS
BDI-II – follow-up	28 (13)	27 (12)	16.5 (15)	11 (23)	0.006
PHQ-9 – follow-up	13 (7)	14 (5)	7.5 (6)	6.5 (13)	0.023
PHQ-2 – follow-up	3 (1)	2 (2)	2 (1.75)	0 (1.75)	0.019
BMQ (necessity)	11.4 ± 2.9	13.1 ± 3.1	13.2 ± 2.9	14.2 ± 3.8	NS
BMQ (concerns)	12.1 ± 2.5	12.7 ± 3.6	13.5 ± 2.6	12.3 ± 3.3	NS
MARS (adherence)	8.1 ± 1.5	7.4 ± 1.7	8.5 ± 1.4	8.2 ± 1.0	NS

Fifteen patients had current or recurrent depression. Table 51 compares these patients with those non-depressed. The only significant differences were in the depression symptom scores as might be predicted. More depressed patients had diabetes and more had experienced clinical events during follow-up, but these differences did not reach statistical significance. There were no differences in either the BMQ or MARS scores.

Table 51 Comparison of depressed and non-depressed (MINI diagnosis) at follow-up

	Depressed	**Non-depressed**	**p-value**
Number	15	26	
Age (years)	60 ± 16	63 ± 17	NS
% Male	60	65	NS
% Married/partner	47	50	NS
% Clinical events	67	36	0.06
% Life events	60	44	NS
% Heart disease	47	31	NS
% Diabetes	60	31	0.067
% Cancer	27	19	NS
Dialysis vintage (years)	5.8 (12.5)	4.2 (3.3)	NS

General fatigue	9 (9)	8.5 (9)	NS
Physical fatigue	10 (7)	10 (7)	NS
Mental fatigue	9 (7)	6 (11)	NS
BDI-II	28 (10)	14.5 (16)	0.001
PHQ-9	14 (6)	7.5 (8)	0.003
PHQ-2	3 (2)	2 (2)	0.003
BMQ (necessity)	12.2 ± 3.1	13.4 ± 3.1	NS
BMQ (concerns)	12.4 ± 2.8	13.2 ± 3.6	NS
MARS (adherence)	7.8 ± 1.6	8.4 ± 1.3	NS

Six patients were found to never have been depressed on the MINI. These six were significantly older than the others (current, recurrent, and past MDD). Their median age was 76.6 years (IQR 10) vs 64.6 (IQR 24). There were no differences with respect to gender, marital status, clinical and life events, dialysis vintage, comorbidities, haematological and biochemical parameters, or BMQ or MARS scores. Depressive symptoms scores were generally lower, though the difference was only significant for PHQ-2 (Table 52). Although there were no differences in MFI domain scores across the whole cohort of MINI diagnoses (see Table 51), MFI domain scores were lower in the six patients who had never been depressed than in all other patients. Differences were not significant for general fatigue (Table 52).

Table 52 Demographic, depressive symptom scores, and MFI domain scores in never-depressed vs other (current, recurrent, and past depression).

Values quoted as median (IQR)

	Depressed (n=35)	**Never depressed (n-6)**	**p-value**
Age (years)	64.9 (24)	76.6 (12)	0.030
BDI-II	22 (15)	11 (23)	NS
PHQ-9	11 (9)	6.5 (13)	NS
PHQ-2	2 (6)	0 (1.75)	0.021

General fatigue	9 (8)	6.5 (5)	NS
Physical fatigue	10 (8)	9 (5)	0.032
Mental fatigue	9 (8)	3.5 (5)	0.049

8.6.5 Beliefs and Attitudes Towards Antidepressants

There were no differences in adherence to antidepressant treatment according to the MARS score between patients with high depression scores (as judged by the follow-up BDI-II score) nor between patients with diagnosed depression and those without (as judged by the MINI). It was apparent, however, that patients with high depression scores at follow-up (BDI-II ≥16) had a significantly lower necessity score on the BMQ (Table 52). Concerns scores were not different between these groups. In addition, neither necessity nor concerns scores were different in patients with MDD diagnosed by the MINI and those without MDD (Tables 51 and 52).

8.6.6 ROC analysis

ROC analysis showed significant relationships between the diagnosis of current or recurrent MDD by MINI (n=15) and BDI-II scores (Area under Curve (AUC) = 0.813: p=0.001; PHQ-9 (AUC = 0.773: p=0.004) and PHQ-2 (AUC = 0.774: p=0.004) (Figure 30 and Table 53). The best cut-off point for the BDI-II was ≥16. This identified 27 patients (66% of sample). Sensitivity at this cut-off point was 100% and specificity was 54%. The best cut-off for PHQ-9 was ≥8. This identified 28 patients (68% of sample). Sensitivity at this cut-off was 100% and specificity was 50%. The PHQ-9 cut-off ≥10 identified 24 patients (59% of sample). Sensitivity at this cut-off point was 80% and specificity was 54%. The best cut-off point for PHQ-2 was ≥2. This identified 28 patients (68% of sample). Sensitivity at this cut-off was 93%. Specificity was 46%. Levels of agreement were κ 0.46, 0.42, and 0.30, respectively) (Table 54).

Figure 30 ROC curve relating BDI-II, PHQ-9, and PHQ-2 to DSM-IV diagnosis of MDD

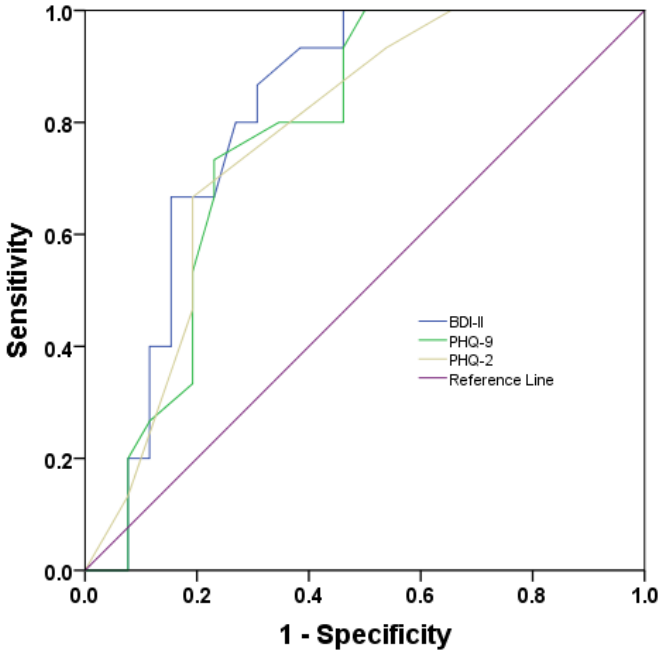


Table 53 Relationship between BDI-II, PHQ-9, and PHQ-2 and the diagnosis of MDD by MINI.

***AUC = Area under Curve**

	AUC*	Std. Error	p-value
BDI-II	*.813*	*.067*	*.001*
PHQ-9	.773	.073	.004
PHQ-2	.774	.073	.004

Table 54 Comparison between cut-off points of BDI-II and PHQ for the diagnosis of MDD

	BDI-II ≥16	PHQ-9 ≥8	PHQ-9 ≥10	PHQ-2 ≥2
% Population identified	66%	68%	59%	68%
Sensitivity	100%	100%	80%	93%
Specificity	54%	50%	54%	46%
Positive predictive value	56%	54%	54%	50%
Negative predictive value	100%	100%	82%	92%
κ values	0.46	0.42	0.30	0.33
p-value	0.000	0.001	0.034	0.010

8.7 Discussion

Two-thirds of HD patients who were taking antidepressants had persistently high or deteriorating depressive symptom scores after around the 12-month follow-up. A high proportion of these (56%) had clinical depression as diagnosed by the MINI. 15% of the cohort had no evidence MDD according to the MINI over their lifetime; however, they were already on antidepressants. Current NICE policy recommends that chronically ill patients with comorbid depression be treated with CBT and/or SSRIs as the first choice. When antidepressants are chosen, the patient should be reviewed after two weeks from the date of commencement, to review side effects, response, and suicidality. If a response is absent or minimal after three to four weeks of treatment with a therapeutic dose of an antidepressant, an increase in the level of support is recommended, along with consideration of either increasing the dose in line with the SPC if there are no significant side effects or switching to another antidepressant. If the person's depression shows some improvement by four weeks, the recommendation is to continue treatment for another two to four weeks, or consider switching to another antidepressant if the response is still not effective, side effects develop, or the patient chooses to change.

In our study, a high proportion had no review of or amendment to their antidepressant prescription during follow-up and NICE guidelines did not appear to be being applied in the many of these patients. This is compatible with previous literature, which suggests that depression is often undertreated in patients with chronic medical illness (468), and that this can lead to negative outcomes (469). Although all patients in this cohort were on antidepressants at baseline, many had inadequate follow-up, were receiving sub-therapeutic doses, or both. This, again, raises the same

question discussed in Chapter 6, about the safe and effective use of antidepressants in this setting, and, indeed, whether they were indicated for some of these patients.

There were 10 different antidepressants used, the commonest being Citalopram, which is not considered to be the drug of choice in this setting due to the high potential for side effects, including prolonged QT interval and bleeding. A few patients (5%) were taking tricyclic antidepressants, despite these being contraindicated for patients with heart disease. This may be especially risky in HD patients as heart disease is very common in this population, accounting for more than 50% of the deaths in uraemic patients (6, 7).

Antidepressant medication was prescribed by GPs in most cases. Nephrologists were not the primary prescribers. There might be a number of reasons. Nephrologists may be more likely to think that depression is 'part of the illness and/or its treatment'. They may also be much more aware of the complexity of this cohort in terms of comorbidity and polypharmacy with its hugely increased potential for adverse drug effects and interactions. They may be reluctant to add to the tablet burden.

The average depressive episode lasts about nine to 12 months without treatment, although about 20% run a chronic course of two years or longer. Once established, chronic episodes last an average of five to eight years (93) and this might have been the reason in our study for many patients' antidepressant status remaining essentially unchanged during follow-up. More often, major depressive episodes recur with increasing frequency. In fact, after a second lifetime episode, the risk of a third is at least 70% within three years (without prophylactic treatment (100)). Early withdrawal of antidepressant medication before three months results in the return of the symptoms, and as the course of the disorder progresses, patients tend to have more frequent episodes that last longer. Over 30 years, the mean number of episodes is five to six (101).

Previous literature explored the impact of fatigue on mood and the overlap with the patient's mental state (41). We found that there was a substantial difference between fatigue scores in patients with high and low BDI-II scores but not, in general, between patients with depression diagnosed by MINI and those without. This testifies to fatigue having a greater influence on depressive symptoms than on the diagnosis of depression. Interestingly, it was only when comparing the never depressed versus the rest that a difference in fatigue was noted compared to those with current, recurrent, or past depression in diagnosed depression. The lower fatigue scores in the never depressed group is remarkable considering the much higher age of this patient group. Fatigue and depression are closely interrelated and depression may manifest as feelings of

tiredness and lack of energy. Depression has also been shown to correlate strongly with overall symptom burden and severity, including fatigue, in HD patients (382).

There were also differences in the necessity score between those with high and low BDI-II, suggesting that people who think the medication is necessary may respond better or actually take the treatment – though this did not persist in multivariate analysis nor reflect in the MARS scores.

The best screening tool for MDD in this high-risk group was the BDI-II. A cut-off point of ≥16 was highly sensitive and adequately specific, which agrees with previous literature (177). Use of the PHQ-9 with a cut-off ≥8 is a suitable, though slightly less specific alternative. Either of these options are suitable screening measures in this high-risk group. Psychiatric evaluation should be considered in patients with scores above these cut-offs. MDD can be confidently excluded in patients with lower BDI-II and PHQ-9 values. The PHQ-9 with a cut-off of ≥10 was less sensitive than a ≥8 cut-off. The PHQ-2 cut-off of ≥2 was less sensitive and also less specific in this high-risk group (Table 54).

8.8 Concluding Remarks

The main differences between depressed and non-depressed diagnosed patients at follow-up were:

1- The severity of the depressive symptoms as judged by the score of the BDI-II, PHQ-9, and PHQ-2.
2- There were small effects of comorbidity (diabetes) and clinical events during follow-up.
3- Fatigue scores relate more to depression symptoms as assessed by the BDI-II scores than to diagnosed depression by the MINI.

BDI-II ≥16 was the best screening tool for the detection of possible depression in this selected cohort. Patients with BDI-II ≥16 require a diagnostic interview. Depression can be safely excluded in those with BDI-II <16. PHQ-9≥ 8 may be a useful alternative.

We found multiple problems with the use of antidepressants in the HD setting:

1- Multiple types of antidepressants were being used, some of which are contraindicated in this setting.
2- There was over-prescription – 15% had never had depression.
3- There was inadequate follow-up.
4- There was sub-optimal adherence to NICE guidelines.
5- There was little evidence of nephrological awareness and supervision.
There is a real need for improvements in depression management in HD patients.

Chapter 9

Final Discussion

Depression is known to be common in HD patients (444, 470), though the diagnosis is challenging due to symptom overlap between depression and uraemia (444). Estimates of the prevalence of depression in this population have varied from as high as 40%, based on screening questionnaires, to around 20%, based on psychiatric interviews (173). This large multicentre study has confirmed that many patients on HD suffer from high depression symptoms. A high proportion (32.5%) screened positive by BDI-II using the cut-off ≥16, which accords with previous literature (173). A similar number (36%) screened positive on the PHQ-9, using a cut-off point of ≥8, which in this study was the cut-off point corresponding to ≥16 on the BDI-II.

One of the major findings was the high prevalence of HD patients receiving treatment for their depression either by antidepressants or psychological therapy, in spite of the dearth of evidence for the efficacy of antidepressants in this setting. There is very little data in the literature on this topic, the only previous report being that of Lopes et al. (228). It was notable that 17% of patients with a high BDI-II score were currently taking antidepressants or receiving psychological therapies (5%), or both (7%) – a total of 29% on one or both of these therapies. It was noticeable that BDI-II screen positive patients receiving antidepressants had higher BDI-II scores than their untreated counterparts. There are number of potential explanations for this. These include the possibility that the treated patients have more severe symptoms of depression. It also raises questions about prescribing practices, patients' adherence, and therapeutic efficacy in this setting.

PHQ-9 and PHQ-2 were found to be acceptable screening tools compared to the BDI-II in dialysis patients, with cut-off points of ≥8 in PHQ-9 and ≥2 in PHQ-2, approximating the BDI-II cut-off of ≥16. Previous literature (175) has suggested that the optimal BDI-II and PHQ-9 cut-off values for the diagnosis of MDD in the HD population were ≥16 and ≥10, respectively. Similarly, we found that the strongest predictor of MDD in patients with a BDI ≥16 was a PHQ-9 ≥10. Hence, there seem to be different PHQ-9 cut-offs for predicting depressive symptoms and diagnosed depression. These differences probably relate to the sensitivity of the BDI-II instrument to somatic symptoms and the overlap of these symptoms in depression and uraemia. These findings may be helpful in interpreting the results of these screening tools in the HD population.

The purpose of the screening phase was to identify HD patients with depression suitable to enter the RCT. In spite of approaching 1,353 potential participants, only 37 were ultimately deemed suitable to be randomised, and only 30 agreed to take part. There were multiple challenges, including language barriers, robust exclusion criteria, most notably patients already receiving antidepressants, and refusal to consent. The refusal rate was in fact very acceptable – 30% at screening, 16% for psychiatric interview, and 3% for the RCT. Considering all of these recruitment challenges, screening seems to have been reasonably successful.

An important finding was that use of antidepressant therapy is common in HD patients, despite little evidence of efficacy in this population and its high potential for adverse effects. This finding has implications for extending this feasibility RCT study into a definitive RCT. This will be discussed later in this section.

