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SPECIAL ARTICLE

Pharmacokinetics of antidepressants in patients undergoing hemodialysis: a narrative literature review

Juliana L. **Constantino**, Vilma A. **Fonseca**

Departamento de Fisiologia e Farmacologia, Instituto Biomédico, Universidade Federal Fluminense (UFF), Niterói, Rio de Janeiro, Brazil.

We conducted a narrative literature review on studies that specifically addressed the pharmacokinetics of antidepressants in patients on hemodialysis. The search included the MEDLINE, LILACS, and Web of Knowledge databases and combined Medical Subject Headings and free-text search terms for chronic kidney disease, end-stage renal disease, renal replacement therapy, depression, and antidepressants; it was limited to studies conducted in humans, with no language or time constraints. The search yielded 212 studies. After screening titles and abstracts, 32 studies were read in full and 11 ultimately met the inclusion criteria and were included in the review. Most of the studies showed no difference in the pharmacokinetics of antidepressant drugs between patients with normal renal function and patients undergoing hemodialysis. However, studies with fluvoxamine and amitriptyline showed that variations in albumin levels might affect serum concentrations of these agents. The included studies have several limitations, and there are many obstacles to the adequate treatment of depression in patients undergoing hemodialysis. Further studies on this topic are needed to support proper treatment of these patients, improving their quality of life and reducing mortality.

Keywords: Antidepressive agents; depressive disorder; renal dialysis; pharmacokinetics; renal insufficiency, chronic

Introduction

Studies have shown that 20% of patients with chronic kidney disease (CKD) experience major depressive disorder (MDD), and that MDD is an independent risk factor for hospitalization and mortality in such patients.[1,2] However, it remains under recognized and undertreated,[3,4] as there are several challenges and limited evidence on how clinicians should address this problem.

First, there is no consensus as to which tool is most suitable to diagnose MDD in this population,[5-7] as depressive symptoms are often mixed with the somatic symptoms associated with CKD.[8] Second, depression in end-stage renal disease may be resistant to treatment with antidepressants, possibly because the cause of depressive symptoms in these patients may be attributable to physical factors, such as uremia, anemia, and electrolyte disturbances.[9,10] In addition, there is very little evidence to support the efficacy and safety of antidepressant medication in CKD patients, especially because these patients are often excluded from major clinical trials because of safety concerns.[11,12] What little evidence is available has largely been obtained in nonrandomized, uncontrolled studies with small samples.[12]

Studies have shown that, in addition to treating depressive symptoms and improving quality of life, sertraline significantly decreases serum levels of proinflammatory substances such as IL-6, which could be a promising strategy to reduce systemic inflammation in CKD patients.[13]

Most antidepressants are metabolized in the liver and highly protein-bound, and, as such, are not removed significantly by dialysis.[10,14] However, the relative activity and mode of excretion of metabolites of these drugs in patients with CKD is often uncertain.[15]

The latest European Renal Best Practice statement, published in 2014, recommends a trial of selective serotonin reuptake inhibitors for 8 to 12 weeks in dialysis patients who have moderate/major depression. Reevaluation after 12 weeks was recommended to avoid ineffective medicalization.[16] Following this recommendation, the Study of Sertraline in Dialysis[17] is an ongoing randomized controlled trial to evaluate the effect of sertraline in patients with depression who are undergoing hemodialysis. This may be the first study to give clinicians an evidence-based conclusion regarding the pharmacotherapy of depression in patients with CKD.

In this context, we conducted a narrative literature review on studies that specifically addressed the pharmacokinetics of antidepressant drugs in patients undergoing hemodialysis.

Methods

The MEDLINE, LILACS, and Web of Knowledge databases were searched with a combination of Medical

Correspondence: Juliana Lima Constantino, Av. Marques do Paraná, 303, CEP 24033-900, Niterói, RJ, Brazil.
E-mail: jlconstantino@id.uff.br
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Subject Headings and free-text queries for CKD, end-stage renal disease, renal replacement therapy, depression, and antidepressants. The search was limited to studies conducted in humans, with no language or time constraints. The inclusion criteria were patients undergoing hemodialysis who were on treatment with antidepressants. Studies that reported only side effects of antidepressant treatment in patients going through hemodialysis were not included. There was no limitation on the tools used to diagnose depression, since there is no consensus in the literature on which tool is more suitable for MDD diagnosis in CKD patients. Finally, all the included studies were fully available online.

A flow diagram of study selection is available as Figure 1 below.

Results

The search yielded 212 studies. After screening of titles and abstracts, 32 studies were read in full. After exclusion of studies that did not met the inclusion criteria and review of the reference lists of selected studies, a total of 11 studies were included in the review. Table 1 summarizes the characteristics of the included studies.

