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NDT Perspectives

Antidepressants for depression in stage 3–5 chronic kidney disease: a systematic review of pharmacokinetics, efficacy and safety with recommendations by European Renal Best Practice (ERBP)*

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Abstract

Background. The prevalence of major depression in stage 5 chronic kidney disease (CKD) varies between 14 and 30%. Patients with CKD who are depressed have a worse quality of life, are hospitalized more often and die sooner than those who are not depressed. Antidepressant drugs are effective in the general population, but whether they improve outcomes in CKD is uncertain. Drug pharmacokinetics are altered in CKD, which may necessitate dose adjustment. We aimed to systematically review available evidence of the pharmacokinetics, efficacy and safety of antidepressant drugs when used in patients with CKD3 to CKD5 (CKD3-5).

Methods. This is a systematic review of randomized clinical trials and observational studies examining antidepressants in patients with CKD3-5, regardless of whether or not patients are on dialysis. Through comprehensive searches of seven databases, we identified all studies examining pharmacokinetic properties or clinical outcomes in patients with CKD3-5. One author assessed studies for eligibility and quality and extracted all data. Antidepressant drugs were the studied intervention. The main outcomes were pharmacokinetic parameters, clinical outcomes such as response to treatment, reduction in depression severity and adverse events.

Results. We identified 28 studies evaluating pharmacokinetic parameters in CKD for 24 antidepressants. Sparse and heterogeneous data precluded informative meta-analysis. Drug clearance in CKD3-5 was markedly reduced for selegiline, amitriptylinoxide, venlafaxine, desvenlafaxine, milnacipran, bupropion, reboxetine and tianeptine. We identified one randomized controlled trial (RCT) in 14 patients on haemodialysis for fluoxetine versus placebo which showed no difference for efficacy and safety measures. One other RCT of escitalopram versus placebo in 62 patients on haemodialysis provided no efficacy data. There were nine non-randomized trials, all suggesting benefit for the antidepressant under investigation. Side-effects were common, but mild in most patients. The limitations of this review include the scarcity of randomized trial data, the small size of the observational studies and possibility of publication bias. In addition, study selection and data extraction were done by one reviewer only, increasing the risk for errors made in handling of the data.

Conclusions. Dose reduction in CKD3-5 is necessary for selegiline, amitriptylinoxide, venlafaxine, desvenlafaxine, milnacipran, bupropion, reboxetine and tianeptine. The evidence on effectiveness of antidepressants versus placebo in patients with CKD3-5, and with the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)-defined depression is insufficient, and in view of the high prevalence, a well-designed RCT is greatly needed.

Keywords: antidepressive agents; depressive disorder, major; renal insufficiency; systematic review

ERBP Recommendations

1.1 We suggest that in patients with CKD3 to CKD5 (CKD3-5) who meet DSM-IV criteria for moderate major depression, active treatment is started (2D).

1.2 We suggest a trial with antidepressant drug therapy can be started. After 8–12 weeks, the treatment effect should be re-evaluated to avoid prolonging ineffective medication (2D).

1.3 We suggest using an selective serotonin re-uptake inhibitor as a first-line agent, if treatment with an antidepressant drug is considered (2C).

Rationale

A recent Cochrane review on antidepressant drug therapy in the physically ill showed antidepressants to be significantly more effective than placebo (odds ratio 2.33, 95% confidence interval 1.8–3, number needed to treat = 6) [1]. For patients with CKD3-5, we identified only one published randomized trial in 14 patients, which did not suggest a beneficial effect of antidepressant drugs. Nine reports of prospective non-controlled studies that evaluated the effect of antidepressant drugs in CKD [2–10] found a benefit for the antidepressant under investigation, yet effect estimates were of similar magnitude for the placebo effect found in the one randomized controlled trial (RCT). As such, there is insufficient evidence for a general recommendation to routinely use an antidepressant agent in patients with CKD3-5 and a DSM-IV-defined depression. However in line with the current treatment guidelines, the high prevalence of depression in patients with CKD3-5 and its negative influence on survival and quality of life, active intervention seems justified. Given the very mild side effects of the studied antidepressants in CKD 3-5, an 8–12-week trial with these drugs can be considered in patients suffering from moderate depression according to DSM-IV [11]. However, the overall poor reporting of side-effects in trials in addition to observational data suggesting an association with increased risk of falls in elderly patients [12], means one should be careful when balancing the potential benefits against their potential harms. In any case, the effectiveness of the treatment should be evaluated after the initial 8–12-week treatment phase and the drug should be withheld when no benefit is observed.