Fatigue is very common in HD patients, the prevalence ranging from 42% to 89% according to the treatment modality and assessment instruments (226). It was not possible in our study to establish prevalence since the MFI lacks validated cut-off points. However, fatigue levels in our HD population were strikingly high in all domains, general, physical, and mental, and similar to those found in oncology patients (459). There were weak relationships with age, gender, weight, and comorbidity, particularly diabetes and heart disease, but no relationship with dialysis vintage, haemoglobin, albumin, or dialysis adequacy. In general, these findings align with previous studies (38, 314, 315, 330, 331, 334). Fatigue scores (all subdomains) were closely related to dialysis recovery time, the closest relationship being the physical component. Physical fatigue was also highly predictive of mortality. There was no impact from any parameters related to depressive symptomatology on the prediction of mortality in the models, including the fatigue domains.

Previous literature has demonstrated strong correlations between depression in HD patients and overall symptom burden (382). The association between fatigue and depression is particularly strong (41, 314, 335, 460). These findings have been confirmed in the present study, which showed strong correlations between BDI-II, PHQ-9, and PHQ-2 scores and the MFI subdomains general, physical, and mental. Fatigue scores were higher in patients with high BDI-II scores (≥16). There were, however, differences in the distributions of the general, physical, and mental fatigue scores in patients with high and low BDI-II scores. Of the MFI domains, mental fatigue was the strongest independent predictor of high depressive symptoms (BDI-II ≥16, PHQ-9 ≥8). Mental fatigue, but not general or physical fatigue, also tended to be higher in patients with MDD compared to those with high depressive symptoms but without MDD. In addition, the dissociation

between the changes in BDI-II and MADRS scores and fatigue scores during the RCT suggests that the change in depression scores during the study was more related to changes in cognitive than somatic components.

Taken together, these findings suggest that, though the relationships are complex, some principles can be established with respect to the role of fatigue in the HD setting. Firstly, post-dialysis recovery time and survival seem to relate more strongly to physical (somatic factors) rather than mental fatigue (cognitive factors). The failure of depression scores to improve models of survival that include physical fatigue suggests that the previously reported effects of depression on mortality (461) may be mediated by physical fatigue. Secondly, high depressive symptoms, and indeed the diagnosis of MDD, relate more strongly to mental fatigue (cognitive factors) rather than physical fatigue (somatic factors). The capacity to distinguish somatic and cognitive factors by such means may be useful in directing further research in these areas with a view to designing specific management strategies.

The progression study was carried out to examine the natural history of antidepressant therapy in patients on HD. The impetus for this came from the finding in the screening study that a significant proportion of the dialysis population were taking antidepressant medication, sometimes without the knowledge of the treating nephrologist, and in spite of the dearth of evidence of efficacy in this setting. Two-thirds of HD patients who were taking antidepressants at baseline had persistently high or deteriorating depressive symptom scores after around the 12-month follow-up. A high proportion of these (56%) had clinical depression. It transpired that, on psychiatric examination, in 15% of this cohort there was no evidence that the patient had ever had MDD over their lifetime. Many had never had the treatment reviewed or amended during follow-up in spite of NICE recommendations. Ten different antidepressants were being used, the commonest being Citalopram, not considered to be the drug of choice in this setting due to the high potential for side effects, including prolonged QT interval and bleeding. A few patients (5%) were taking tricyclic antidepressants despite these being contraindicated for patients with heart disease, which is common in this setting (6, 7). Antidepressants were prescribed by GPs in most cases. There may be a number of reasons for this. Nephrologists may be more likely to think that depression is 'part of the illness and its treatment', may also be much more aware of the complexity of this cohort in terms of comorbidity and polypharmacy with its hugely increased potential for adverse drug effects and interactions, as well as adding to the tablet burden. Previous literature suggests that depression is often unrecognised and undertreated in patients with chronic medical illness (468),

and that this can lead to negative outcomes (469). It might be added to this that, in HD patients, even when depression is recognised it is usually sub-optimally treated. Our findings also suggest that antidepressants are often prescribed inappropriately for patients who are not depressed.

Perhaps one of the most important points is that the GP practice on prescribing antidepressants should be addressed either by teaching and raising the awareness of prescriptions guidelines or encouraged through Commissioning for Quality and Innovation driven by NHS England. This is scheme intended to deliver clinical quality improvements and drive transformational change eg; improving the outcomes and experience of patients with mental health needs, or The Quality, Innovation, Productivity and Prevention programme which is a large-scale programme developed by the Department of Health to drive forward quality improvements in NHS care. These range from improving commissioning or purchasing of care for patients with long-term conditions, to improving how organisations are run, staffed and supplied.

There is also a strong argument for more involvement for nephrologists in the assessment, diagnosis and management of depression in their patients. This would involve a drive to increase the awareness of nephrologists about the condition and a lowered threshold for direct involvement of psychiatrist in the care of these patients.

In summary, we found multiple problems with the use of antidepressants in the HD setting:

1- Multiple types of antidepressants were being used, some of which are contraindicated in this setting.
2- There was over-prescription – 15% had never had depression.
3- There was inadequate follow-up.
4- There was little evidence of adherence to NICE guidelines.
5- There was little evidence of nephrological awareness and supervision.

These raise major issues of safety and efficacy, which need to be addressed by education and further empirical study.

This brings us to the final element of these studies. The feasibility RCT reported here is the largest randomised trial of antidepressant use in HD patients to date. We recruited 30 patients and 21 (70%) patients completed the six-month study. Recruitment to the RCT was difficult. Over 70% of the 231 positively BDI-II screened patients were ineligible or unwilling to consent to psychiatric interview. The commonest reason for non-eligibility was current antidepressant medication and/or psychological therapy. Patients also seemed to have concerns about adding to already considerable pill burdens and about becoming dependent on antidepressant drugs. Adverse events were

common and, though they occurred with similar frequency in treatment and placebo groups, more patients withdrew in the treatment group because of them. The only death that occurred was in the treatment group. Depression scores (BDI-II and MADRS) improved significantly in both sertraline and placebo groups over six months. There was no significant difference between the groups, similar to previous findings in other chronic illnesses (471, 472).

This study raises concerns about the benefits and risks of antidepressants in patients on HD, a highly comorbid group with a huge pill burden confounding their high prevalence of depression. The study suggests that current practice patterns may be subjecting patients to substantial risk for little or no benefit. Identifying whether antidepressant medication is effective in this context is a major clinical need.

The European Renal Best Practice Group recommends that 'The evidence on the effectiveness of antidepressants versus placebo in patients with CKD stages 3-5, and with DSM-IV-defined depression is insufficient, and in view of the high prevalence, a well-designed RCT is greatly needed' (230). This sentiment is echoed by a recent Cochrane review (458): 'Despite the high prevalence of depression in dialysis patients and the relative priority that patients place on effective treatments, evidence for antidepressant medication in the dialysis setting is sparse and data are generally inconclusive. The relative benefits and harms of antidepressant therapy in dialysis patients are poorly known and large randomised studies of antidepressants versus placebo are required'.

This feasibility RCT suggests that a definitive trial would require significant amendments to study design to enhance its chances of success. These have been outlined in the RCT chapter. We believe that, though it would be difficult to conduct such a large randomised placebo-controlled trial of antidepressants in this group of patients, it is important to carry this out, given the prevalence of depression in the HD population, uncertainty about the efficacy and safety of antidepressants, the widespread use of these agents, and current sub-optimal practice patterns, all of which have been highlighted by the series of studies reported here.

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List of Appendices

Appendix 1 – Ethical Approval

NRES Committee London - Bentham
Research Ethics Committee
Offices Health
Research Authority
NRES Committee London
Bentham Ground Floor,
Skipton House
80 London Road
London SE1 6LH

Telephone: 020 797 22551

Facsimile: 020 797 22592

01 November 2012

Professor Ken Farrington
East and North Hertfordshire NHS Trust
Coreys Mill Lane
Stevenage
SG1 4AB

Dear Professor Farrington

Study title:	**A Pilot Randomised Controlled Trial of Drug Treatment for Depression in Patients undergoing Haemodialysis**
REC reference:	**12/LO/1554**
Protocol number:	**CTIMPMCRENAL12**
EudraCT number:	**2012-000547-27**

Thank you for your letter of 03 October 2012, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a sub-committee of the REC.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites listed in the application, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter		02 September 2012
Investigator CV	Dr Ayman Guirguis	
Investigator CV	Naomi Fineberg	
Other: NRES Unfavourable opinion letter		04 July 2012
Other: Response to unfavourable opinion letter		16 July 2012
Other: Committee response to letter dated 16th July 2012		01 August 2012
Other: Letter to researchers after meeting with Professor Katz and Professor Farrington		29 August 2012
Other: Renal Association Guidelines		
Other: Summary of product characteristics- Sertralin 1A Pharma 50mg and 100mg coated tablets		
Other: RfPB Programme- Reviewer reference 1		
Other: RfPB Programme- Reviewer reference 2		
Other: RfPB Programme- Reviewer reference 3		
Other: RfPB Programme- Reviewer reference 4		
Other: RfPB Programme- Reviewer reference 5		
Protocol	3.0	03 October 2012
REC application		03 September 2012
Response to Request for Further Information		03 October 2012

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
-
-
-
-

Adding new sites and investigators
Notification of serious breaches of the protocol
Progress and safety reports
Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/LO/1554	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Professor David Katz
Chair

Email: NRESCommittee.London-Bentham@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Dr Karin Friedli, University of Hertfordshire

Mrs Fiona Smith, East and North Hertfordshire NHS Trust

Safeguarding public health

MHRA

Dr K Farrington
EAST AND NORTH HERTFORDSHIRE NHS TRUST
LISTER HOSPITAL
COREY'S MILL LANE
STEVENAGE
HERTFORDSHIRE
SG1 4AB
UNITED KINGDOM

08/08/2012

Dear Dr K Farrington

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference:	31057/0005/001-0001
Eudract Number:	2012-000547-27
Product:	Sertraline
Protocol number:	CTIMPMCRENAL12

NOTICE OF ACCEPTANCE OF AMENDED REQUEST

I am writing to inform you that the Licensing Authority accepts your amended request for a clinical trial authorisation (CTA), received on 07/08/2012.

FOR INFORMATION
Since the Teva tablets are not listed in the application form, this source of sertraline is not approved. If you wish to have an alternative source available, you may wish to submit a substantial amendment before there is a supply issue. This would constitute a change to the application form/xml file only.

The authorisation is effective from the date of this letter although your trial may be suspended or terminated at any time by the Licensing Authority in accordance with regulation 31. You must notify the Licensing Authority within 90 days of the trial ending.

Finally, you are reminded that a favourable opinion from the Ethics Committee is also required before this trial can proceed; changes made as part of your amended request may need to be notified to the Ethics Committee.

Yours sincerely,

Clinical Trials Unit
MHRA

Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road London SW1W 9SZ
T 0203 080 6000 www.mhra.gov.uk

An executive agency of the Department of Health

NRES Committee London – Harrow

Bristol REC Centre Level 3, Block B

Whitefriars

Lewins Mead
Bristol BS1 2NT
Tel: 01173 421383
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24 January 2013

Professor Ken Farrington
East and North Hertfordshire NHS Trust
Coreys Mill Lane
Stevenage SG1 4AB

Dear Professor Farrington

Study title:	**A Pilot Randomised Controlled Trial of Drug Treatment for Depression in Patients undergoing Haemodialysis**
REC reference:	**12/LO/1554**
Protocol number:	**CTIMPMCRENAL12**
EudraCT number:	**2012-000547-27**
Amendment number:	**Substantial Amendment 1**
Amendment date:	**21 January 2013**
IRAS project ID:	**100774**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Revised Label	2	21 January 2013
Protocol	4	18 January 2013
European Commission Notification of Substantial Amendment Form	Substantial Amendment 1	21 January 2013
Covering Letter		21 January 2013

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

12/LO/1554:	**Please quote this number on all correspondence**

Yours sincerely

PP

Miss Stephanie Ellis
Chair

E-mail: nrescommittee.london-harrow@nhs.net

Enclosures: *List of names and professions of members who took part in the Review*

Copy to: *Mrs Fiona Smith, East and North Hertfordshire NHS Trust*
Dr Karin Friedli

NRES Committee London - Bentham

Attendance at Sub-Committee of the REC meeting on 25 January 2013

Name	*Profession*	*Capacity*
Miss Stephanie Ellis	Former Civil Servant	Lay
Dr John Keen	General Practitioner	Expert

NRES Committee London – Harrow
Bristol REC Centre Level 3, Block B
Whitefriars
Lewins Mead
Bristol BS1 2NT
Tel: 01173 421383
Fax: 01173 420455

18 July 2013

Professor Ken Farrington

East and North Hertfordshire NHS Trust

Coreys Mill Lane

Stevenage

SG1 4AB

Dear Professor Farrington

Study title:	**A Pilot Randomised Controlled Trial of Drug Treatment for Depression in Patients undergoing Haemodialysis**
REC reference:	**12/LO/1554**
Protocol number:	**CTIMPMCRENAL12**
EudraCT number:	**2012-000547-27**
Amendment number:	**Substantial Amendment 2**
Amendment date:	**16th July 2013**
IRAS project ID:	**100774**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Revised Label	5	11 April 2013
Substantial Amendment Form Signature		16 July 2013
Protocol	5.0	05 July 2013
European Commission Notification of Substantial Amendment Form	Substantial Amendment 2	
Covering Letter		16 July 2013
Questionnaire: SF-36 Scoring		
Questionnaire: SF-36 Questionnaire		
Questionnaire: MFI- English		

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

12/LO/1554:	**Please quote this number on all correspondence**

Yours sincerely

pp

Dr John Keen
Chair

E-mail: nrescommittee.london-harrow@nhs.net

Enclosures: *List of names and professions of members who took part in the Review*

Copy to: *Mrs Fiona Smith, East and North Hertfordshire NHS Trust*
Dr Karin Friedli

NRES Committee London - Harrow

Attendance at Sub-Committee of the REC meeting in correspondence

Name	*Profession*	*Capacity*
Miss Stephanie Ellis	Former Civil Servant	Lay Plus
Dr John Keen	GP	Expert

Health Research Authority

NRES Committee London – Harrow
Bristol REC Centre Level 3, Block B
Whitefriars
Lewins Mead
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22 August 2013

Professor Ken Farrington
East and North Hertfordshire NHS Trust
Coreys Mill Lane
Stevenage
SG1 4AB

Dear Professor Farrington

Study title:	**A Pilot Randomised Controlled Trial of Drug Treatment for Depression in Patients undergoing Haemodialysis**
REC reference:	**12/LO/1554**
Protocol number:	**CTIMPMCRENAL12**
EudraCT number:	**2012-000547-27**
Amendment number:	**Minor Amendment 1**
Amendment date:	**20 August 2013**
IRAS project ID:	**100774**

Thank you for your letter of 20 August 2013, notifying the Committee of the above amendment.

It is noted that you do not consider this to be a substantial amendment to the clinical trial authorisation, as defined in the Medicines for Human Use (Clinical Trials) Regulations 2004, and that ethical review by the Committee is therefore not required.

Documents received

The documents received were as follows:

Document	Version	Date
Participant Consent Form: Consent Form 3 - Patient Experience Interview Phase	5	05 July 2013
Participant Information Sheet: PIS 1 - Screening and Prevalence Phase	5	05 July 2013
GP/Consultant Information Sheets	5	05 July 2013
Participant Information Sheet: PIS 2 - Psychiatric Assessment and Clinical Trial Phase	5	05 July 2013
Participant Consent Form: Consent Form 2b - Trial Outcome Phase	5	05 July 2013
Notification of a Minor Amendment		20 August 2013
Serious Adverse Event Reporting Form	5	05 July 2013
Participant Consent Form: Consent Form 1 - Screening and Prevalence Phase	5	05 July 2013
Participant Information Sheet: Short PIS 1	5	05 July 2013
Interview Schedules/Topic Guides	5	05 July 2013
Participant Information Sheet: PIS 3 - Patient Experience Interview Phase	5	05 July 2013
Participant Consent Form: Consent Form 2a - Consent to Assessment with psychiatrists	5	05 July 2013
Participant Information Sheet: Short PIS 2	5	05 July 2013

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice .

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

12/LO/1554: Please quote this number on all correspondence

Yours sincerely

Libby Watson
Committee Co-ordinator

E-mail: nrescommittee.london-harrow@nhs.net

Copy to: *Mrs Fiona Smith, East and North Hertfordshire NHS Trust*
Dr Karin Friedli

NHS
Health Research Authority

NRES Committee London – Harrow

Bristol REC Centre Level 3, Block B
Whitefriars
Lewins Mead
Bristol BS1 2NT
Tel: 01173 421383
Fax: 01173 420455

20 January 2014

Professor Ken Farrington
East and North Hertfordshire NHS Trust
Coreys Mill Lane
Stevenage
SG1 4AB

Dear Professor Farrington

Study title:	**A Pilot Randomised Controlled Trial of Drug Treatment for Depression in Patients undergoing Haemodialysis**
REC reference:	**12/LO/1554**
Protocol number:	**CTIMPMCRENAL12**
EudraCT number:	**2012-000547-27**
Amendment number:	**Updates to Protocol including text and methodology.**
Amendment date:	**09 January 2014**
IRAS project ID:	**100774**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The Committee Members approved the changes to update the Protocol including text and methodology.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved document

The documents reviewed and approved at the meeting were:

Document	Version	Date
Covering Letter		09 January 2014
Protocol	6.0	09 January 2014

European Commission Notification of Substantial Amendment Form	Updates to Protocol including text and methodology .	09 January 2014

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

12/LO/1554: Please quote this number on all correspondence

Yours sincerely

Pp Miss Shelly Glaister-Young
Alternate Vice- Chair

E-mail: nrescommittee.London-Harrow@nhs.net

Enclosures: *List of names and professions of members who took part in the Review*

Copy to: Mrs Fiona Smith, East and North Hertfordshire NHS Trust
Fiona.smith@whht.nhs.uk

Dr Karin Friedli

k.friedli@herts.ac.uk

NHS
Health Research Authority

NRES Committee London– Harrow

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Fax: 01173 420455

23 April 2014

Dr Karin Friedli
Clicir, University of Hertfordshire
Health Research Building
College Lane, Hatfield
AL10 9AB

Dear Dr Friedli

Study title:	**A Pilot Randomised Controlled Trial of Drug Treatment for Depression in Patients undergoing Haemodialysis**
REC reference:	**12/LO/1554**
Protocol number:	**CTIMPMCRENAL12**
EudraCT number:	**2012-000547-27**
Amendment number:	**Minor Amendment 2 Version Control**
Amendment date:	**19 March 2014**
IRAS project ID:	**100774**

Thank you for your letter of 19 March 2014, notifying the Committee of the above amendment.

It is noted that you do not consider this to be a substantial amendment to the clinical trial authorisation, as defined in the Medicines for Human Use (Clinical Trials) Regulations 2004, and that ethical review by the Committee is therefore not required.

Documents received

The documents received were as follows:

Document	Version	Date
Assertid CRF SAE Form	6.1 (Clean & Tracked)	19 March 2014
Protocol	6.0	09 January 2014
Notification of a Minor Amendment	Minor Amendment 2 Version Control	19 March 2014
Participant Information Sheet: PIS 1	6	09 January 2014
Participant Information Sheet: PIS 2	6	09 January 2014
Participant Information Sheet: PIS 3	6	09 January 2014
Protocol	6.1	19 March 2014

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

12/LO/1554:	**Please quote this number on all correspondence**

Yours sincerely

Miss Natasha Bridgeman REC Assistant

E-mail: nrescommittee.london-harrow@nhs.net

Copy to: *Mrs Fiona Smith, East and North Hertfordshire NHS Trust*
Ken Farrington, East and North Hertfordshire NHS Trust

NHS
Health Research Authority

NRES Committee London – Harrow

Bristol REC Centre Level 3, Block B
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Lewins Mead
Bristol BS1 2NT
Tel: 01173 421383
Fax: 01173 420455

25 April 2014

Dr Karin Friedli
Clicir, University of Hertfordshire
Health Research Building
College Lane, Hatfield
AL10 9AB

Dear Dr Friedli

Study title:	**A Pilot Randomised Controlled Trial of Drug Treatment for Depression in Patients undergoing Haemodialysis**
REC reference:	**12/LO/1554**
Protocol number:	**CTIMPMCRENAL12**
EudraCT number:	**2012-000547-27**
Amendment number:	**Minor Amendment 3**
Amendment date:	**11 April 2014**
IRAS project ID:	**100774**

Thank you for your letter of 11 April 2014, notifying the Committee of the above amendment.

It is noted that you do not consider this to be a substantial amendment to the clinical trial authorisation, as defined in the Medicines for Human Use (Clinical Trials) Regulations 2004, and that ethical review by the Committee is therefore not required.

Documents received

The documents received were as follows:

Document	Version	Date
Protocol	6.2 (Clean&Tracked)	11 April 2014
Notification of a Minor Amendment		11 April 2014

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

12/LO/1554:	**Please quote this number on all correspondence**

Yours sincerely

Miss Natasha Bridgeman REC Assistant

E-mail: nrescommittee.london-harrow@nhs.net

Copy to: *Mrs Fiona Smith, East and North Hertfordshire NHS Trust*
Ken Farrington, East and North Hertfordshire NHS Trust

Health Research Authority

NRES Committee East of England - Cambridge South

The Old Chapel Royal Standard Place

Nottingham NG1 6FS

Telephone: 0115 883 9525

04 June 2014

Dr Ayman Guirguis
University Of Hertfordshire
Centre for Lifespan and Chronic Illness Research Room 1F424
Health Research Building
College Lane AL10 9AB

Dear Dr Guirguis

Study title:	**Progression Of Depressive Symptoms In Haemodialysis Patients On Antidepressants**
REC reference:	**14/EE/0143**
Protocol number:	**RD2014-30**
IRAS project ID:	**151298**

Thank you for your letter of 19 May 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Ms Trish Wheat, nrescommittee.eastofengland-cambridgesouth@nhs.net

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made.
Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Approved documents

The final list of documents reviewed and approved by the Committee is as follows

Document	*Version*	*Date*
Covering letter on headed paper		31 March 2014
Interview schedules or topic guides for participants	1.0	09 April 2014
Other [Case Report Form]	1	28 February 2014
Other [GP Letter]	1.0	28 February 2014
Participant consent form	1	28 February 2014
Participant information sheet (PIS) [including tracked (lay) changes]	2.0	13 May 2014
REC Application Form	151298/586431/1/541	27 March 2014
Research protocol or project proposal	1.0	28 February 2014
Response to Request for Further Information		19 May 2014
Summary CV for Chief Investigator (CI)	Dr Ayman Guirguis	
Summary CV for Chief Investigator (CI)	Dr Karin Friedli	
Summary CV for Chief Investigator (CI)	Ken Farrington	
Summary CV for Chief Investigator (CI)	Naomi Fineberg	

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:

http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/EE/0143	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

pp

Dr Leslie Gelling Chair

Email:nrescommittee.eastofengland-cambridgesouth@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Dr Shan Gowrie-Mohan*

Mrs Fiona Smith, East and North Hertfordshire NHS Trust

NRES Committee London – Harrow

Bristol REC Centre Level 3, Block B

Whitefriars

Lewins Mead
Bristol BS1 2NT
Tel: 01173 421383
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01 June 2015

Ken Farrington

East and North Hertfordshire NHS Trust

Coreys Mill Lane

Stevenage

SG1 4AB

Dear Mr Farrington

Study title:	**A Pilot Randomised Controlled Trial of Drug Treatment for Depression in Patients undergoing Haemodialysis**
REC reference:	**12/LO/1554**
Protocol number:	**CTIMPMCRENAL12**
EudraCT number:	**2012-000547-27**
Amendment number:	**2**
Amendment date:	**23 April 2015**
IRAS project ID:	**100774**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper		22 April 2015
Notice of Substantial Amendment (CTIMP)	2	23 April 2015
Other [Archiving for the Assertid Study]	1	09 March 2015
Participant information sheet (PIS)	7	01 June 2015
Research protocol or project proposal	7.0	20 April 2015
Sample diary card/patient card	1	13 May 2013

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval
All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance
This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

12/LO/1554:	**Please quote this number on all correspondence**

Yours sincerely

P.P. Bridgeman.

Dr Jan Downer

Chair

E-mail: nrescommittee.london-harrow@nhs.net

Enclosures: ***List of names and professions of members who took part in the review***

Copy to: ***Mrs Fiona Smith, East and North Hertfordshire NHS Trust***

Dr Karin Fried

NRES Committee London - Harrow

Attendance at Sub-Committee of the REC meeting on 01 May 2015

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Jan Downer	Consultant Anaesthetist (Chair)	Yes	
Reverend Catherine McBride	Vicar	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Natasha Bridgeman	REC Assistant

ASSERTID Amendment Log - Version 1.8 dated 20/1/2016

Submission type and version	Substantial or non-substantial	Reason for amendment	Submitted to ethics	Approved by ethics	Submitted to MHRA	Approved by MHRA	CTA issued	Submitted to Sponsor and NHS R&D	Approved by Sponsor and NHS R&D	Status
Protocol 1.0, dated 17/4/12	N/A	Original Submission	24/04/2012	Not approved, Letter dated 4/7/12	22/06/2012	Grounds of non-acceptance, letter dated 26/7/12		N/A		Planning
Protocol 1.0, dated 17/4/12	Right to amend request to MHRA				07/08/2012	08/08/2012	08/08/2012			Planning
Protocol 2.0, dated 2/9/12		New application to ethics committee	02/09/2012	Provisional opinion, Letter dated 1/10/12						Planning
Protocol 3.0, dated 3/10/12	Further information to provisional opinion		03/10/2012	Approval, Letter dated 1/11/12						Planning
Protocol 3.0, dated 3/10/12	Substantial amendment to CTA application	Changes had been requested by ethics			18/10/2012	22/11/2012				Planning
Protocol 4.0, dated 18/1/3	Substantial amendment to ethics and CTA application	Changes in safety or integrity of trial subjects, changes in conduct/management of trial, clarification to protocol	21/01/2013	Approval, Letter dated 24/1/13	21/01/2013	26/02/2013		25/03/2013	02/04/2013	R&D approval at ENHT 2/4/13
Protocol 4.0, dated 18/1/13										R&D approval at Southend 20/5/13
Protocol 5.0, date 5/7/13	Substantial amendment to ethics	Added short patient information sheets, added two self-report questionnaires, clarification	16/07/2013	Approval, Letter dated 18/07/2013	Informed MHRA	Acknowledgement letter dated 2/8/2013				R&D approval in Birmingham 20/8/13

Appendix 2 – List of Abstracts

AMERICAN SOCIETY OF NEPHROLOGY- Philadelphia, PA- Nov 11-16 2014

COMPARISON OF COMMON SCREENING TOOLS FOR DEPRESSION IN HAEMODIALYSIS PATIENTS

Guirguis, A.[1, 2, 3], Friedli, K.[2], Fineberg, N.A., [2, 3], Day, C.[4], Almond. M.[5], Davenport, A.[5], Da Silva- Gane, M[1]., Chilcot, J.[7], Wellsted, D. [2], Farrington, K.[1, 2]

[1]E&N Herts NHS Trust, [2] University of Herts, [3]Herts Partnership University NHS Foundation Trust, [4]University Hospitals Birmingham NHS Foundation Trust, [5]Southend University Hospital NHS Foundation Trust, [6]Royal Free London NHS Foundation Trust and [7]King's College London

BACKGROUND: Depression is common in haemodialysis (HD) but diagnosis is difficult because of overlapping somatic symptoms of uraemia and depression. The Beck Depression Inventory -II (BDI-II) is a useful screening tool with good psychometric properties. A cut-off score ≥ 16 indicates probable depression in this setting. There are few data on other commonly used screening tools. We determined cut-off values for the Patient Health Questionnaire 9 (PHQ-9) and Patient Health Questionnaire 2 (PHQ-2), corresponding to BDI-II ≥ 16 in the HD setting.

METHODS: We studied HD patients at 3 UK renal centres. Inclusion criteria were dialysis vintage >3 months, aged >18 years and ability to read and speak English. Patients were screened for depression with the BDI-II and PHQ-9. We used ROC analysis to determine the cut-off points for the PHQ-9 and PHQ-2 corresponding to a BDI-II cut-off ≥ 16. We also determined levels of agreement.

RESULTS: In 494 patients (61% males) median interquartile range for the BDI-II, PHQ-9 and PHQ-2 were 10(5-19), 5(2-11), and 1(0-2) respectively. Using the BDI-II cut-off, the area under the curve in the ROC analysis for the PHQ-9 and PHQ-2 were 0.94 (CI 0.92-0.96) and 0.89 (CI 0.86-0.93) respectively with optimal cut-off points of ≥ 8 for PHQ-9 and ≥2 for PHQ2 (sensitivity 87% and 84%, and specificity 88% and 86% respectively). The proportion of patients with BDI ≥16 was 34%, with PHQ-9 ≥8 was 38% and PHQ-2 ≥ 2 was 38%. Levels of agreement of PHQ-9 > 8 and PHQ-2 ≥2 with BDI-II ≥ 16 were substantial ($\kappa = 0.724$ and 0.678 respectively).

CONCLUSION: The PHQ-9 and PHQ-2 are acceptable screening tools compared to the BDI-II in dialysis patients. Cut-off scores PHQ-9 ≥ 8 and PHQ-2 ≥2 compare well to a BDI-II cut-off ≥ 16. Use of simple screening tools may help detect depression in HD patients.

The ASSertID Study: Feasibility RCT of Drug Treatment for Depression in Patients on Haemodialysis

Guirguis, A.[1, 2, 3], Friedli, K.[2], Fineberg, N.A., [2, 3], Day, C.[4], Almond. M.[5], Davenport, A.[5], Da Silva- Gane, M[1]., Chilcot, J.[7], Wellsted, D. [2], Farrington, K.[1, 2]

[1]E&N Herts NHS Trust, [2] University of Herts, [3]Herts Partnership University NHS Foundation Trust, [4]University Hospitals Birmingham NHS Foundation Trust, [5]Southend University Hospital NHS Foundation Trust, [6]Royal Free London NHS Foundation Trust and [7]King's College London

INTRODUCTION: Major Depressive Disorder (MDD) is common in patients on Haemodialysis (HD). Management is difficult. There are few studies of antidepressants, little evidence of a benefit and significant risks of adverse events. Hence we undertook feasibility RCT of sertraline versus placebo.

METHODS: A screening phase identified patients with Beck Depression Inventory score (BDI-II) ≥16. Those screen + ve patients, who met the eligibility criteria, underwent psychiatric assessment (Mini International Neuropsychiatric Interview). Treatment for depression in the previous 3 months was an exclusion criterion. Those with mild to moderate MDD and MADRS score ≥18 were invited to enter the Trial phase in which patients were randomised to sertraline or placebo. Review by study psychiatrist and nurses took place at 2 weeks then monthly for 6 months. Initial dose was 50 mg with titration to 100 mg if required.