We found one study regarding pharmacokinetics of tianeptine,[18] one on citalopram,[19] one on fluvoxamine,[20] one on sertraline, [21] one on nefazodone, [22] one on nortriptyline, [23] one on amitriptyline, [24] three on mirtazapine,[24-26] and two on fluoxetine[27,28] in patients undergoing hemodialysis. Our findings are described below.

Tianeptine

A single 12.5 mg oral dose of tianeptine was used to determine dialytic clearance of tianeptine and its metabolite (pentanoic acid analogue of tianeptine) in eight patients undergoing dialysis. The dialyzability of the two substances was found to be low (3.9±9.9 mL/min and 19.2±8.6 mL/min for parent tianeptine and its pentanoic acid analogue, respectively). These results showed that patients can be given tianeptine without considering the dialysis.[18]

Citalopram

The concentration of citalopram and its metabolites (desmethylcitalopram and didesmethylcitalopram) in serum and urine were compared in four patients undergoing hemodialysis and eight healthy controls after a single dose of citalopram. There was a statistically significant difference between groups in renal clearance of citalopram, which was lower in the patients undergoing hemodialysis (1.70 mL/min versus 66.2 mL/min, $p < 0.001$). Hemodialysis cleared about 1% of citalopram and its metabolites. The authors concluded that hemodialysis does not significantly affect the pharmacokinetic parameters of citalopram and its metabolites.[19]

Fluvoxamine

Plasma fluvoxamine concentrations were examined in three patients on maintenance hemodialysis who had

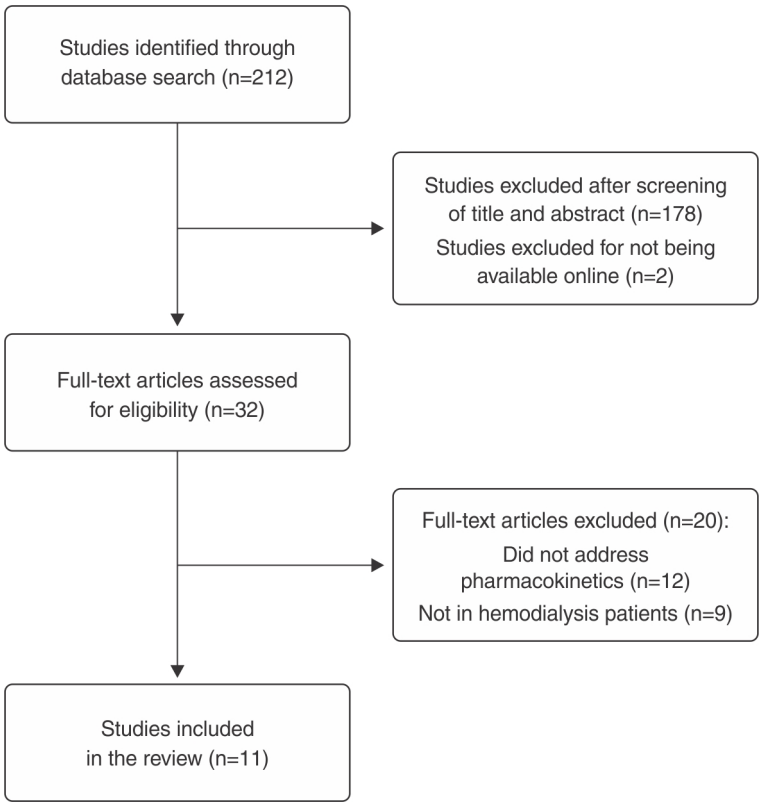

Figure 1 Flowchart for the selection of studies of this review.