Non-pharmacological treatments might provide equal benefit, without the potential harms and can represent valuable alternatives to antidepressant drug therapy. As they were not studied in this review, we refrained from making any statements. Of all the clinically studied compounds in patients with (CKD3-5), all but one belong to the class of selective serotonin reuptake inhibitors. Hence, from an evidence-based viewpoint, it seems reasonable to advocate the use of these agents as the first-line treatment of choice.

Introduction

Major depression is diagnosed when symptoms of persistent unreactive mood and loss of all interest or pleasure are accompanied by insomnia, fatigue, lethargy, loss of energy or appetite, poor concentration, restlessness, inappropriate guilt and/or morbid thoughts of death [13]. With an estimated prevalence of 14–30%, major depression is the most common psychological problem in patients with stage 5 chronic kidney disease (CKD5) [14–16].

Aside from having a worse quality of life, depressed patients with CKD are hospitalized more often and die sooner than those who are not depressed [16–18]. Proposed causal mechanisms to explain these poor outcomes include inflammation as well as non-adherence to therapy, an unhealthy lifestyle and poor nutrition [16]. It is reasonable to assume that successfully treating depression would improve overall wellbeing in these patients, but whether it will lead to better survival is uncertain.

Antidepressants are effective in treating depression in the general population [19, 20]. Around 50–65% of patients have reduced symptoms when treated with antidepressants compared with 25–30% when treated with placebo [20]. Improvement is usually observed within the first 3 weeks of starting therapy, but can take up to 6 weeks to become apparent.

Antidepressant drugs act by increasing the activity of one or more of the neurotransmitters serotonin, noradrenaline and/or dopamine in the central nervous synapses, by either preventing their enzymatic breakdown in the synaptic cleft, inhibiting re-uptake across the presynaptic cellular membrane, stimulating release from the presynaptic cells or stimulating effects on the postsynaptic receptor.

CKD may affect antidepressant pharmacokinetics unpredictably for several reasons. Impaired kidney function decreases drug excretion, but may also lead to reduced intestinal availability by slowed gastric emptying. Drug accumulation may result from altered absorption or hepatic metabolism and protein binding may differ according to the acidity of the drug [21]. Finally, dialysis may remove a drug to such extent that a substitution dose is needed to preserve the desired effect [22]. As a result, dose adjustments based on data from the general population and the expected influence of renal impairment may be highly inaccurate.

In a recently updated Cochrane review on the use of antidepressants in the physically ill, Rayner *et al.* [23] identified only two small randomized, placebo controlled trials, conducted in, respectively, 14 and 62 patients with CKD5 [24, 25]. We are not aware of any previous attempts to systematically summarize the pharmacokinetic data.

Given these uncertainties, we aimed to identify antidepressant compounds that might need dose adjustments in CKD3-5 and to identify both the benefits and harms of antidepressant medications in the management of CKD3-5 patients with depression.

Materials and methods

Criteria for considering studies for this review

We considered all study types in which an antidepressant drug was studied prospectively in humans. Neither randomized allocation nor a non-randomized control group was considered an absolute prerequisite, and we imposed no restrictions based on the number of participants in each trial. Because rare but potentially life-threatening side-effects are not necessarily captured by trials, we included all reports of serious adverse events, regardless of study design.

We included studies enrolling adults or children with CKD stage 3 (CKD3), 4 (CKD4) or 5 (CKD5) as defined by the KDOQI guidelines [26]. That is, we included all patients with an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 of body-surface area, calculated using the Modification of Diet in Renal Disease formula or any other glomerular filtration rate estimation equation. For trials evaluating the efficacy of an antidepressant, we required participants to have a diagnosis of depression, although we did not specify the diagnostic tools used to make the diagnosis. We excluded trials in which antidepressants were prescribed primarily to treat symptoms other than depression.

All drug compounds listed as antidepressants according to the British National Formulary [27], the American Hospital Formulary Service Drug Information [28] or the Dutch Farmacotherapeutisch Kompas [29]