RESULTS: 1355 patients were approached and 715 consented for screening. BDI-II ≥16 was present in 231 (32.3%). Forty-two (18.2%) were receiving anti-depressants, psychological therapy or 16 both, so were excluded. Sixty-three underwent psychiatric assessment. MDD was diagnosed in 37 and 30 of these (mean age 61 ±15; 71% male; 60% white) agreed to be randomised. Nine had a past history of depression. Twenty-one (70%) completed the trial, 8 (of 15) on sertraline and 13 (of 15) on placebo. Over 6 months, there was a reduction in BDI-II and MADRS scores ($t(17)=6.3$, $p<0.001$ and $t(20)=11.3$, $p<0.001$ respectively). The reductions were not statistically different in sertraline and placebo groups. Fewer on sertraline completed the trial (6 withdrawals and one death versus 2 withdrawals on placebo [$X2=3.97$, $p=0.046$]). There was a trend towards a more rapid fall in MADRS scores over the first 2 months in the sertraline group (effect size 0.37: lower bound >0).

CONCLUSION: This small study is nevertheless the largest RCT of an anti-depressant in HD patients. There was a similar significant improvement in depression over 6 months in both groups. Recovery may have been quicker on the active drug.

IS DEPRESSION "UNDERRECOGNISED AND UNDERTREATED" IN HAEMODILAYIS PATIENTS

Guirguis, A.[1, 2, 3], Friedli, K.[2], Fineberg, N.A., [2, 3], Day, C.[4], Almond. M.[5], Davenport, A.[5], Da Silva- Gane, M[1]., Chilcot, J.[7], Wellsted, D. [2], Farrington, K.[1, 2]

[1]E&N Herts NHS Trust, [2] University of Herts, [3]Herts Partnership University NHS Foundation Trust, [4]University Hospitals Birmingham NHS Foundation Trust, [5]Southend University Hospital NHS Foundation Trust, [6]Royal Free London NHS Foundation Trust and [7]King's College London

AIMS: To recognise the degree to which depressive symptoms in End Stage Renal Disease (ESRD) patients undergoing haemodialysis (HD) are recognised and treated or not.

BACKGROUND: Depression is often said to be unrecognized and undertreated in patients with chronic medical illness leading to negative outcomes. Part of the problem may be symptom overlap between depression and uraemia. Prevalence estimates of depression in this population vary widely from 15% to 69%. Depressive symptoms in ESRD may negatively affect general health awareness mortality rate, treatment adherence and inpatient hospitalisation. It is therefore an important health issue in this population.

METHODS: We studied all haemodialysis patients at 3 renal centres across England. Inclusion criteria were; having been on dialysis >3 months, >18years of age and being able to read and speak English. All eligible patients were screened for depression using Beck Depressive Inventory Version II (BDI-II). Medication status was obtained by patients self-reports and medical records.

RESULTS: In 480 HD patients (Male 310 (64.6%) mean age was 64.2 ±16.1 years. The mean BDI-II was 13.6, ±11.3. Of these, 168 patients (35%) scored ≥ 16 on the BDI-II representing moderate depressive symptomatology. They were younger than the non-depressed sub-group (mean age 60.6 v 66.1 years: $p = 0.004$). 89 patients (18.5% of the whole HD group) were already taking antidepressants-25 of 312 patients with low BDI (8.1%) and 64 of 168 with high BDI (38%). In those with high BDI-patients taking antidepressants had a higher mean BDI score (30.6 ± 10.4 v 25.0 ± 7.2: $p< 0.001$) than untreated patients. They tend to be younger (55.9 SD 16.6 v 62.2 SD 16.5 years: $p = 0.081$) but appeared to be similar with respect to gender, ethnicity, marital status, educational background, dialysis vintage or comorbidity. They had higher median scores in the BDI domains of worthlessness, past failure, and suicidal thoughts ($p < 0.01$ in all cases).

CONCLUSION: >1/3 HD patients had BDI-II ≥ 16 concordant with moderate depressive symptomatology. Antidepressants were commonly prescribed in this group and those taking antidepressants had high depressive symptomatology compared to their untreated counterpart, questioning the value of antidepressants in this cohort. This is contrary to many previous findings which suggest that depression is under-diagnosed and undertreated in this population. Prospective studies are required to investigate the diagnosis and management of depression in HD patients.

RELATIONSHIP OF DEPRESSIVE SYMPTOMS WITH PROLONED POST-DIALYSIS RECOVERY TIMES

Guirguis, A.[1, 2, 3], Friedli, K.[2], Fineberg, N.A., [2, 3], Day, C.[4], Almond. M.[5], Davenport, A.[5], Da Silva- Gane, M[1]., Chilcot, J.[7], Wellsted, D. [2], Farrington, K.[1, 2]

[1]E&N Herts NHS Trust, [2] University of Herts, [3]Herts Partnership University NHS Foundation Trust, [4]University Hospitals Birmingham NHS Foundation Trust, [5]Southend University Hospital NHS Foundation Trust, [6]Royal Free London NHS Foundation Trust and [7]King's College London

BACKGROUND: The length of time taken for a subject to recover following a haemodialysis session can be prolonged. This self-report parameter has been advocated as a marker of the quality of haemodialysis delivery but the factors associated with the phenomenon have received little attention. This is important since there is little point accumulating data on an indicator of quality if it cannot be modified. Depression is a potential contributant to prolonged self-report recovery times. This study investigates this relationship in a large cohort of centre-based haemodialysis patients.

METHODS: We measured depressive symptoms using the Beck depression Inventory (BDI-II) in subjects on centre-based haemodialysis for more than 3 months in 5 UK centres. Subjects were also asked to provide an estimate of the time it normally took them to recover fully following a haemodialysis session. Demographic and clinical information was also collected including self-report comorbidity. In a smaller cohort of patients we screened for fatigue using the Multifactorial Fatigue Inventory (MFI).

RESULTS: A total of 689 subjects were studied. In these subjects recovery time was reported as less than one hour in 23.7%, 1 to 4 hours in 26.3%, 4 to 8 hours in 14.9% , 8 to 12 hours in 10.9%, and over 12 hours in 22.4%. The median BDI-II score was closely related to recovery time being respectively 6 (range 35), 11 (range 45), 12 (range 52), 14 (range 47), 12 (range 57) in these time periods ($p < 0.001$). In patients with prolonged recovery times (>8 hours), median BDI-II score was significantly higher than in those with faster recoveries [12(range 57) v 8(range 52): p<001]. More had a history of depression in the prolonged recovery group (34.2% v 20.4%: $p < 0.001$), more were taking antidepressants (27.1% v 15.9%: $p < 0.001$) and more had significant depressive symptoms - BDI-II >15 (47% v 33%: $p < 0.001$). Median age was slightly but not significantly less in those prolonged recovery (64 v 69 years), and women were more prevalent in this group (45% v 32%:p =.0.001). There was no relation to ethnicity or co-morbidity (diabetes, heart disease, cancer, lung and liver disease), though there was a significant centre effect with the proportion of subjects reporting long recovery varying from 26.4% to 44.7% among the 5 centres ($p = 0.002$). The best logistic regression model of prolonged recovery time included centre, gender, past history of depression, and BDI-II score but explained only 10% of the variation. In a smaller cohort (N = 445) of the same population the mean General Fatigue Score (component of the MFI) was also found to be significantly higher in those with prolonged recovery (14.6 ± 3.4 v 12.3 ±3.9: p <0.001). Adding

this to the previous logistic regression model improved its predictive power to 17% but rendered BDI-II score non-significant in the model.

CONCLUSIONS: There is only a weak association of depressive symptoms with post-dialysis recovery time and this is likely to be mediated by the somatic element of the BDI-II score to which the symptom of fatigue is a major contributant.

COMPARISON OF PATIENT HEALTH QUESTIONNAIRE 9 AND BECK DEPRESSION INVENTORY VERSION II FOR DEPRESSION SCREENING IN HAEMODIALYSIS PATIENTS

Friedli, K.[1], Guirguis, A.[1, 2], Fineberg, N.A. [2, 3], Day, C.[4], Almond. M.[5], Davenport, A.[5], Da Silva- Gane, M[2]., Chilcot, J.[7], Wellsted, D. [2], Farrington, K.[1, 2]

[1]University of Hertfordshire, [2]East and North Hertfordshire NHS Trust, [3]Hertfordshire Partnership University NHS Foundation Trust, [4]University Hospitals Birmingham NHS Foundation Trust, [5]Southend University Hospital NHS Foundation Trust, [6]Royal Free London NHS Foundation Trust, [7]King's College London

BACKGROUND: Depression is common in haemodialysis (HD) patients but diagnosis is difficult because of the considerable overlap between symptoms with those of uraemia. Use of simple screening tools such as the Beck Depression Inventory Version II (BDI-II) may be helpful in identifying patients likely to be depressed but screening cut-off points – indicative of a high likelihood of diagnosed depression – are higher than those for the general population. For the BDI-II the widely accepted cut-off is ≥ 16 but there is little data on the corresponding cut-off values for other commonly used screening tools. We aimed to compare screening cut-off values for the Patient Health Questionnaire 9 (PHQ-9) with that of the BDI-II in the HD population.

METHOD: We surveyed HD patients at 3 renal centres across England as part of a larger study. Inclusion criteria were dialysis vintage > 3 months, aged >18 years and ability to read and speak English. Eligible patients were screened for depression using the BDI-II and PHQ-9. We compared the two measures and using the recognised cut-off point on the BDI-II of ≥ 16 we used Receiver Operating Characteristics (ROC) analysis to determine the cut-off point on the PHQ-9 scale. We then determined levels of agreement between these cut-off points using Cohen's κ statistic.

RESULTS: 337 patients (62% males) completed the screening questionnaires. Median (interquartile range) for the BDI-II and PHQ-9 were 10(5-20) and 5(2-11) respectively. There was a significant correlation between the PHQ-9 and the BDI-II (rho 0.89: P <0.001). Using the BDI-II cut-off, the area under the curve in the ROC

analysis for the PHQ-9 was 0.96 (CI 0.94-0.98) and the optimal cut-off point for PHQ-9 was ≥8 (sensitivity 88%, specificity 89%). There was substantial agreement between PHQ-9 ≥ 8 and BDI-II ≥ 16 ($\kappa = 0.758$: $p < 0.001$), exceeding the levels of agreement for all other possible PHQ-9 cut-off points. However 6.8% of patients with PHQ-9 < 8 had a BDI-II score ≥ 16, whilst 18.5% of those with a PHQ-9 ≥8 had a BDI-II score <16.

CONCLUSION: Our results suggest that the PHQ-9 is an acceptable screening tool compared to the BDI-II in dialysis patients, with a cut-off point of ≥ 8 approximating a BDI-II cut-off ≥ 16. The availability of simple screening tools in clinical practice may assist the detection of depression in the HD population and lead to better clinical outcomes.

DEPRESSIVE SYMPTOMS PREDICT POST DIALYSIS RECOVERY TIME

Friedli, K.[1], Guirguis, A.[1, 2], Fineberg, N.A. [2, 3], Day, C.[4], Almond. M.[5], Davenport, A.[5], Da Silva- Gane, M[2]., Chilcot, J.[7], Wellsted, D. [2], Farrington, K.[1, 2]

[1]University of Hertfordshire, [2]East and North Hertfordshire NHS Trust, [3]Hertfordshire Partnership University NHS Foundation Trust, [4]University Hospitals Birmingham NHS Foundation Trust, [5]Southend University Hospital NHS Foundation Trust, [6]Royal Free London NHS Foundation Trust, [7]King's College London

BACKGROUND: Delayed recovery post dialysis is a frequent complaint in haemodialysis patients. Its duration is not predicted by clinical measures such as; nutrition, laboratory results, or the adequacy of dialysis. Furthermore, patients with this problem experience significant limitations in their day to day activities, including participation in social activities, on the day of dialysis.

METHOD: We conducted a survey of haemodialysis patients at 3 renal centres across England as part of a larger study. Inclusion criteria were dialysis vintage > 3 months, age over 18 years and ability to read and speak English. Eligible patients were screened for depression using The Beck Depressive Inventory Version II (BDI-II) and Patient Health Questionnaire 9(PHQ-9). Post-dialysis recovery duration was collected using patients self-reports, categorised as (<1hr, 1-4hrs, 4-8hrs, 8-12hrs, >12hrs).

RESULTS: In 332 HD patients (male 62.7%: mean age 64.2 ±16.1 years), mean BDI-II and PHQ-9 was 13.6± 11.3, 6.9 ± 6.2 respectively. 111 (35%) scored ≥ 16 on BDI-II, representing moderate depressive symptomatology. Recovery time was < 1hr in 25.7%, 1-2hrs in 20.4%, 4-8hrs in 26.3%, 8-12hrs in 10.9% and >12hrs in 14.8%. In groups with recovery time >8 hrs, the mean BDI-II was significantly higher than those with shorter recovery times (17.0 ± 12.3 versus 11.6 ± 10.0, $p<0.001$). Corresponding values for PHQ-9 were 8.7 ± 6.9 versus 6.0 ± 5.6 ($p< 0.001$). A higher recovery time was more common in females (46.3% versus 29.7%, $p=0.002$) and in those with a past history of depression ($p=0.004$). There were marginal differences in age (65.5 ± 15.9 versus 61.9 ± 16.1, $p<0.054$). There were no differences in comorbidity (heart disease, cancer, amputation, lung disease and liver disease), ethnicity, body weight, blood pressure, haemoglobin, albumin, Kt/V,

dialysis vintage, number of previous transplants, marital status, or maximum educational attainment. In logistic regression, depression screening score (BDI or PHQ9) and gender were the only significant predictors of recovery time > 8 hours.

CONCLUSION: Prolonged recovery time following dialysis is more common in women and associated with high depression screening scores.

British Renal Society/ Renal Association, Glasgow- 29 Apr – 02 May, 2014

DEPRESSIVE SYMPTOMS ARE COMMON IN HAEMODIALYSIS PATIENTS DESPITE ANTIDEPRESSANT PHARMACOTHERAPY

Guirguis, A.[1, 2, 3], Friedli, K.[2], Fineberg, N.A., [2, 3], Day, C.[4], Almond. M.[5], Davenport, A.[5], Da Silva- Gane, M[1]., Chilcot, J.[7], Wellsted, D. [2], Farrington, K.[1, 2]

[1]E&N Herts NHS Trust, [2] University of Herts, [3]Herts Partnership University NHS Foundation Trust, [4]University Hospitals Birmingham NHS Foundation Trust, [5]Southend University Hospital NHS Foundation Trust, [6]Royal Free London NHS Foundation Trust and [7]King's College London

INTRODUCTION: Under-recognition of depression in patients with end-stage renal disease (ESRD) contributed to by symptom overlap with those of the uraemic syndrome, results in wide variation in prevalence estimates ranging from 15% to 69%. Depressive symptoms in ESRD may negatively affect quality of life, mortality rate, treatment adherence and hospitalisation. We aimed to determine the frequency of depressive symptoms and antidepressant medications in ESRD patients undergoing haemodialysis (HD).

METHODS: We studied HD patients at 3 UK renal centres. Inclusion criteria: being on dialysis for over 3 months, age over 18 years and proficiency in English. All eligible patients were screened using Beck Depressive Inventory Version II (BDI-II). Medication status was obtained by patient self-report and from medical records.

RESULTS: In 317 HD patients (male 62.7%: mean age 64.2 ±16.1 years) mean BDI-II was 13.6 ± 11.3. 111 (35%) scored ≥ 16 on BDI-II, representing moderate depressive symptomatology. These were younger than those with lower BDI (mean age 60.6 v 66.1 years: $p = 0.004$), and more had a past-history of depression (53% vs 16%: $p < 0.001$). 45 (14% of the whole HD group) were already taking antidepressants - 16 of 206 patients with low BDI (7.8%) and 29 of 111 with high BDI (26%). In those with high BDI-patients taking antidepressants had a higher mean BDI score (30.6 ± 10.4 vs 25.0 ± 7.2: $p < 0.001$) than untreated patients. They were younger (55.9 ±16.6 vs 62.2 ± 16.5 years: $p = 0.081$) but appear to be similar with respect to gender, ethnicity, marital status, educational background, dialysis vintage or comorbidity. They had higher median scores in the BDI domains of worthlessness, past failure, and suicidal thoughts ($p < 0.01$ in all cases).