Table 1 Summary of the included studies

Title	Author	Year/ Country	Participants	Methods	Tool used for depression diagnosis
Tianeptine and its main metabolite. Disposition in chronic renal failure and haemodialysis	Salvadori[18]	1990/ France	20 patients with CKD (14 on HD) and 8 patients with normal kidney function	Blood samples were taken before and at 13 different time points after drug intake for the healthy patients. For patients on HD, dialysis was initiated 2 h after drug administration. Arterial and venous blood samples entering and leaving the dialyzer were simultaneously obtained 1 h after the onset of hemodialysis.	Not specified
Citalopram pharmacokinetics in patients with chronic renal failure and the effect of haemodialysis	Spigset[19]	2000/ Sweden	4 patients on HD and 8 healthy controls	Concentrations of citalopram and its metabolites were measured in urine and in serum from the artery leading to the dialyzer and in the dialysate. The drug was given the day after HD. Venous blood samples were collected at 16 different time points after citalopram intake. Urine was collected the first 24 h after drug intake.	Not specified
Efficacy and pharmacokinetics of fluvoxamine maleate in patients with mild depression undergoing hemodialysis	Kamo[20]	2004/ Japan	7 patients on HD with comorbid mild depression	Blood was collected before medication and at 6 different time points after intake of medication for comparison of the plasma concentrations of fluvoxamine.	Mild depression according to ICD-10 and HDRS-17 (score of 14 or higher)
Hemodialyzability of sertraline	Schwenk[21]	1995/ USA	2 patients on HD	The drug was administered after hemodialysis. During the next hemodialysis session, simultaneous pre- and post-dialyzer blood samples were obtained at the start of dialysis and hourly throughout until completion. All spent dialysate was collected hourly, quantified, and an aliquot retained. Additional blood samples were obtained approximately 20 h after dialysis and prior to the next treatment.	Not specified
Response to nefazodone in a depressed patient with end-stage renal disease	Seabolt[22]	2001/ USA	1 patient on HD	Pre- and post-dialysis nefazodone serum concentrations were measured.	HDRS
The pharmacokinetics of nortriptyline in patients with chronic renal failure	Dawlilng[23]	1981/ United Kingdom	20 patients with CKD (8 on HD)	Patients received the drug immediately following dialysis. Plasma nortriptyline half-life and total hepatic intrinsic clearance were calculated.	Not specified
Therapeutic drug monitoring of antidepressants in haemodialysis patients	Unterecker[24]	2012/ Germany	32 patients on HD	The serum concentration of the drug was measured in two blood samples. The first was obtained immediately after puncture of the dialysis port, and the second just before disconnecting the patient from the dialysis machine.	Not specified
Mirtazapine oral single dose kinetics in patients with different degrees of renal failure	Bengtsson[25]	1998/ United Kingdom	40 patients (2 on HD)	Blood samples were taken at 25 different time points after ingestion of the drug.	Not specified
No influence of dialysis on mirtazapine – a case report	Schlotterbeck[26]	2008/ Germany	1 patient on HD	Plasma was obtained before a dialysis session and once again four hours later, the extracted dialysate for the concentration was also analyzed.	Not specified
Fluoxetine in depressed patients on dialysis	Blumenfield[27]	1997/ USA	7 healthy controls and 6 patients on HD	Blood samples were obtained to measure the plasma concentration of the drug in 6 different moments.	HDRS (total score of at least 16 on the first seventeen items)
Fluoxetine in depressed patients with renal failure and in depressed patients with normal kidney function	Levy[28]	1996/ USA	9 healthy patients and 7 patients on HD	Plasma concentrations of the drug were measured on 9 different moments.	Clinical interview and a score of at least 16 on first HDRS-17

CKD = chronic kidney disease; HD = hemodialysis; HDRS-17 = 17-item Hamilton Depression Rating Scale.

mild depression. Patients took 50 mg/day fluvoxamine maleate for 28 days. Hemodialysis decreased the plasma fluvoxamine concentration by 22.04±1.8%. Albumin concentrations in plasma were also measured before and after dialysis. The mean albumin concentration was 4.02±0.13 g/dL before dialysis, and was raised to 12.15± 3.16% by hemodialysis. Although there was no statistically significant association between decreased plasma concentration of fluvoxamine and plasma concentration of albumin, the authors found a tendency for the dialyzed rate of fluvoxamine to become lower when the plasma albumin concentration was higher.[20]

Sertraline

Two patients undergoing hemodialysis were administered 100 mg of sertraline after the procedure. At the next hemodialysis session, blood samples to measure sertraline serum concentrations were taken before, after, and hourly during the procedure. Blood samples were also obtained 20 h after the procedure and prior to the next session. The initial sertraline serum concentrations were compared between the two patients undergoing hemodialysis and subjects with normal renal function who had also received 100 mg of sertraline. There was no significant difference between the groups, implying that absorption and distribution of the drug are not altered by hemodialysis, which suggests that post-hemodialysis supplementation is unnecessary.[21]

Nefazodone

A single case report of a dialysis-dependent patient on 150 mg of nefazodone showed pre- and post-dialysis nefazodone serum concentrations of 0.4 and 0.25 mcg/mL respectively. These results suggest that drug levels of nefazodone may be affected by dialysis. However, clinical response was not affected.[22]

Nortriptyline

The pharmacokinetics of single oral doses of 75 mg nortriptyline were studied in eight patients undergoing hemodialysis and 12 controls not undergoing hemodialysis. No differences were observed between the dialyzed and non-dialyzed groups. Comparisons of nortriptyline half-life and clearance between the patients and physically healthy subjects revealed no significant differences. These results suggest that CKD is not associated with significant changes in nortriptyline metabolism as measured by its half-life or clearance. However, the study showed extreme interindividual variability, reinforcing the fact that antidepressants should be used with caution in this patient population and concentrations monitored whenever possible.[23]