Table 1. Suggested dosing scheme with normal and impaired renal function

Class compound	Dose in normal renal function	Dose in eGFR 30–60 mL/min	Dose in eGFR 15–30 mL/min	Dose in eGFR <15 mL/min	Dose in RRT[b] (HD[c], PD[d] and HDF[e])
Monoamine oxidase inhibitor					
Isocarboxacid	30–60 mg daily in single or divided doses	No adjustment	No adjustment	No adjustment	No adjustment
Phenelzine	45–90 mg daily in three divided doses	No adjustment	No adjustment	No adjustment	No adjustment
Pirasidol	No information	No data	No data	No data	No data
Tranylcypromine	30–60 mg daily in two divided doses, morning and early afternoon	No adjustment	30 mg, increase carefully	30 mg, increase carefully	30 mg, increase carefully
Selegiline	5–10 mg daily in single or divided doses	5 mg, increase carefully[a]	5 mg daily[a]	5 mg daily[a]	5 mg daily
Tricyclic antidepressants					
Clomipramine	10–250 mg daily, single or divided doses	No adjustment	10 mg, increase carefully	10 mg, increase carefully	10 mg, increase carefully
Desipramine	25–300 mg daily, single or divided doses	No adjustment	No adjustment	25 mg, increase carefully	25 mg, increase carefully[a]
Lofepramine	140–210 mg daily, two-three divided doses	No adjustment	No adjustment	140 mg, increase carefully	140 mg, increase carefully
Nortriptyline	30–150 mg daily, single or divided doses	No adjustment[a]	No adjustment[a]	No adjustment[a]	No adjustment[a]
Amitriptyline	75–200 mg daily, single dose	No adjustment	No adjustment	No adjustment	No adjustment[a]
Amitriptylinoxide	30–300 mg daily	No adjustment	15 mg, increase carefully	15–150 mg daily[a]	15–150 mg daily
Dibenzepine	240–720 mg daily	No adjustment	240 mg, increase carefully	240 mg, increase carefully	240 mg, increase carefully
Dosulepine	75–225 mg daily, max single dose 150 mg	No adjustment	75 mg, increase carefully	75 mg, increase carefully	75 mg, increase carefully
Doxepine	10–300 mg daily, max single dose 100 mg	No adjustment	No adjustment	No adjustment	No adjustment[a]
Imipramine	10–200 mg daily, single or divided doses	No adjustment	10 mg, increase carefully	10 mg, increase carefully[a]	10 mg, increase carefully[a]
Melitracen	25–225 mg daily, two-three divided doses	No data	No data	No data	No data
Protriptyline	15–60 mg daily, single or divided doses	No adjustment	15 mg, increase carefully	15 mg, increase carefully	15 mg, increase carefully
Mianserin	30–90 mg daily, max single dose 60 mg	30 mg, increase carefully	30 mg, increase carefully	30 mg, increase carefully	30 mg, increase carefully
Amoxapine	75–400 mg daily, single or divided doses	No adjustment	No adjustment	No adjustment	No adjustment
Maprotiline	50–200 mg daily, single or divided doses	No adjustment	50 mg, increase carefully	50 mg, increase carefully	50 mg, increase carefully[a]
Selective serotonin re-uptake inhibitor					
Citalopram	10–40 mg daily in single dose	No adjustment[a]	No adjustment[a]	No adjustment[a]	No adjustment[a]
Escitalopram	10–20 mg daily in single dose	No adjustment	10 mg, increase carefully[a]	10 mg, increase carefully	10 mg, increase carefully
Fluvoxamine	50–300 mg daily, max single dose 150 mg	No adjustment	No adjustment	No adjustment	No adjustment[a]
Fluoxetine	20–60 mg daily, in single dose	No adjustment[a]	No adjustment[a]	No adjustment[a]	No adjustment[a]
Paroxetine	20–50 mg daily, in single dose	10 mg, increase carefully[a]	10 mg, increase carefully[a]	10 mg, increase carefully[a]	10 mg, increase carefully[a]
Sertraline	50–200 mg daily in single dose	No adjustment	50 mg, increase carefully	25 mg, consider reducing max dose	25 mg, consider reducing max dose[a]
Serotonin norepinephrin re-uptake inhibitor					
Venlafaxine	75–225 mg daily, three divided doses	No adjustment	37.5–112.5 mg	37.5–112.5 mg	37.5–112.5 mg[a]
Desvenlafaxine	50 mg daily, single dose	25 mg, increase carefully[a]	25 mg daily[a]	25 mg daily[a]	25 mg daily[a]
Duloxetine	40–120 mg daily, single or divided doses	No adjustment	40 mg, increase carefully[a]	40 mg, increase carefully[a]	40 mg, increase carefully[a]
Milnacipran	50–100 mg daily, two divided doses	25 mg, increase carefully[a]	25–50 mg[a]	25–50 mg	25–50 mg
Serotonin modulator					
Nefazodone	100–600 mg daily, two divided doses	100 mg, increase carefully[a]	100 mg, increase carefully[a]	100 mg, increase carefully[a]	100 mg, increase carefully
Trazodone	150–600 mg daily, divided doses	No adjustment[a]	No adjustment[a]	150 mg, increase carefully[a]	150 mg, increase carefully

(*continued*)