CONCLUSIONS: Over 1/3 of HD patients had moderate depressive symptomatology, concurring with existing literature. BDI scores were high despite antidepressant treatment in many, often higher than in untreated patients with high BDI, questioning the effectiveness of antidepressant pharmacotherapy in this population. Prospective studies of antidepressant efficacy in ESRD are required.

British Renal Society/ Renal Association, Glasgow- 29 Apr – 02 May, 2014

STRONG ASSOCIATION OF FATIGUE AND DEPRESSIVE SYMPTOMS IN HAEMODIALYIS PATIENTS

Guirguis, A.[1, 2, 3], Friedli, K.[2], Fineberg, N.A., [2, 3], Day, C.[4], Almond. M.[5], Davenport, A.[5], Da Silva- Gane, M[1]., Chilcot, J.[7], Wellsted, D. [2], Farrington, K.[1, 2]

[1]E&N Herts NHS Trust, [2] University of Herts, [3]Herts Partnership University NHS Foundation Trust, [4]University Hospitals Birmingham NHS Foundation Trust, [5]Southend University Hospital NHS Foundation Trust, [6]Royal Free London NHS Foundation Trust and [7]King's College London

INTRODUCTION: Fatigue is a psychosomatic syndrome that is common in chronic disease. It is the major overlapping symptom linking depression and advanced kidney disease. The literature regarding the prevalence and determinants of fatigue in haemodialysis patients is sparse. We undertook this study in order to investigate the associations between fatigue and demographic, clinical and psychological factors in patients on Haemodialysis (HD).

METHOD: We studied 104 unselected HD patients across 3 UK renal centres .Patients were screened for fatigue using Multidimensional Fatigue Inventory (MFI), and for depression using Beck Depressive Inventory Version II (BDI-II) and Patient Health Questionnaire 9 (PHQ-9). Demographic and clinical data were also collected.

RESULTS: Mean age was (61.1±16.7). 71% were male. 72.1% were white. Median dialysis vintage was 31.5 (IQR 70.8) months. 31.7% were diabetics, 30.8% had heart disease, 7.7% had a previous stroke, 7.7% had previous history of cancer and 30.7% had a past history of depression. 34% had a high BDI score (>16). There was a weak negative correlation between age and Mental Fatigue score (rho = -0.227: p=0.02) but no relation between gender or ethnicity and any fatigue subscale. Dialysis vintage correlated with Mental Fatigue score (rho 0.290: p=0.005) but with no other fatigue subscale score. Patients with diabetes had higher scores for General Fatigue (14.2±3.0 v 12.6±3.6: p=0.026) and Physical Fatigue (15.9±3.0 v14.0±4.0: p=0.013), but Mental Fatigue scores was not different to that in non-diabetic. Patients with a high BDI score had higher scores in all 3 fatigue subscales than those below this threshold (General 15.1±2.5v12.2±3.5, Mental 11.8±4.3v8.2±3.7, Physical 16.4±2.9v13.7±4.0: p<0.001 in all cases). There were strong correlations between

BDI score and General Fatigue (rho=0.542: p<0.001), Mental Fatigue score (rho=0.429: p<0.001) and Physical Fatigue score (rho= 0.419: p<0.001). Corresponding values for PHQ-9 were (rho=0.492, 0.470, 0.400: p<0.001) in all cases. In a series of multivariate models controlled for age, gender, ethnicity, dialysis vintage, marital status, diabetes, multi-morbidity, past history of depression, pre-dialysis systolic blood pressure, haemoglobin, albumin and Kt/V, the major factor associating with all fatigue scores (general, mental and physical subscales) was depressive symptoms measured by either BDI or PHQ-9. The most powerful model $R^2 = 0.43$ described the association of BDI with Mental Fatigue and included dialysis vintage (p=0.01), diabetes (p=0.046) and haemoglobin (p= 0.030) as other significant factors.

CONCLUSION: Depression scores are the strongly associated with all fatigue subscales General, Mental and Physical. This emphasise the strong overlap of depressive symptoms and fatigue in this population which complicates the diagnosis of depression.

CHARACTERISTICS OF FATIGUE AND DEPRESSIVE SYMPTOMS IN HAEMODIALYSIS PATIENTS

Guirguis, A.[1, 2], Friedli, K.[2], Fineberg, N.A. [2, 3], Day, C.[4], Almond. M.[5], Davenport, A.[5], Da Silva- Gane, M[2]., Chilcot, J.[7], Wellsted, D. [2], Farrington, K.[1, 2]

[1]East and North Hertfordshire NHS Trust, [2] University of Hertfordshire, [3]Hertfordshire Partnership University NHS Foundation Trust, [4]University Hospitals Birmingham NHS Foundation Trust, [5]Southend University Hospital NHS Foundation Trust, [6]Royal Free London NHS Foundation Trust,[7]King's College London

AIMS AND HYPOTHESIS: We undertook this study in order to investigate whether there are distinctive characteristics of fatigue as defined by the Multidimensional Fatigue Inventory (MFI), which may relate more strongly to depressive symptomatology than other characteristics. This knowledge could lead to refinements of the screening tools for depression in this cohort.

BACKGROUNDS: Depressive symptomatology is very common in patients with advanced kidney disease. Diagnosis of depression in these patients is complicated by overlapping symptoms. Fatigue is a psychosomatic syndrome that is also common in chronic disease, and a key area of overlap. Its prevalence ranges from 42% - 89% according to treatment modality and assessment instruments employed.

METHODS: We studied 244 unselected HD patients across 3 UK renal centres. Inclusion criteria: being on dialysis for over 3 months, age over 18 years and proficiency in English. Patients were screened for fatigue using MFI, and for depression using Beck Depressive Inventory Version II (BDI-II). Demographic and clinical data were also collected.

RESULTS: Mean age was (63.1±17.6). 64.3% were male. 71.3% were white. Median dialysis vintage was 31.5 (IQR 70.8) months. Mean BDI-II score was (12.7±10.5). 34.7% had a high BDI score (>16).Mean scores in the different MFI domains were 13.2 ± 3.8 for General Fatigue, 9.5 ± 4.3 for Mental Fatigue and 14.7 ± 4.1 for Physical Fatigue. BDI score correlated with age (rho = -0.223: p = 0.001), and all the fatigue scales - General (rho = 0.641: p <0.001), Mental (rho = 0.573: p < 0.001), Physical (rho = 0.521: p < 0.001). In models adjusted for age, gender, ethnicity, and marital status, the best predictor of BDI-II Score was Mental Fatigue

accounting for 41% of the variation (adjusted R-square = 0.412: $p < 0.001$), followed by General Fatigue accounting for 38% (adjusted R-square = 0.377 : $p < 0.001$) and Physical Fatigue accounting for 29% (adjusted R-square = 0.294: $p < 0.001$). For high depression scores (BDI-II $\geq$ 16) adjusted for the same factors Mental (Nagelkerke R-square 0.410: $p < 0.001$), and General (Nagelkerke R-square 0.412: $p < 0.001$) had similar predictive power which was superior to that of Physical Fatigue (Nagelkerke R-square 0.372: $p < 0.001$).

CONCLUSIONS: BDI-II scores and those in all 3 MFI subscales were highly correlated. Adjusted scores for Mental Fatigue performed marginally better than General Fatigue scores in predicting BDI-II but similarly in predicting high BDI-II scores. Physical Fatigue scores were less predictive on both counts. It may be possible to adjust depression screening methodology to take more account of Mental Fatigue. The relationships between scores in MFI domains and diagnosed depression need to be studied.

CHARACTERISTICS OF FATIGUE AND DEPRESSIVE SYMPTOMS IN HAEMODIALYSIS PATIENTS

Guirguis, A.[1, 2, 3], Friedli, K.[2], Fineberg, N.A., [2, 3], Day, C.[4], Almond. M.[5], Davenport, A.[5], Da Silva- Gane, M[1]., Chilcot, J.[7], Wellsted, D. [2], Farrington, K.[1, 2]

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ethnicity, and marital status, the best predictor of BDI-II Score was Mental Fatigue accounting for 41% of the variation (adjusted R-square = 0.412: $p < 0.001$), followed by General Fatigue accounting for 38% (adjusted R-square = 0.377 : $p < 0.001$) and Physical Fatigue accounting for 29% (adjusted R-square = 0.294: $p < 0.001$). For high depression scores (BDI-II $\geq$ 16) adjusted for the same factors Mental (Nagelkerke R-square 0.410: $p < 0.001$), and General (Nagelkerke R-square 0.412: $p < 0.001$) had similar predictive power which was superior to that of Physical Fatigue (Nagelkerke R-square 0.372: $p < 0.001$)

CONCLUSION: BDI-II scores and those in all 3 MFI subscales were highly correlated. Adjusted scores for Mental Fatigue performed marginally better than General Fatigue scores in predicting BDI-II but similarly in predicting high BDI-II scores. Physical Fatigue scores were less predictive on both counts. It may be possible to adjust depression screening methodology to take more account of Mental Fatigue. The relationships between scores in MFI domains and diagnosed depression need to be studied.

Appendix 3 – Prizes

British Association for Psychopharmacology

36 Cambridge Place • Hills Road • Cambridge • CB2 1NS
Tel: 01223 358 395 • Fax: 01223 321 268 • www.bap.org.uk

Executive Officer Mrs Susan Chandler • Tel: 01223 358 428 • susan@bap.org.uk Assistant to the Executive Officer Mrs Lynne Harmer • Tel: 01223 358 421 • lynne@bap.org
Online Resources and Communications Developer Miss Sarah Channing-Wright • Tel: 01223 358 396 • sarah@bap.org.uk

This is to certify that

POSTER AWARD IS PRESENTED

TO

DR AYMAN GUIRGUIS

At the BAP Summer Meeting held 20 – 23 July 2014 in Cambridge

In Recognition to

Best-IN-GROUP-POSTER

IS DEPRESSION "UNDERRECOGNISED AND UNDERTREATED" IN HAEMODILAYIS PATIENTS

Lynne Harmer
BAP Assistant to the Executive Officer

The Royal College of Psychiatrists
hereby certifies that
Dr Ayman ***Guirguis*** *K* ***Friedli*** *N* ***Fineberg*** *C* ***Day*** *M* ***Almond*** *A* ***Davenport*** *M* ***Da Silva-Gane*** *J* ***Chilcot*** *D* ***Wellsted*** *k* ***Farrington***

Presented/Authored the poster

CHARACTERISTICS OF FATIGUE AND DEPRESSIVE SYMPTOMS IN HAEMODIALYSIS PATIENTS

At

International Congress of the Royal College of Psychiatrists 2014
The Barbican Centre, London, UK
On

25 June 2014

And *Dr GUIRGUIS* was awarded

the BEST- IN- GROUP POSTER

PRIZE

Professor Peter Woodruff
Faculty of Academic Psychiatry

Royal College of Psychiatrists registered office: 21 Prescot Street, London, E1 8BB Tel: +44(0)20 7235 2351 Fax: +44 (0)20 3701 2761
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THE RENAL ASSOCIATION
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The Scottish Renal Association

BRITISH RENAL SOCIETY
MULTI-PROFESSIONAL TEAM

UKKW 2014

The UKKW 2014
Poster Award
is presented to

Ayman Guirguis

In recognition of

Best-in-group Poster

Simon Ball
BRS President

David Wheeler
RA President

Appendix 4 – List of Publications

Friedli et al. BMC Nephrology (2015) 16:172
DOI 10.1186/s12882-015-0170-x

BMC Nephrology

STUDY PROTOCOL Open Access

A study of sertraline in dialysis (ASSertID): a protocol for a pilot randomised controlled trial of drug treatment for depression in patients undergoing haemodialysis

Karin Friedli[1*], Michael Almond[4,10], Clara Day[3], Joseph Chilcot[6], Maria da Silva Gane[1,2], Andrew Davenport[5], Ayman Guirguis[2,7,10], Naomi Fineberg[7,10], Benjamin Spencer[8,9], David Wellsted[1] and Ken Farrington[2,10]

Abstract

Background: The prevalence of depression in people receiving haemodialysis is high with estimates varying between 20 and 40 %. There is little research on the effectiveness of antidepressants in dialysis patients with the few clinical trials suffering significant methodological issues. We plan to carry out a study to evaluate the feasibility of conducting a randomised controlled trial in patients on haemodialysis who have diagnosed Major Depressive Disorder.

Methods/Design: The study has two phases, a screening phase and the randomised controlled trial. Patients will be screened initially with the Beck Depression Inventory to estimate the number of patients who score 16 or above. These patients will be invited to an interview with a psychiatrist who will invite those with a diagnosis of Major Depressive Disorder to take part in the trial. Consenting patients will be randomised to either Sertraline or placebo. Patients will be followed-up for 6 months.
Demographic and clinical data will be collected at screening interview, baseline interview and 2 weeks, and every month (up to 6 months) after baseline. The primary outcome is to evaluate the feasibility of conducting a randomised, double blind, placebo pilot trial in haemodialysis patients with depression. Secondary outcomes include estimation of the variability in the outcome measures for the treatment and placebo arms, which will allow for a future adequately powered definitive trial. Analysis will primarily be descriptive, including the number of patients eligible for the trial, drug exposure of Sertraline in haemodialysis patients and the patient experience of participating in this trial.

Discussion: There is an urgent need for this research in the dialysis population because of the dearth of good quality and adequately powered studies. Research with renal patients is particularly difficult as they often have complex medical needs. This research will therefore not only assess the outcome of anti-depressants in haemodialysis patients with depression but also the process of running a randomised controlled trial in this population. Hence, the outputs of this feasibility study will be used to inform the design and methodology of a definitive study, adequately powered to determine the efficacy of anti-depressants in patient on haemodialysis with depression.

Trial registration: ISRCTN registry ISRCTN06146268 and EudraCT reference: 2012-000547-27.

Keywords: Depression, End stage renal disease, Haemodialysis, Sertraline, Feasibility RCT

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Full list of author information is available at the end of the article

Article

Sertraline Versus Placebo in Patients with Major Depressive Disorder Undergoing Hemodialysis: A Randomized, Controlled Feasibility Trial

Karin Friedli, Ayman Guirguis, Michael Almond, Clara Day, Joseph Chilcot, Maria Da Silva-Gane, Andrew Davenport, Naomi A. Fineberg, Benjamin Spencer, David Wellsted, and Ken Farrington

Abstract

Background and objectives Depression is common in patients on hemodialysis, but data on the benefits and risks of antidepressants in this setting are limited. We conducted a multicenter, randomized, double-blind, placebo-controlled trial of sertraline over 6 months in patients on hemodialysis with depression to determine study feasibility, safety, and effectiveness.

Design, setting, participants, & measurements Patients on hemodialysis at five United Kingdom renal centers completed the Beck Depression Inventory II. Those scoring ≥16 and not already on treatment for depression were invited to undergo diagnostic interview to confirm major depressive disorder. Eligible patients with major depressive disorder were randomized to receive the study medication—either sertraline or placebo. Outcomes included recruitment and dropout rates, change in the Montgomery–Asberg Depression Rating Scale and Beck Depression Inventory II, and qualitative information to guide design of a large-scale trial.

Results In total, 709 patients were screened and enrolled between April of 2013 and October of 2014; 231 (32.6%) had Beck Depression Inventory II scores ≥16, and 68 (29%) of these were already receiving treatment for depression. Sixty-three underwent diagnostic interview, 37 were diagnosed with major depressive disorder, and 30 were randomized; 21 completed the trial: eight of 15 on sertraline and 13 of 15 on placebo (P=0.05). Dropouts due to adverse and serious adverse events were greater in the sertraline group. All occurred in the first 3 months. Over 6 months, depression scores improved in both groups. Beck Depression Inventory II score fell from 29.1±8.4 to 17.3±12.4 (P<0.001), and Montgomery–Asberg Depression Rating Scale score fell from 24.5±4.1 to 10.3±5.8 (P<0.001). There were no differences between sertraline and placebo groups.