Mirtazapine

In a study with 17 patients undergoing hemodialysis, mean serum concentrations of mirtazapine decreased significantly after hemodialysis (before, 53.45 ng/mL; after, 38.31 ng/mL; $p < 0.036$).[24] Another study compared a group of 10 patients with severe renal dysfunction, seven of whom were undergoing hemodialysis, and 10 healthy patients given a single oral dose of 15 mg mirtazapine. Patients with renal dysfunction experienced an approximately 50% reduction in clearance and a 215% increase in area under the curve for the plasma concentration compared to the 10 healthy volunteers. These results suggest a potential risk of mirtazapine accumulation in patients with renal dysfunction and the need to use conservative doses.[25] However, one case report of a patient also using 15 mg/day mirtazapine found that dialysis with a low-flux hemofilter did not have any significant effect on plasma concentrations of mirtazapine or its metabolite demethylmirtazapine.[26]

Amitriptyline

Mean serum concentrations of amitriptyline and its active metabolite, nortriptyline, were measured in 15 patients undergoing hemodialysis. The first blood sample was obtained immediately after puncture of the dialysis port, and the second just before disconnecting the patient from the dialysis machine. The results showed that the mean serum concentration of the sum of amitriptyline and nortriptyline decreased significantly with hemodialysis (before: 75.52 ng/mL; after: 59.35 ng/mL; $p < 0.001$).[24]

Fluoxetine

In an open label study, patients undergoing hemodialysis had serum plasma concentrations of fluoxetine and norfluoxetine similar to those of patients with normal renal function.[27] Another study compared the steady-state plasma concentrations of the sum of fluoxetine plus its metabolite norfluoxetine in patients undergoing hemodialysis and patients with normal renal function, with both groups completing 8 weeks of treatment with fluoxetine; there was no statistically significant between-group difference.[28] Both studies used a dose of 20 mg per day. The results suggest that renal failure and the process of hemodialysis do not substantially alter the pharmacokinetics of fluoxetine or its major metabolite norfluoxetine.

Discussion

Most of the studies included in this review found no differences in the pharmacokinetics of antidepressant drugs between patients with normal renal function and patients undergoing hemodialysis. However, studies with fluvoxamine and amitriptyline showed that variations in albumin levels might affect serum levels of these agents. The other studies did not consider this variable. In patients with CKD, albumin levels may become low for several reasons, especially decreased synthesis caused by inadequate nutrition and chronic inflammation, but also because of plasma volume expansion, albumin redistribution, exogenous loss, and an increased fractional catabolic rate.[29] The National Kidney Foundation Kidney Disease Dialysis Outcomes Quality Initiative (KDOQI) practice guidelines recommend a target serum albumin level of $\geqslant$ 4.0 g/dL

for adults who are on hemodialysis, as lower levels are associated with higher mortality.[30]

It is important to highlight that all the studies included herein had small sample sizes and were uncontrolled and nonrandomized; thus, their findings have several limitations. The studies also did not mention controlling for other variables, such as use of other drugs that might affect the serum levels of antidepressants, which is especially important because polypharmacy is common among patients on hemodialysis.[31,32] All the studies recommended further research into the pharmacokinetics of antidepressants in patients undergoing hemodialysis.

The upcoming results of the Study of Sertraline In Dialysis[17] may provide some answers on this matter; however, as its name implies, this study only includes sertraline. Considering that the clinical response to psychopharmaceuticals is subject to extreme interindividual variability,[33] it is important to carry out further investigations with other antidepressants.

The current recommendation from the British Columbia Renal Agency is to use selective serotonin reuptake inhibitors as first-line therapy for treatment of depression in patients on hemodialysis.[34] We consider that sertraline 25 mg/day could be an interesting option, since the current literature suggests that post-hemodialysis supplementation is unnecessary[21] and sertraline has no major drug-drug interactions.[34]

Besides the lack of evidence-based information for clinicians to prescribe and correctly treat depression in patients undergoing hemodialysis, there is also the challenge of adherence to treatment, since studies have shown that these patients often are not open to treatment and do not make regular use of their prescribed medication.[35,36] Studies on this topic are important to produce strong evidence on the efficacy and safety of treatment, so that clinicians can work with their patients to improve adherence.

In conclusion, most of the studies included in this review found that the pharmacokinetics of antidepressants agents are unaffected by hemodialysis. However, these findings have several limitations, and there are many obstacles to adequate treatment of depression in patients undergoing hemodialysis. All studies used small samples and yielded results that cannot be generalized. Further studies on this topic are needed to support proper treatment of these correctly, improving their quality of life and reducing mortality.

Disclosure

The authors report no conflicts of interest.

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