Table 1. Continued

Class compound	Dose in normal renal function	Dose in eGFR 30–60 mL/min	Dose in eGFR 15–30 mL/min	Dose in eGFR <15 mL/min	Dose in RRT[b] (HD[c], PD[d] and HDF[e])
Noradrenergics and specific serotonergics					
Mirtazapine	15–45 mg in single or two divided doses	No adjustment	15 mg, increase carefully	15 mg, increase carefully[a]	15 mg, increase carefully[a]
Norepinephrine dopamine re-uptake inhibitors					
Bupropion	200–450 mg, max single dose 150 mg	150 mg daily[a]	150 mg daily[a]	150 mg daily[a]	150 mg daily[a]
Dopamine receptor agonist					
Trimipramine	50–300 mg daily, max single dose 200 mg	No adjustment	No adjustment	50 mg, increase carefully[a]	50 mg, increase carefully
Reversible mono-amiono oxidase-inhibitor					
Moclobemide	300–600 mg daily, in three divided doses	No adjustment[a]	No adjustment[a]	No adjustment[a]	No adjustment[a]
Selective serotonin re-uptake enhancer					
Tianeptine	25–37.5 mg daily in two-three divided doses	12.5 mg, increase carefully	12.5–25 mg[a]	12.5–25 mg[a]	12.5–25 mg[a]
Melatonergic antidepressant					
Agomelatine	25–50 mg daily in single dose	No adjustment	No adjustment	No adjustment	No adjustment
Selective norepinephrine re-uptake inhibitor					
Reboxetine	8–12 mg daily in two-three divided doses	4–6 mg daily[a]	4–6 mg daily[a]	4–6 mg daily[a]	4–6 mg daily
Viloxazine	200–600 mg, divided doses	Not studied	Not studied	Not studied	Not studied

[a]Dose suggestions are based on extrapolated and/or indirect data only, unless marked with a.
[b]RRT, renal replacement therapy.
[c]HD, haemodialysis.
[d]PD, peritoneal dialysis.
[e]HDF, haemodiafiltration.

Table 2. Types of pharmacological outcome measures

Symbol	Definition	Unit of measurement
M	Molecular mass	D, g/mol
A	Degree of absorption from gastro-intestinal tract	Qualitatively, % of total oral dose
F	Bioavailability	% of intravenous dose reaching systemic circulation
C_{max}	Peak plasma concentration	ng/mL
t_{max}	Time to peak plasma concentration	h
V_d	Apparent distribution volume	L or L/kg
PPB	Degree of plasma protein binding	% of total plasma concentration
AUC	Area under the curve	unitless
$t_{½}$	Elimination half-life	h
CL/F	Plasma clearance after oral administration as calculated from the area under the curve in a plasma concentration time curve	L/h
CLr	Plasma clearance by the kidney	L/h
Cld	Plasma clearance by dialysis	L/h

were eligible for this review.(Table 1) We excluded mood-stabilising drugs such as lithium, even if they had been used to treat depression.

The first outcome category consisted of basic pharmacokinetic parameters reflecting the different aspects of absorption, bioavailability, drug distribution, metabolism and excretion (Table 2). The second category comprised measures of efficacy and harm. Here, the main outcomes were response to treatment, improvement upon treatment and change in depression severity as defined by the investigators and according to whatever scale they used. We also looked at hospitalization rate, all-cause mortality, suicide or suicide attempts, withdrawal from dialysis, adherence to treatment for CKD, quality of life and effect on nutritional parameters. An attempt was made to report on adverse events attributable to the antidepressant intervention as a measure of tolerability and the number of dropouts from the antidepressant therapy as a proxy of acceptability.

Search methods for identification of studies

The search strategies we used to retrieve studies from the bibliographic databases combined medical subject headings and text words for CKD, end-stage renal disease, depression and antidepressants, limiting to studies conducted in humans. We did not apply a methodological filter nor did we impose any restriction on language. The search strategies are detailed in Supplementary Appendix 1.

To identify studies for inclusion in this review, in December 2011, we searched The Cochrane Renal Group Specialized Register, CENTRAL in the Cochrane Library, MEDLINE from 1950, EMBASE from 1980, PsychINFO from 1967, International Pharmaceutical Abstracts from 1950, Clinical trial registries endorsed by the International Committee of Medical Journal Editors, reference lists of nephrology textbooks, pharmaceutical reference works, review articles and relevant studies.

Data collection, extraction, analysis and assessment of risk of bias

Both initial screening of all titles and abstracts, subsequent full-paper assessment of potentially eligible studies and extraction of the data from included studies was done by E.V.N. All studies reported in a language other than English were translated before assessment. Additional data were requested from authors for the randomized controlled trials (RCTs) only.

The quality of the included studies was assessed by E.V.N., without blinding to authorship or journal. We did not formally evaluate the risk of bias in the pharmacokinetic studies, as no validated tool exists. Instead, we described the process for participant selection, participant

characteristics, completeness of outcome reporting, addressing of all active metabolites, reporting of analytic procedures and mathematical model building. For randomized trials describing efficacy, we used the risk of bias checklist as recommended by the Cochrane handbook for systematic reviews on interventions [30]. For non-randomized or uncontrolled trials and observational studies, we highlighted the design features that may introduce bias [31].