Conclusions Although small, this is the largest randomized trial to date of antidepressant medication in patients on hemodialysis. Our results highlight recruitment issues. No benefit was observed, but trial size and the substantial dropout render consideration of benefit inconclusive. A definitive trial could use shorter follow-up and include depressed patients already taking antidepressants.

Clin J Am Soc Nephrol 12: 280–286, 2017. doi: 10.2215/CJN.02120216

Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

Correspondence: Ken Farrington, Renal Unit, Lister Hospital, Stevenage, SG1 4AB, United Kingdom. E-mail: ken.farrington@nhs.net

Introduction

The prevalence of adult patients receiving RRT continues to increase across the developed world. In 2012, the numbers on dialysis ranged from 133 per 1 million population in South Africa to 2903 per 1 million population in Taiwan (1). Patients on dialysis have high morbidity and mortality. Patients' experience of living with dialysis is significantly affected by many factors, including physical symptoms, substantial comorbidity (particularly cardiovascular), complex dialysis regimens, high pill burdens, and the need for dietary and fluid restrictions (2–4).

Although common in this setting, depression is difficult to diagnose, not least because of the symptom overlap between depression and advanced kidney disease (5–7). Estimates of prevalence of depression in patients on dialysis vary between 39% on the basis of screening and 23% on the basis of psychiatric interview (8). Depression is associated with reduced quality of life, increased prevalence of cardiovascular disease, and increased mortality. It may lead to reduced treatment adherence, reduced self-care behavior, and subsequently, greater health care resource use (9–11). The prevailing view is that depression is often unrecognized, and therefore, only a small proportion of patients receives treatment (12–15). There is little research on treatment options, particularly in relation to the use of antidepressant medication (12). A 2009 Cochrane review identified only one small randomized, controlled trial (RCT) with 14 patients. Results were inconclusive (16,17). It is perhaps unsurprising that recent systematic reviews recommended a large well designed RCT in this setting (8,18).

National Institute for Health and Care Excellence (NICE) guidance for depression in adults with chronic

Appendix 5 – Participants' Information Sheets and Consent

Participant Information Sheet 1

FULL STUDY TITLE: A Pilot Randomised Controlled Trial of Drug Treatment for Depression in Patients undergoing Haemodialysis

Short Study Title: ASSERTID (A study of Sertraline in Dialysis)

Screening and Prevalence Phase

We would like to invite you to take part in our research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. The research nurse will be happy to discuss any questions you may have. Take time to decide whether or not you wish to take part. Thank you for reading this.

WHAT IS THE RESEARCH ABOUT?

The aim of this phase of the study is to find out how people on haemodialysis feel. In particular, we are interested in knowing more about the mood and feeling of tiredness of people on haemodialysis. The research will investigate how many people on haemodialysis have low mood (for example feeling sad or down) and feeling tired with no energy, so that we can assess whether additional care to try and help with low mood should routinely be offered to people on haemodialysis. The study as a whole will look at helping people on haemodialysis with these problems. If you are affected by low mood, you may be invited to take part in another phase of this study.

WHY HAVE I BEEN INVITED?

You have been approached about this phase of the study because you use are on haemodialysis. We would like to ask all patients on haemodialysis to take part to find out the number of patients affected by low mood.

DO I HAVE TO TAKE PART?

It is up to you to decide to join this phase of the study. We will describe the study and go through this information sheet. If you agree to take part, we will ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This will not affect the standard of care you receive.

WHAT WILL HAPPEN TO ME IF I TAKE PART AND WHAT WILL I HAVE TO DO?

If you agree to take part, you will need to answer a number of questions. This should take between 15 and 20 minutes. First the research nurse will approach you on a

dialysis day and ask you a small number of questions about your kidney disease, whether you have any other medical problems and whether you have ever been treated for depression. The research nurse will collect some of this information from your medical notes, in particular results of recent blood tests and blood pressure recordings. Secondly, the research nurse will ask you to complete two short questionnaires, by ticking boxes. These questionnaires are standardised questionnaires which are used routinely in the NHS.

WHAT WILL HAPPEN TO ME IF I DO NOT WANT TO TAKE PART?

It is completely your decision whether you take part in this phase of the study and you will not be forced into the study. If you do take part now this does not mean that you have to take part in later phases of the study. You are free to withdraw at any time. Your level of care will not be affected in any way if you decide not to participate.

ARE THERE ANY POSSIBLE BENEFITS IN MY TAKING PART?

There may not be any direct benefits for you taking part in this phase of the study. However, if the questions you answer seem to show you are feeling low, in discussion with you we will offer to refer you to someone who may be able to help. This might be your nephrologist, your general practitioner or a member of the mental health care team such as a renal counsellor or a psychiatrist to discuss what options are available to you.

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART?

You will be asked some questions about your mood, using questionnaires that are routinely used for this purpose. Occasionally these questions can be a bit upsetting so it is important to remember that you do not have to answer any questions you do not want to.

WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL?

All information collected about you will be kept strictly confidential. We follow ethical and legal practices and all information about you will be handled in confidence. All data collection sheets and questionnaires will be assigned a number and will not have your name on, so you could not be recognised from it. The data collected, including the questionnaires will be stored in locked filing cabinets in the hospital renal unit research offices. Only authorised persons will have access. All data entered on the electronic database will be securely entered and accessed by authorised research personnel only through a password protected system. If you join the study, some parts of your medical records and the data collected for the study may be looked at by authorised persons from the University of Hertfordshire and the participating NHS Trusts (East and North Herts NHS Trust, University Hospital Birmingham NHS Foundation Trust, Royal Free Hampstead NHS Trust and Southend University Hospital Foundation Trust) to check that the study is being

carried out correctly. Sometimes regulatory authorities also need to look at the records. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed by them outside the research site. Data will be stored for 15 years and will be destroyed after this time.

WHAT WILL HAPPEN IF I DON'T CARRY ON WITH THE STUDY?

You are free to withdraw from the study at any time, simply by telling a research nurse your wish to do so. You do not have to give a reason. If you withdraw completely from the study, we would still like to use the data collected up to your withdrawal, but is we do, we will ensure that you cannot be identified from such data.

WHAT WILL HAPPEN TO THE RESULTS OF THE STUDY?

The results of the study will be published in medical and health journals and will be presented at meetings. Any research publications will not identify you individually. If you would like a copy of the published research, let one of the researchers know, and we would be delighted to send any publications describing the results of this research to you when they become available.

WHO IS ORGANISING AND FUNDING THE STUDY?

Professor Ken Farrington, a kidney doctor at the Lister Hospital in Stevenage, Hertfordshire is the lead investigator. He is organising the study, together with three other kidney doctors from different hospitals, as well as other health care professionals and a team of researchers. East and North Herts NHS Trust and the University of Hertfordshire are the sponsors of this study. The sponsors have received funding from the National Institute for Health Research to conduct this study.

WHAT IF THERE IS A PROBLEM?

As this phase of the study only involves answering some questions there is unlikely to be any problems. If you have any concern about any aspect of this study, you should ask to speak to the Trial Manager or the Chief Investigator, who will do their best to answer your questions (contact details: University of Hertfordshire, CLiCIR, College Lane, Hatfield, tel: 01707 286472). If you remain unhappy and wish to complain about any aspect of the way you are approached or treated during the course of this study, you can contact your local PALS office (Patient Advice and Liaison Service) at your hospital. If you require independent advice about making a complaint or seeking compensation, you may wish to contact the Independent Complaints Advocacy Service (ICAS).

Formal complaints should be addressed to:

Insert local site PALS

Insert local site ICAS details

DOES YOUR GP (GENERAL PRACTITIONER) GET INVOLVED?

If you agree to take part in this phase of the study, we would like to inform your GP about your participation if you are found to have low mood.

WHO HAS REVIEWED THE STUDY?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has received ethical approval from the National Research Ethics Committee *(Add a reference).*

FURTHER INFORMATION AND CONTACT DETAILS

If you have any further questions about this research (general or specific), please feel free to speak to the Trial Manager on 01707 286472. *Add local PI and research nurse at each site.*

THANK YOU FOR TAKING TIME TO READ THIS INFORMATION SHEET.

Participant Information Sheet 2

FULL STUDY TITLE: A Pilot Randomised Controlled Trial of Drug Treatment for Depression in Patients undergoing Haemodialysis

Short Study Title: ASSERTID (A study of Sertraline in Dialysis)

Psychiatric Assessment and Clinical Trial Phase

We would like to invite you to take part in our research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. The research nurse will be happy to discuss any questions you may have. Take time to decide whether or not you wish to take part. Thank you for reading this.

WHAT IS THE RESEARCH ABOUT?

We realise that a significant number of patients on haemodialysis suffer from low mood and feeling tired with no energy, and we are keen to find out more to help these symptoms. We are particularly interested in looking at the use of anti-depressant tablets in helping patients on haemodialysis who are also depressed.

To find out if anti-depressants help patients on haemodialysis who are depressed, we need to do a "double blind" randomised controlled placebo trial.

- A **placebo** is a medication that looks exactly the same as the study medication but which has no effects
- A **randomised** trial means that you are allocated to either treatment medication or placebo by chance
- **Double blind** means that neither you nor your doctor will know in which treatment group you are (although if your doctor needs to find out he/she can do so).
- Sometimes this is simply called a **clinical trial**.

There are several steps in this part of the study:

1. You will be seen by the trial psychiatrist at your dialysis unit who will decide whether they think you have symptoms of clinical depression
2. If you are felt to be depressed you will be offered the opportunity to enter the next phase of the trial
3. If you decide to take part you will be allocated, by chance, either the treatment medication or inactive placebo. You will have a fifty percent chance of receiving the anti-depressants and a fifty percent chance of receiving the placebo tablet. Neither you nor your doctor or research team will know which group you are in.

The reason we are doing this type of clinical trial is to:

1. find out if the antidepressant works
2. to see if patients can tolerate the medication without bad side effects.

Information from this quite small study help us to design in future a much larger study in helping patients on haemodialysis with depression.

WHY HAVE I BEEN INVITED?

You already agreed to take part in an earlier phase of the study and we found out that you may be suffering from low mood. The research nurse should have already had a chat to you about your low mood and possible options for further care, including this study. If you expressed interest, the research nurse would have invited you to take part in this phase of the study. If you would rather not take part in this study, we will refer you back to your kidney doctor and the renal team. They will be responsible for further options of your care, such as referral to your general practitioner or referral to a mental health care professional if this is appropriate and you wish it.

DO I HAVE TO TAKE PART?

It is up to you to decide to join this phase of the study. We will describe the study and go through this information sheet. If you agree to take part, we will ask you to sign a consent form to see the psychiatrist. If you are diagnosed with depression after the interview, we will invite you take part in the clinical trial. The psychiatrist will repeat the information about the clinical trial to you as well as other options of care and ask you to sign a separate consent form. You are free to withdraw at any time, without giving a reason. This will not affect the standard of care you receive.

WHAT WILL HAPPEN TO ME IF I TAKE PART AND WHAT WILL I HAVE TO DO?

If you agree to take part, you first need to sign the consent form to see a psychiatrist. The research nurse will arrange a mutually convenient appointment for you to see the psychiatrist. It will probably be on one of your dialysis days. You will be talking to the psychiatrist in a private room and it will take between one and one and a half hours. The psychiatrist will ask a number of general questions about your health as well as specific ones regarding your mental health. They will ask about any previous treatment you may have had for mental disorders. At the end of the interview, the psychiatrist will make a diagnosis.

If you are diagnosed with depression, the psychiatrist will ask you to sign a second consent form to participate in the clinical trial. Then the psychiatrist will randomly put you in the anti-depressant or placebo group that is by chance. You have a fifty percent chance of receiving the anti-depressant and a fifty percent change of receiving the placebo tablet. Neither you, the psychiatrist, the other doctors nor the nurses will know which treatment group you are in. The psychiatrist will give you a prescription to give to your renal nurse. The renal nurse will collect the special study prescription for you. The study medication is packaged in bottles with a study label giving clear instructions on how to take the medicines. You will be asked to take the study medication once a day over the next six months.

In addition to taking the tablets you will be asked a number of questions about yourself, your health and the medication by the research nurse, psychiatrist and your kidney doctor on a monthly basis. They will also ask you to complete a number of questionnaires every two months. The research nurse or doctor will also look at your medical records to collect or confirm some of information about your medical condition. We will take two additional blood tests to look at the levels of the anti-depressant in your blood. These blood samples will be stored until the end of the study when they will be sent to a laboratory for analysis.

We may also ask you to take part in an additional phase of this study which will involve talking to a researcher about your experiences of taking part in this study. We will give you more details about this phase of the study at a later stage and then ask you to confirm whether you wish to participate in this additional phase of the

study. You will not have to take part in this additional phase of the study if you do not want to.

WHAT WILL HAPPEN TO ME IF I DO NOT WANT TO TAKE PART?

It is completely your decision whether you take part in the psychiatric interview and the clinical trial and you will not be forced into the study. If you agree to the psychiatric interview, you can change your mind about taking part in the clinical trial. Your level of care will not be affected in any way if you decide not to participate.

If you decide to not take part or change your mind, we will offer you alternative options of care which may be appropriate for you should you wish it. This will include referral back to your kidney doctor and their team, referral to your general practitioner, referral to a mental health care team or referral to the renal counsellor/psychologist. You may be prescribed an anti-depressant through these alternative options of care.

ARE THERE ANY POSSIBLE BENEFITS IN MY TAKING PART?

Firstly, we will be able to tell you if you suffer from depression. Secondly, you will have the opportunity of joining the clinical trial. We cannot promise the trial will help you, but if you receive treatment with the anti-depressant your mood may improve. The information we get from this study will also help improve the treatment of people with end stage kidney disease and depression. You will have extra contacts with the nursing and medical staff including the psychiatrist throughout the study period of 6 months, who will monitor you carefully.

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART?

You will be asked questions about your mood by the psychiatrist and by completing questionnaires. Occasionally these questions can be a bit upsetting so it is important to remember that you do not have to answer any questions you do not want to.

We cannot promise the trial will help you. You do not know if you are taking the anti-depressant or the placebo. This means that you may feel better but you may also feel worse and your depression may get worse. You will have increased contact with the research nurses and the psychiatrist who can help you if you do get worse. Again,

it is important that you feel free to withdraw at any time and you do not have to give a reason.

WHAT ARE THE SIDE EFFECTS OF THE TREATMENT RECEIVED?

Along with the useful effects of the anti-depressant, most medicines can cause unwanted side effects although not everyone experiences them. Most side effects lessen as your body adjust to the new medicine. Common symptoms are tiredness, feeling dizzy, dry mouth, feeling sick and feeling restless. In past studies, up to 30 per cent of people have reported feeling sick or restless, up to 24 per cent have reported diarrhoea, and up to 16 to 17 percent have reported dizziness, dry mouth or tiredness. There are some very small risks of serious side effects (less than 1 per cent) such as causing rhythm problems in the heart or internal bleeding for instance in the stomach. Part of the objective of this study is to assess the side effects experienced by renal patients.

WHAT HAPPENS WHEN THE RESEARCH STUDY STOPS?

After six months when the clinical trial comes to an end, you will be asked to take a smaller dose of the study medication for one or two weeks. Then your kidney doctor will discuss with the study psychiatrist and together with you, decide whether to recommend any further care for you, including referral to another health care professional or starting medication again.

WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL?