Data reporting

We reported both pharmacokinetic and clinical results in tables (See Supplementary Appendix 2 and 3). Sparse and heterogeneous data precluded informative formal meta-analysis. For many drugs, not all pharmacokinetic parameters were known for individuals with renal impairment. In such cases, drug disposition was predicted from knowledge of the drug's pharmacokinetics in patients with normal kidney function. Hence, we provided data generated in the general population, retrieved from six reference works [27–29, 32–33] and supplemented this with data from studies conducted specifically in patients with CKD.

For pharmacokinetic data, we presented findings as continuous data with measures of central tendency and distribution as reported by the original authors. We reported exact P-values where possible.

For efficacy measures, we reported categorical data in absolute numbers. For controlled trials, we had planned to supply the results in terms of relative risks and their 95% confidence interval (95% CI). Both of the two identified controlled trials, however, reported results only on a continuous scale. We reported these results as a mean difference and 95% confidence interval when possible. For uncontrolled trials, findings were reported as change from baseline or as group means at beginning and end of the trial. Standard deviations were supplied where possible. If significance tests had been conducted, mean change from baseline, 95% confidence intervals and P-values were reported as in the original article. If standard errors were not available, attempts were made to calculate the 95% confidence interval from exact P-values if they were available.

Results

Pharmacokinetics

Characteristics of included studies. We identified 33 published reports [2, 3, 21, 35–64] of 28 studies investigating pharmacokinetic parameters for 24 antidepressant medications. (Figure 1) Twelve studies exclusively included patients with CKD5 treated either with peritoneal dialysis [50, 60] or haemodialysis [2, 3, 45, 47, 50, 51, 55, 57, 58, 61, 63]. One study included only patients with CKD5, who were not yet on dialysis [44]. Another study included patients with CKD4 and CKD5 treated either conservatively or with haemodialysis [53, 54]. Thirteen studies also included patients with CKD3 [35, 38, 40–43, 46, 48, 49, 56, 59, 62, 64], and in three, it was not possible to distinguish between CKD3 and more advanced CKD [21, 35, 48]. Finally, we accepted one study that had included one patient with CKD2 as well as two with CKD3 and five with CKD4, where individual patient data could not be extracted [52].

Four trials only looked at drug removal through dialysis [3, 45, 55, 57]. Two were *in vitro* studies of plasma protein binding [21, 51]. The 21 others were full pharmacokinetic studies, but reported outcomes incompletely [2, 35–44, 46–50, 52–54, 56, 58–64].

Of the 21 pharmacokinetics studies, five reported six of the nine pre-specified outcome measures [21, 41, 48, 61, 64], five reported five [36, 49, 53, 54, 56, 58, 59, 63], six reported four [39, 44, 62] or three [35, 37, 38, 46], and three reported two [42, 43, 47] or one [60]. (Table 2)

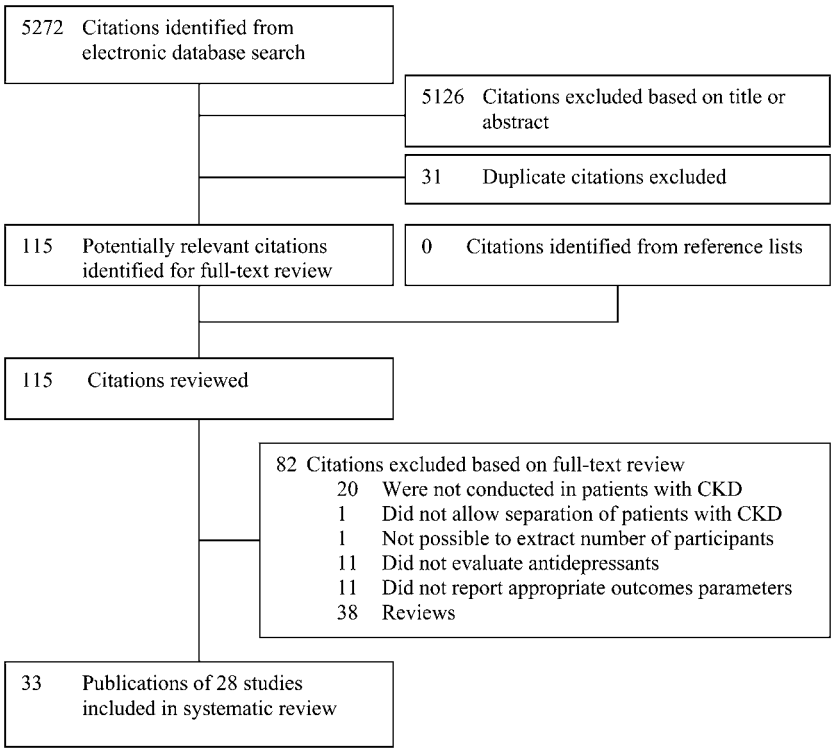

Fig. 1. Selection process for inclusion of studies in review of pharmacokinetics.

Finally, three studies only reported serum concentrations of the drug under investigation [2, 40, 50].

On average, the number of participants with CKD in each trial was small. Only three studies included >20 patients [21, 51, 64], 12 included between 11 and 20 [36–44, 46, 49, 50, 53, 54, 56, 59], 11 included between 2 and 10 [2, 3, 35, 47, 48, 52, 57, 58, 60, 62, 63], and 2 only included 1 patient [45, 55].

Fourteen studies mentioned inclusion or exclusion criteria. Only seven stated them explicitly [2, 36, 39, 49, 56, 59, 61, 63, 64]. Of the 19 trials that included dialysis patients, nine detailed both the frequency and duration of the dialysis procedure and the type of dialyser or the dialysis solutions used [21, 42, 43, 47, 51, 57, 58, 60, 61, 63]. Two studies provided details about frequency and duration only [3, 50].

No study clearly described the selection process. Underlying renal disease was explicitly reported in nine trials [40, 42, 43, 47–50, 58–60, 63], but only three studies detailed other comorbidities [2, 51, 57], and only eight listed other medications patients were chronically taking [35, 42, 43, 45, 50, 51, 57, 60, 63].

Of 23 trials needing control groups (all but the four dialysis studies), only five trials presented inclusion and or exclusion criteria for controls [2, 48, 61, 62, 64]. Characteristics were generally poorly described. Age, sex and or body weight were provided by 16 studies [2, 35–39, 42–44, 48–52, 58, 60, 62, 64].

Three trials studied both single and multiple dosing [40, 42, 43, 58]. In the 24 others, authors limited analyses to only single [21, 35, 38, 39, 41, 44, 46–48, 51–54, 56, 57, 59–64] or multiple dosing [2, 3, 37, 45, 50].

Of the 21 studies that should have addressed the pharmacokinetics of the active metabolite [2, 21, 35–37, 40–45, 47, 49, 51, 53–57, 59–63], only 15 did so [2, 35–37, 42–44, 47, 49, 51, 53–56, 59, 61–63]. The others only discussed the parent drug.

Analytic procedures used to measure drug concentrations were detailed in 21 trials [2, 21, 35, 37–39, 41–44, 48, 50–52, 56–64]. Only limited detail was given in seven trials [36, 40, 46, 47, 49, 53–55]. One did not mention them at all [56].

Of the 21 full pharmacokinetic studies, 17 described mathematical model building. Two allowed for non-linear kinetics [48, 63], whereas all others assumed a one-compartment model or linear kinetics [35, 37–39, 42–44, 46, 52–54, 56, 58–62, 64].

Findings. Drug elimination was studied in patients with CKD3-5 including haemodialysis patients on a non-dialysis day. Elimination half-life was importantly prolonged and/or drug clearance markedly reduced after oral intake for amitriptylinoxide [44], venlafaxine [61], desvenlafaxine [64], milnacipran [52], bupropion [62] and reboxetine [41]. For selegiline, the elimination half-life could not be reliably calculated but the area under the plasma concentration curve was significantly increased [50]. Mirtazapine had a reduced plasma clearance after oral intake, but not a prolonged elimination half-life [55].

For tianeptine neither elimination half-life nor clearance after oral intake was different for the parent compound [53, 54]. However, the elimination half-life of its active metabolite was markedly increased [53, 54]. For imipramine [50], sertraline [57] and nefazodone [38], on average the half-life was importantly increased numerically, although in these small and underpowered studies none of the differences in half-life were significant when compared with healthy controls. For amitriptyline [60], doxepine [47], citalopram [48, 58], fluoxetine [36, 49], trazodone [40] and moclobemide [56, 59], the various pharmacokinetic parameters were similar between patients with advanced CKD and healthy controls. Interindividual variability of parameters was high in all trials.

Removal by haemodialysis was directly tested for nine compounds during a 4-h session with a low-flux dialyser. For fluvoxamine, there was an average 21% reduction in its plasma concentration during the dialysis session in three patients under evaluation [3]. Only limited amounts of desipramine [50], nortriptyline [42], amitriptyline [60], doxepin [47], citalopram [58], fluoxetine [49], venlafaxine [61], trazodone [45] and mirtazapine [55] were removed by dialysis. Drug removal was only assessed for patients undergoing standard haemodialysis. No information was identified for the more efficient strategies such as high-flux dialysis, haemodiafiltration and daily or long dialysis. There was no specific information on removal by peritoneal dialysis.