All information collected about you will be kept strictly confidential. We follow ethical and legal practices and all information about you will be handled in confidence. All data collection sheets and questionnaires will be assigned a number and will not have your name on, so you could not be recognised from it. The data collected, including the questionnaires will be stored in locked filing cabinets on the renal unit. Only authorised persons will have access. All data entered on the electronic database will be securely entered and accessed by authorised research personnel only through a password protected system. If you join the study, some parts of your medical records and the data collected for the study may be looked at by authorised persons from the University of Hertfordshire, the Norwich Clinical Trials Unit and the participating NHS Trusts (East and North Herts NHS Trust, University Hospital Birmingham NHS Foundation Trust, Royal Free Hampstead

NHS Trust and Southend University Hospital Foundation Trust) to check that the study is being carried out correctly. Sometimes regulatory authorities also need to look at the records. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed by them outside the research site. Data will be stored for 15 years and will be destroyed after this time.

WHAT WILL HAPPEN IF I DON'T CARRY ON WITH THE STUDY?

You are free to withdraw from the study at any time, simply by telling a research nurse, kidney doctor or psychiatrist your wishes. You do not have to give a reason. You can withdraw from treatment but keep in contact with us to let us know your progress. If you decide to withdraw from treatment you will be advised to stop taking the treatment gradually, over a few days, as there is a possibility that you could experience mild withdrawal symptoms which usually do not last. Information collected may still be used, but we will ensure that you cannot be identified from such information. The stored blood samples that can still be identified as yours will be destroyed if you wish.

WHAT WILL HAPPEN TO THE RESULTS OF THE STUDY?

The results of the study will be published in medical and health journals and will be presented at meetings. Any research publications will not identify you individually. If you would like a copy of the published research, let one of the researchers know, and we would be delighted to send any publications describing the results of this research to you when they become available.

DOES YOUR GP (General practitioner) get involved?

If you agree to take part in this phase of the study, we will inform your GP about your participation. We will tell your GP that you are taking part in the trial and that you are suffering from depression.

WHO IS ORGANISING AND FUNDING THE STUDY?

Professor Ken Farrington, a kidney doctor at the Lister Hospital in Stevenage, Hertfordshire is the lead investigator. He is organising the study, together with three other kidney doctors from different hospitals, as well as other health care professionals and a team of researchers. East and North Herts NHS Trust and the

University of Hertfordshire are the sponsors of this study. The sponsors have received funding from the National Institute for Health Research to conduct this study.

WHAT IF THERE IS A PROBLEM?

We do not anticipate any major problems arising from taking the medication since Sertraline has been used for very many years to treat depression. However all medications have potential side effects. It is an important part of the study to record what side effects occur, and we will monitor very closely, and treat them appropriately. This may involve stopping the medication. Also since half of the patients in the study will be taking placebo rather than the active drug, it is possible that your depression may get worse. We think this is also unlikely to occur but are monitoring very closely for this too. In the event of worsening depression we may need to withdraw you from the study and take the advice of the study psychiatrist to recommend definitive treatment. If you have any concern about any aspect of this study, you should ask to speak to the Trial Manager or the Chief Investigator, who will do their best to answer your questions (contact details: University of Hertfordshire, CLiCIR, College Lane, Hatfield, tel: 01707 286472). If you remain unhappy and wish to complain about any aspect of the way you are approached or treated during the course of this study, you can contact your local PALS office (Patient Advice and Liaison Service) at your hospital. In the unlikely event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against your hospital, but you may have to pay your legal costs. The normal National Health Service complaints mechanism, PALS, will be available to you and you can get independent advice about making a complaint or seeking compensation from the Independent Complaints Advocacy Service (ICAS).

Formal complaints should be addressed to:

Insert local site PALS

Insert local site ICAS details –

WHO HAS REVIEWED THE STUDY?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee. For clinical trials, the Medicines and Healthcare Products Regulatory Authority looks at the research processes. These organisations are here to protect your interests. This study has received ethical approval from the National Research Ethics Committee (*Add a reference)* as well as approval from the Medicines and Healthcare Products Regulatory Authority to run the clinical trial *(add reference).*

FURTHER INFORMATION AND CONTACT DETAILS

If you have any further questions about this research, please feel free to speak to the Trial Manager on 01707 286472. *Add local PI and research nurse at each site.*

THANK YOU FOR TAKING TIME TO READ THIS INFORMATION SHEET.

Participant Information Sheet 3

FULL STUDY TITLE: A Pilot Randomised Controlled Trial of Drug Treatment for Depression in Patients undergoing Haemodialysis

Short Study Title: ASSERTID (A study of Sertraline in Dialysis)

Patient Experience Interview Phase

We would like to invite you to take part in our research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. The research nurse will be happy to discuss any questions you may have. Take time to decide whether or not you wish to take part. Thank you for reading this.

WHAT IS THE RESEARCH ABOUT?

We are interested in listening to your views and opinions on your participation in the current clinical trial looking at whether taking medication help patients on haemodialysis and who have depression. We would like to explore what it feels like taking part in the clinical trial, taking the study medication and answering the questionnaires.

WHY HAVE I BEEN INVITED?

You are currently taking part in a clinical trial looking at whether taking medication helps patients on dialysis and who have depression. We are seeking feedback from patients who would like to talk to us.

DO I HAVE TO TAKE PART?

It is up to you to decide to join this phase of the study. We will describe the study and go through this information sheet. If you agree to take part, we will ask you to sign a consent form to see the researcher who will conduct the interview. You are free to withdraw at any time, without giving a reason. This will not affect the standard of care you receive.

WHAT WILL HAPPEN TO ME IF I TAKE PART AND WHAT WILL I HAVE TO DO?

If you agree to take part, we will ask you to sign the consent form to see the researcher. The research nurse will arrange an appointment for you to see the researcher. It will probably be on one of your dialysis day. You will be talking to the researcher in a private room and it will take between half an hour and one hour. The researcher will ask a number of questions about your views on participating in the clinical trial, taking the study medication and about the questionnaires and questions asked by the research nurse and psychiatrist. We are interested in your opinions and there are no right or wrong answers. With your permission the interview will be audio recorded but the recordings will be deleted at the end of the study. Your comments will be used to make recommendations for running future and larger studies in patients with end stage renal disease and depression.

WHAT WILL HAPPEN TO ME IF I DO NOT WANT TO TAKE PART?

It is completely your decision whether you take part in the patient experience interview and you will not be forced to do so. Your level of care will not be affected in any way if you decide not to participate.

ARE THERE ANY POSSIBLE BENEFITS IN MY TAKING PART?

You will be able to provide feedback on how you felt participating in this clinical trial and able to inform the researchers about what you felt was good and what was bad about the whole trial. Your feedback will help us to design future studies.

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART?

We cannot foresee any disadvantages to taking part in this study; however it is important to remember that you do not have to answer any questions you do not want to.

WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL?

All information collected about you will be kept strictly confidential. We follow ethical and legal practices and all information about you will be handled in confidence. All data collected will be assigned a number and will not have your name on it, so you could not be recognised from it. The data collected will be stored

in locked filing cabinets in the hospital renal unit research office. Only authorised persons will have access. All data entered on the electronic database will be securely entered and accessed by authorised research personnel only through a password protected system. If you join the study, some parts of your medical records and the data collected for the study may be looked at by authorised persons from the University of Hertfordshire and the participating NHS Trusts (East and North Herts NHS Trust, University Hospital Birmingham NHS Foundation Trust, Royal Free Hampstead NHS Trust and Southend University Hospital Foundation Trust) to check that the study is being carried out correctly. Sometimes regulatory authorities also need to look at the records. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed by them outside the research site. Data will be stored for 15 years and will be destroyed after this time.

DOES YOUR GP (General practitioner) get involved?

If you agreed to inform your GP about phase 2 of the study, your GP will already know that you are participating in the trial. We will not need to tell them specifically that you are participating in an interview about the clinical trial. If you did not want your GP to know about your participation in phase 2 of the study, we will respect your wishes and not tell them about this phase of the study.

WHAT WILL HAPPEN IF I DON'T CARRY ON WITH THE STUDY?

You are free to withdraw from the interview at any time, simply tell the qualitative researcher that you want to stop the interview. You do not have to give a reason. If you withdraw completely from the interview, we would still like to use the data collected before your withdrawal, but if we do, we will ensure that you cannot be identified from such data.

WHAT WILL HAPPEN TO THE RESULTS OF THE STUDY?

The results of the study will be published in medical and health journals and will be presented at meetings. Any research publications will not identify you individually. If you would like a copy of the published research, let one of the researchers know, and we would be delighted to send any publications describing the results of this research to you when they become available.

WHO IS ORGANISING AND FUNDING THE STUDY?

Professor Ken Farrington, a kidney doctor at the Lister Hospital in Stevenage, Hertfordshire is the lead investigator. He is organising the study, together with three other kidney doctors from different hospitals, as well as other health care professionals and a team of researchers. East and North Herts NHS Trust and the University of Hertfordshire are the sponsors of this study. The sponsors have received funding from the National Institute for Health Research to conduct this study.

WHAT IF THERE IS A PROBLEM?

As this phase of the study only involves talking to the researcher and answering some questions there is unlikely to be any problems. If you have any concern about any aspect of this study, you should ask to speak to the Trial Manager or the Chief Investigator, who will do their best to answer your questions (contact details: University of Hertfordshire, CLiCIR, College Lane, Hatfield, tel: 01707 286472). If you remain unhappy and wish to complain about any aspect of the way you are approached or treated during the course of this study, you can contact your local PALS office (Patient Advice and Liaison Service) at your hospital. In the unlikely event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against your hospital, but you may have to pay your legal costs. The normal National Health Service complaints mechanism, PALS, will be available to you and you can get independent advice about making a complaint or seeking compensation from the Independent Complaints Advocacy Service (ICAS).

Formal complaints should be addressed to:

Insert local site PALS

Insert local site ICAS details –

WHO HAS REVIEWED THE STUDY?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has received ethical approval from the National Research Ethics Committee (*Add a reference).*

FURTHER INFORMATION AND CONTACT DETAILS

If you have any further questions about this research, please feel free to speak to the Trial Manager on 01707 286472. *Add local PI and research nurse at each site.*

THANK YOU FOR TAKING TIME TO READ THIS INFORMATION SHEET.

Participant Information Sheet

Study Title: **PROGRESSION OF DEPRESSIVE SYMPTOMS IN HAEMODIALYSIS PATIENTS ON ANTIDEPRESSANTS**

We would like to invite you to take part in our research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. The research nurse will be happy to discuss any questions you may have. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is the research about?

The aim of this study is to find out how the symptoms of low mood and depression change over time when taking anti-depressant medication. The research psychiatrist will ask you a number of questions about your mood, health and medications you are taking at the moment. He will also ask you to complete four short questionnaires. He will decide whether you have symptoms of clinical diagnosis of depression.

We are also interested in listening to your views and experiences about anti-depressants and the need for them. Another researcher will see you and ask you some questions.

Information from this study will help us to give better advice to patients with kidney disease and depression.

Why have I been invited?

About 6 to 15 months ago, you agreed to take part in the screening phase of the ASSERTID study and you were taking anti-depressant medication at the time. The research psychiatrist would like to ask all these patients who were taking antidepressants at the time and find out how their mood changed over time. This is why we have invited you to participate in the study.

Do I have to take part?

It is up to you to decide to join this study. We will describe the study to you and go through this information sheet. If you agree to take part appointment will be arranged, at a time convenient to you. We will then ask you to sign a consent form.

You are free to withdraw at any time, without giving a reason. This will not affect the standard of care you receive.

What will happen to me if I take part and what will I have to do?

If you agree and consent to take part, we will arrange for you to see the research psychiatrist. This will probably be on one of your dialysis days. Should you prefer to be seen on a non-dialysis day, we will pay the full taxi fare. You will answer some questions and fill in four short questionnaires. There are two questionnaires on mood and two questionnaires about your medicines. It will take about one and half to two hours. He will ask you questions about your medical history, including your kidney disease, your psychiatric history, including your mood, and about your medication. He will also collect information about your antidepressant treatment and your medical history from your medical notes, in particular results from recent blood tests. He will also look at the data collected from the previous ASSSERTID study. Your general practitioner and nephrologist will be told of the result of the psychiatric assessment and with your consent we will access your medical records for the collection of required clinical data.

A small proportion of participants will be asked to see another researcher. This will probably be on one of your dialysis days. You will see the researcher in a private room and it will take between half an hour and one hour. The researcher will ask a number of questions about your views and your beliefs about antidepressants and the need for them. We are interested in your opinions and there are no right or wrong answers. With your permission the interview will be audio recorded but the recordings will be deleted at the end of the study.

Should you become distressed at any point during the assessment, we will ask you if you wish to stop the interview and decide with you whether any additional support such as counselling would be helpful.

What will happen to me if I do not want to take part?

It is completely your decision whether you take part and you will not be forced into the study. You can change your mind about taking part at any time-from the time you are approached till the appointment time and even during the interview if you wish. You will be given the researcher's contact details to discuss this or any other any

points you may wish to. Your level of care will not be affected in any way if you decide not to participate.

Are there any possible benefits in my taking part?

Firstly, we will be able to tell you if there are any improvements in your mood symptoms. We do this by comparing the results of the new and old score of mood questionnaires. We will also tell you if suffer from clinical depression. The information we get from this study will also help improve the treatment of people with end stage kidney disease and depression.

What are the possible disadvantage and risks of taking part?

You will be asked questions about your mood by the research psychiatrist and by completing questionnaires. Sometimes these questions can be a bit upsetting so it is important to remember that you do not have to answer any questions you do not want to. If this happens during the interview it can be stopped at any point and we can discuss whether counselling or any other psychological therapy might be helpful.

Will my taking part in the study be kept confidential?

All information collected about you will be kept strictly confidential. We follow ethical and legal practices and all information about you will be handled in confidence. All data collection sheets and questionnaires will be assigned a number and will not have your name on, so you could not be recognised from it. This number is the same number used from the ASSERTID study. The data from the ASSERTID study will also be used. The data collected, including the questionnaires will be stored in locked filing cabinets on the renal unit. Only authorised persons will have access. If you join the study, some parts of your medical records and the data collected for the study may be looked at by authorised persons from the University of Hertfordshire or your Trust (East and North Herts NHS Trust, University Hospital Birmingham NHS Foundation Trust, Royal Free Hampstead NHS Trust, Southend University Hospital Foundation Trust or Basildon and Thurrock University Hospitals) to check that the study is being carried out correctly. Sometimes regulatory authorities also need to look at the records. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed by them outside the research site. Data will be stored for 3 years and will be destroyed after this time.

What will happen to the results of the study?

The results of the study will be published in medical and health journals and will be presented at meetings. Any research publications will not identify you individually. If you would like a copy of the published research, let one of the researchers know and we will send you any publications describing the results of this research to you when they become available.

Does your GP (General Practitioner) get involved?

If you agree to take part in this phase of the study, with your permission we will tell your GP about your participation and the result of the psychiatric assessment.

What if there is a problem?

If you have any concern about any aspect of this study, you should ask to speak to the Dr Guirguis chief investigator, who will do their best to answer your questions.

Contact details: University of Hertfordshire, CLiCIR, College Lane, Hatfield, tel: 01707 284131), or via email a.guirguis3@herts.ac.uk.

If you remain unhappy and wish to complain about any aspect of the way you are approached or treated during the course of this study, you can contact your local PALS office (Patient Advice and Liaison Service) at your hospital.

In the unlikely event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against your hospital, but you may have to pay your legal costs. The normal National Health Service complaints mechanism, PALS, will be available to you and you can get independent advice about making a complaint. Formal complaints should be addressed to: *Insert local site PALS Insert local site ICAS details*

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee. These organisations are here to protect your interests.

Further information and contact details

If you have any further questions about this research, please feel free to speak to the Chief Investigator Dr Ayman Guirguis on 01707 284131. *Add local nephrologist and research nurse at each site.*

THANK YOU FOR TAKING TIME TO READ THIS INFORMATION SHEET

Consent Form 1(ASSERTID – ICF 1– Final version 5.0 5.7.13)

A Pilot Randomised Controlled Trial of Drug Treatment for Depression in Patients undergoing Haemodialysis: ASSERTID

(Screening and Prevalence Phase)

Study patient identification number (PID):

Name of Researcher:

Please initial each statement to show you have read and provide consent for the following statements:

1. I confirm that I have read the information sheet dated ... (Version ...) for the above study and have had the opportunity to ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and I am free to withdraw consent at any time, without giving a reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the research team, from the regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. All data will be handled confidentially. ☐

4. I agree to my GP being informed of my participation if I am found to have low mood. ☐

5. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient (printed)	Date	Signature
_____	_____	_____
Name of Person taking consent (printed)	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in the medical notes.

Consent Form 2a (ASSERTID – ICF2a Final Version 5.0 5.7.13)

A Pilot Randomised Controlled Trial of Drug Treatment for Depression in Patients undergoing Haemodialysis: ASSERTID

(Consent to Assessment with the Psychiatrist)

Study patient identification number (PID):

Name of Researcher:

Please initial each statement to show you have read and provide consent for the following statements:

1. I confirm that I have read the information sheet dated ... (Version ...) for the above study and have had the opportunity to ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and I am free to withdraw consent at any time, without giving a reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the research team, from the regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. All data will be handled confidentially. ☐

4. I agree to my GP being informed should I be diagnosed with depression. ☐

5. I agree to take part in the assessment with the psychiatrist. ☐

_____	_____	_____
Name of Patient (printed)	Date	Signature
_____	_____	_____
Name of Person taking consent (printed)	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in the medical notes.

Consent Form 2b (ASSERTID ICF2b Final version 5.0 5.7.13)

A Pilot Randomised Controlled Trial of Drug Treatment for Depression in Patients undergoing Haemodialysis: ASSERTID

(Trial Outcome Phase)

Study patient identification number (PID):

Name of Researcher:

Please initial each statement to show you have read and provide consent for the following statements:

1. I confirm that I have read the information sheet dated ... (Version ...) for the above study and have had the opportunity to ask questions and have had these answered satisfactorily. ☐

2. I agree to have two additional blood samples taken. ☐

3. I understand that my participation is voluntary and I am free to withdraw consent at any time, without giving a reason, without my medical care or legal rights being affected. ☐

4. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the research team, from the regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. All data will be handled confidentially. ☐

5. I agree to my GP being informed of my participation in this study. ☐

6. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient (printed)	Date	Signature
_____	_____	_____
Name of Person taking consent (printed)	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in the medical notes.

Consent Form 3 (ASSERTID ICF3 Final Version 5.0 5.7.13)

A Pilot Randomised Controlled Trial of Drug Treatment for Depression in Patients undergoing Haemodialysis: ASSERTID

(Patient Experience Interview Phase)

Study patient identification number (PID):

Name of Researcher:

Please initial each statement to show you have read and provide consent for the following statements:

1. I confirm that I have read the information sheet dated ... (Version ...) for the above study and have had the opportunity to ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and I am free to withdraw consent at any time, without giving a reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the research team, from the regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. All data will be handled confidentially. ☐

4. I agree to have my conversation audiotaped. ☐

5. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient (printed)	Date	Signature
_____	_____	_____
Name of Person taking consent (printed)	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in the medical notes.

Consent Form

PROGRESSION OF DEPRESSIVE SYMPTOMS IN HAEMODIALYSIS PATIENTS ON ANTIDEPRESSANTS

Study patient identification number (PID):

Name of Researcher:

Please initial each statement to show you have read and provide consent for the following statements:

6. I confirm that I have read the information sheet for the above study and have had the opportunity to ask questions and have had these answered satisfactorily. ☐

7. I understand that my participation is voluntary and I am free to withdraw consent at any time, without giving a reason, without my medical care or legal rights being affected. ☐

8. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the research team, from the regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. All data will be handled confidentially. ☐

9. I agree to have my data previously provided to the ASSERTID study used in this study ☐

10. I agree to my GP being informed of my particiation . ☐

11. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient (printed)	Date	Signature
_____	_____	_____
Name of Person taking consent (printed)	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in the medical notes.

Appendix 6 – Questionnaires

PHQ-9 QUESTIONNIAIRE

Over the **last 2 weeks**, how often have you been bothered by any of the following problems?
(Please circle your answer)

		Not at all	Several days	More than half the days	Nearly every day
1.	Little interest or pleasure in doing things	0	1	2	3
2.	Feeling down, depressed, or hopeless	0	1	2	3
3.	Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4.	Feeling tired or having little energy	0	1	2	3
5.	Poor appetite or overeating	0	1	2	3
6.	Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3
7.	Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8.	Moving or speaking so slowly that other could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9.	Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Date Completed ☐☐ / ☐☐☐ / ☐☐☐☐

(Complete date as day, month, year i.e. 13/NOV/2008)

MFI® MULTIDIMENSIONAL FATIGUE INVENTORY

® E. Smets, B.Garssen, B. Bonke (2013)

Instructions:

By means of the following statements we would like to get an idea of how you have been feeling **lately**.

There is, for example, the statement:

"I FEEL RELAXED"

If you think that this is **entirely true**, that indeed you have been feeling relaxed lately, please, place an **X** in the extreme left box; like this:

yes, that is true ☒1 ❑2 ❑3 ❑4 ❑5 **no, that is not true**

The more you **disagree** with the statement, the more you can place an **X** in the direction of "no, that is not true". Please do not miss out a statement and place only one **X** in a box for each statement.

1	I Feel Fit.	**Yes, that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**
2	Physically, I feel only able to do little.	**Yes, that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**
3	I feel like doing all sort of nice things.	**Yes, that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**
4	I Feel very active.	**Yes ,that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**
5	I Feel tired.	**Yes ,that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**
6	I think I do a lot in a day.	**Yes ,that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**
7	When I am doing something I can keep my thoughts on it	**Yes ,that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**
8	Physically I can take on a lot.	**Yes ,that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**
9	I dread having to do things.	**Yes ,that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**
10	I think I do very little in a day.	**Yes ,that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**
11	I can concentrate well.	**Yes ,that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**
12	I am rested.	**Yes ,that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**
13	It took a lot of effort to concentrate on things	**Yes ,that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**
14	Physically I feel I am in a bad condition.	**Yes ,that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**
15	I have a lot of plans.	**Yes ,that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**
16	I tire easily.	**Yes ,that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**
17	I get little done.	**Yes ,that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**
18	I don't feel like doing anything.	**Yes ,that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**
19	My thoughts easily wonder.	**Yes ,that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**
20	Physically I feel I am in an Excellent condition.	**Yes ,that is true**	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	**No, that is not true**

Your Health and Well-Being

Energy/Fatigue Subscale

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

For each of the following questions, please tick the one box that best describes your answer.

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks . . .

(Circle One Number on Each Line)

	All of the time	Most of the time	A Good bit of the time	Some of the time	A little of the time	None of the time
1. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
2. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
3. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
4. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version

6.0.0 M.I.N.I. 6.0.0 (October 10, 2010) (10/10/10)

DSM-IV

MINI MENTAL STATE EXAMINATION

			Max points	Patient score
1.	**Orientation**	a. Can you tell me today's (date)/(month)/(year)? Which (day of the week) is it today? Can you also tell me which (season) it is?	5	_____
		b. What city/town are we in? What is the (county)/(country)? What (building) are we in and on what (floor)?	5	_____
2.	**Registration**	I should like to test your memory (name three common objects:e.g"apple, table, penny") Can you repeat the words I said? (repeat up to 6 trials until all three are remembered) (record the number of trials needed here_____)	3	_____
3.	**Attention & Calculation**	a. From 100 keep subtracting 7 and give each answer: Stop after 5 answers. (93-86-79-72-65) *Alternatively* b. Spell the word 'WORLD' backwards (D_L_R_O_W)	5	_____
4.	**Recall**	What were the three words I asked you to say earlier?	3	_____
		(*skip this test if all three objects were not remembered during registration test)*		
5.	**Language**			
	Naming	Name these objects (show a watch) (show a pencil)	2	_____
	Repeating	Repeat the following: "no ifs, ands or buts"	1	_____
6.	**Reading**	(show card or write "CLOSE YOUR EYES") Read this sentence and do what it says Now can you write a short sentence for me?	1 1	_____ _____
7.	**Three Stage Command**	(Present paper) Take this paper in your left (or right) hand, Fold it in half and put it on the floor.	3	_____
8.	**Construction**	Will you copy this drawing please?	1	_____

Total Score_____ /30

Montgomery-Åsberg Depression Rating Scale
(MADRS)

1. Apparent sadness Representing despondency, gloom and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up. (Please tick one)	
0. = No sadness.	☐
1.	☐
2. = Looks dispirited but does brighten up without difficulty.	☐
3.	☐
4. = Appears sad and unhappy most of the time.	☐
6. = Looks miserable all the time. Extremely despondent.	☐

2. Reported sadness Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. (Please tick one)	
0. = Occasional sadness in keeping with the circumstances.	☐
1.	☐
2. = Sad or low but brightens up without difficulty.	☐
3.	☐
4. = Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.	☐
5.	☐
6. = Continuous or unvarying sadness, misery or despondency.	☐

3. Inner tension Representing feelings or ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for. (Please tick one)	
0. = Placid. Only fleeting inner tension.	☐
1.	☐
2. = Occasional feelings of edginess and ill-defined discomfort.	☐
3.	☐
4. = Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.	☐
5.	☐
6. = Unrelenting dread or anguish. Overwhelming panic.	☐

4. Reduced sleep Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well. (Please tick one)	
0. = Sleeps as usual.	☐
1.	☐
2. = Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.	☐
3.	☐
4. = Sleep reduced or broken by at least 2 hours.	☐
5.	☐
6. = Less than 2 or 3 hours sleep.	☐

5. Reduced appetite Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat. (Please tick one)	
0. = Normal or increased appetite.	☐
1.	☐
2. = Slightly reduced appetite.	☐
3.	☐
4. = No appetite. Food is tasteless.	☐
5.	☐
6. = Needs persuasion to eat at all.	☐

6. Concentration difficulties Representing difficulties in collecting one's thoughts mounting to an incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced. (Please tick one)	
0. = No difficulties in concentrating.	☐
1.	☐
2. = Occasional difficulties in collecting one's thoughts.	☐
3.	☐
4. = Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.	☐
5.	☐
6. = Unable to read or converse without great difficulty.	☐

7. Lassitude Representing difficulty in getting started or slowness in initiating and performing everyday activities. (Please tick one)	
0. = Hardly any difficulty in getting started. No sluggishness.	☐
1.	☐
2. = Difficulties in starting activities.	☐
3.	☐
4 = Difficulties in starting simple routine activities, which are carried out with effort.	☐
5.	☐
6. = Complete lassitude. Unable to do anything without help.	☐

8. Inability to feel Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced. (Please tick one)	
0. = Normal interest in the surroundings and in other people.	☐
1.	☐
2. = Reduced ability to enjoy usual interests.	☐
3.	☐
4. = Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.	☐
5.	☐
6. = The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.	☐

9. Pessimistic thoughts Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin. (Please tick one)	
0. = No pessimistic thoughts.	☐
1.	☐
2. = Fluctuating ideas of failure, self-reproach or self-depreciation.	☐
3.	☐
4. = Persistent self-accusation, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.	☐
5.	☐
6. = Delusions of ruin, remorse or irredeemable sin. Self-accusations, which are absurd and unshakable.	☐

10. Suicidal thoughts Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicide attempts should not in themselves influence the rating. (Please tick one)	
0. = Enjoys life or takes it as it comes.	☐
1.	☐
2. = Weary of life. Only fleeting suicidal thoughts.	☐
3.	☐
4. = Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intension.	☐
5.	☐
6. = Explicit plans for suicide when there is an opportunity. Active preparations for suicide.	☐

Clinical Global Impression Scale for Severity (CGIs)

The rating considers the clinician's entire experience with the disorder under investigation and the severity of that condition at the current time. Note that it is the severity of the particular condition that is rated, and not psychiatric illness generally.

0 = not assessed

1 = normal, not ill

2 = borderline ill

3 = mildly ill

4 = moderately ill

5 = markedly ill

6 = severely ill

7 = among the most extremely ill CGIs = ☐

Clinical Global Impression Scale for Improvement (CGIi)

The rating considers the degree of change since the start of the current treatment plan. The rating does not consider whether the improvement is related to therapy or not.

0 = not assessed

1 = very much improved

2 = much improved

3 = minimally improved

4 = unchanged

5 = minimally worse

6 = much worse

7 = very much worse

CGIi = ☐

P4 Screener

Have you had thoughts of actually hurting yourself?

NO YES

4 Screening Questions

1. Have you ever attempted to harm yourself in the past?

NO YES

2. Have you thought about how you might actually hurt yourself?

NO YES → [How? _____]

3. There's a big difference between having a thought and acting on a thought. How likely do you think it is that you will act on these thoughts about hurting yourself or ending your life some time over the next month?

a. Not at all likely _____
b. Somewhat likely _____
c. Very likely _____

4. Is there anything that would prevent or keep you from harming yourself?

NO YES → [What? _____]

	Shaded ("Risk") Response	
Risk Category	Items 1 and 2	Items 3 and 4
Minimal	Neither is shaded	Neither is shaded
Lower	At least 1 item is shaded	Neither is shaded
Higher		At least 1 item is shaded

The Medication Adherence Rating Scale (MARS)

Please respond to the following statements by ticking the answer which best describes your behaviour or the attitude you have held toward your medication in the past week.

QUESTION	YES	NO
1- Do you ever forget to take your medication?		
2- Are you careless at times about taking your medicine?		
3- When you feel better, do you sometimes stop taking your medicine?		
4- Sometimes if you feel worse when you take the medicine, do you stop taking it?		
5- I take my medication only when I am sick.		
6- It is unnatural for my mind and body to be controlled by medication.		
7- My thoughts are clearer on medication.		
8- By staying on medication, I can prevent getting sick.		
9- I feel weird, like a 'zombie', on medication.		
10- Medication makes me feel tired and sluggish.		

BELIEFS ABOUT MEDICINES QUESTIONNAIRE (BMQ)

BMQ –Specific

Your views about medicines prescribed to you.

• I would like to ask you about your personal views about medicines prescribed for your depression.

• These are statements other people have made about their antidepressant medication.

• Please indicate the extent to which you agree or disagree with them by placing a cross in the appropriate box.

• There are no right or wrong answers. I am interested in your personal views.

• Please only cross one box per question.

1) My health at present depends on my antidepressant medicines

Strongly agree	Agree	Uncertain	Disagree	strongly disagree
☐	☐	☐	☐	☐

2) Having to take antidepressant medication worries me

Strongly agree	Agree	Uncertain	Disagree	strongly disagree
☐	☐	☐	☐	☐

3) My life would be impossible without my antidepressant medication

Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
☐	☐	☐	☐	☐

4) Without my antidepressant medication I would be very ill

Strongly agree ☐ Agree ☐ Uncertain ☐ Disagree ☐ Strongly disagree ☐

5) I sometimes worry about the long term effects of my antidepressant medication

Strongly agree ☐ Agree ☐ Uncertain ☐ Disagree ☐ Strongly disagree ☐

6) My antidepressant medication is mystery to me

Strongly agree ☐ Agree ☐ Uncertain ☐ Disagree ☐ Strongly disagree ☐

7) My health in the future will depend on my antidepressant medication

Strongly agree ☐ Agree ☐ Uncertain ☐ Disagree ☐ Strongly disagree ☐

8) My antidepressant medication disrupts my life

Strongly agree ☐ Agree ☐ Uncertain ☐ Disagree ☐ Strongly disagree ☐

9) I sometimes worry about becoming too dependent on my antidepressant medication

Strongly agree ☐ Agree ☐ uncertain ☐ Disagree ☐ Strongly disagree ☐

10) My antidepressant medication protects me from becoming worse.

Strongly agree ☐ Agree ☐ uncertain ☐ Disagree ☐ Strongly disagree ☐