The potential need for a dose increase in patients on haemodialysis was evaluated in two studies. For two patients treated with amitriptyline, the elimination half-life was similar to that in the general population [50]. For six patients taking fluoxetine, the steady-state serum concentration was numerically higher but not significantly different compared with six participants with normal renal function [37].

Effectiveness and safety

We identified only three RCTs of antidepressant medications (Figure 2).

One trial is still ongoing (CAST-trial-NCT00946998) and aiming to include 200 participants to evaluate sertraline in a 12-week placebo-controlled randomized trial in patients with CKD3-5 who are diagnosed with major depressive disorder.

The two trials that have been finalized were both conducted in individuals on haemodialysis [24, 25], and required a diagnosis based on a clinical interview using criteria from the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the gold standard for psychiatric diagnosis [13].

In the first trial, escitalopram was compared with placebo in 62 patients, but the report was only published as an abstract [25]. The investigators suggested an improvement in depression scores but provided no end-point data. Participants had no serious adverse events. Methodology was insufficiently detailed to allow a clear judgement of the risk of bias. We tried to contact the authors for additional information but did not receive a response.

A second study of fluoxetine versus placebo, provided adequate outcome data, but included only 14 patients [24]. On average, after 8 weeks, patients treated with fluoxetine

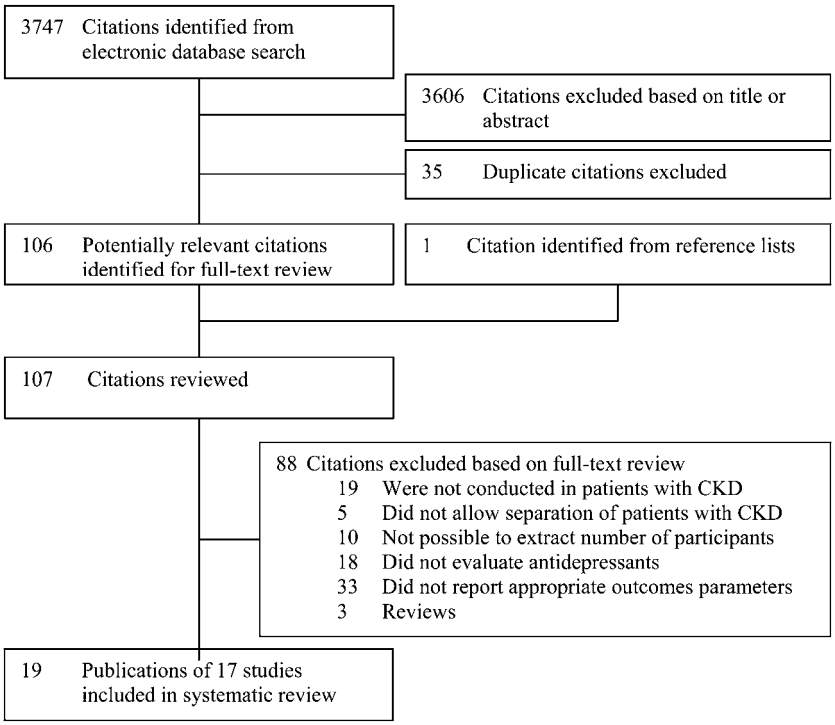

Fig. 2. Selection process for inclusion of studies in review of efficacy and safety.

had a 10-point reduction in depression severity on the 63-point Beck Depression Inventory (BDI) scale and a 9-point reduction on the 53-point Hamilton Depression Scale (HAM-D). The results were similar for patients treated with placebo. Adherence was not measured.

The number of adverse events was numerically higher in those receiving fluoxetine (34 events in six patients) than in those receiving placebo (22 events in seven patients). Hypotension was reported in four patients in the fluoxetine group versus one in the placebo group. The severity of these events was not specified. Overall, we judged the risk of bias to be low, with adequate sequence generation, allocation concealment, blinding of all participant health-carers, outcome assessors and data analysts, complete reporting of all outcomes and addressing missing data.

We identified nine non-randomized uncontrolled trials, including 7–44 participants each [2–10]. In six studies, patients had to meet the criteria for major depressive disorder as outlined in the DSM-III [2, 4], or DSM-IV clinical psychiatric interview [5, 7, 9, 10, 65, 66]. The three others used various screening tools with a chosen cut-off as inclusion criterion [3, 6, 8]. One evaluated the effects of a tricyclic antidepressant [4], whereas the eight others investigated one of the selective serotonin reuptake inhibitors.

In three studies, response by the end of the 4–8-week trial, as defined by a HAM-D score <18 or a reduction of 50% from baseline, varied between 39 and 80% [3, 4, 6]. After 8–12 weeks, depression severity decreased 7–9 points on the BDI scale in four studies [5, 8, 9, 10], and 2–12 points on the HAM-D scale after 8 weeks in two other studies [2, 7].

There were no data on hospitalization rate, all-cause mortality, suicide or suicide attempts and withdrawal from dialysis or for adherence to treatment for CKD.

Two groups investigated the effect of antidepressant treatment on nutritional parameters [6, 7]. In an uncontrolled trial with paroxetine [7], a significant increase in three measures of protein intake was observed. Plasma concentrations of albumin on average increased from 37.3 to 38.7 g/L and those of blood urea nitrogen from 24.3 to 30.2 mmol/L. Normalized protein catabolic rate as a marker of protein intake, significantly increased from 1.04 to 1.17 g/kg/day [7]. The clinical relevance of this outcome might be questioned, given that both values are above the suggested lower limit for malnutrition in dialysis patients of 1 g/kg/day [67].

Conversely, in a non-randomized uncontrolled study conducted in 39 patients on haemodialysis, Lee *et al.* [6] found no evidence that fluoxetine significantly changed body weight, fat-free mass or arm-muscle index.

Adverse events were reported in five trials. The percentage of people suffering from side-effects in these trials varied between 9 and 100%. Complaints were mainly minor and included dizziness, nausea, headache, sedation and somnolence. However, in up to 28% of those suffering side-effects, these caused the patient to discontinue treatment [2–4, 7, 65]. In the one study with a tricyclic agent [4], the investigators stated all patients reported side-effects, most frequently dizziness and dry mouth. However, there was no report of cardiotoxicity and most complaints caused only minor discomfort.

We did identify three retrospective case-reports of serious adverse events associated with the use of a

tricyclic compound in patients with severe CKD [68–70]. These included a cardiac arrest associated with the use of maprotiline [68], after exclusion of electrolyte disorders, a case of severe hyperventilation attributed to nortriptyline [70], after exclusion of organic causes of hyperventilation and the development of malignant neuroleptic syndrome in a patient started on amoxapine [69].

We also identified one case report of repeated deep venous thrombosis and subsequent pulmonary embolism in a patient treated with fluoxetine [71], and one case in which a patient developed paranoid ideations while on venlafaxine [72].

Discussion

Summary of main results. For patients with CKD, clearance of various antidepressants is altered. Elimination half-life is prolonged and/or clearance after oral intake markedly reduced for selegiline [50], amitriptylinoxide [44], venlafaxine [61], desvenlafaxine [64], milnacipran [52], bupropion [62] and reboxetine [41]. For tianeptine, there is a marked increase in the elimination half-life of its active metabolite [53, 54]. There was large inter-individual variability in every trial and findings are based on single studies, all with methodological shortcomings.

There is no high-quality evidence from randomized trials that suggests antidepressants are more effective than placebo in treating depression in patients with CKD3–5. In addition, there are even only a few reports of prospective observational studies that evaluate the effect of antidepressant drugs in CKD [2–9]. All these studies suggested treatment improved depression after 8–12 weeks but when compared with the only placebo-controlled trial, the magnitude of effect was similar to that of placebo. Side-effects were common, but seemed to be mild in most patients.

Findings in the context of other published literature. A recent Cochrane review on antidepressant drug therapy in the physically ill showed antidepressants to be significantly more effective than placebo (odds ratio 2.33, 95% CI 1.8–3, number needed to treat = 6). At 6–8 weeks, there were more dropouts among patients treated with antidepressants than among patients treated with placebo (number needed to harm = 19) [23].

Of the common side-effects of antidepressant medications, dry mouth and sexual dysfunction were more frequently reported by patients treated with antidepressants.

There was no significant difference in response or adverse effects between tricyclic antidepressants or selective serotonin re-uptake inhibitors. Unfortunately, this meta-analysis included only one trial conducted in patients with CKD.

Strengths and limitations of this study. To our knowledge, this summary of the pharmacokinetics of antidepressants in CKD is the most extensive of its kind at present. It was based on six standard reference works in pharmacology and supplemented with original data from 41 primary studies. We identified these trials by systematically searching seven electronic databases and the reference lists of every obtained publication. However, for most compounds, parameter estimates were still based on single studies with few study subjects and, for all of the studies, we identified methodological flaws.

Given our knowledge of the recent Cochrane review [23] and our expectation of sparse controlled trial data, we decided to include data from uncontrolled trials to help inform practice.

All published non-controlled trials found a benefit for the antidepressant under investigation, yet effect estimates were similar for the placebo effect found by Blumenfield *et al.* in their RCT [24]. Indeed, in depression, on average one-third of participants in clinical trials respond to placebo, making the estimation of any effect size without a placebo control arm problematic. In addition, as on average 21% discontinued the treatment, failure to include outcomes for these patients in the analysis, may have caused the effect size to be overly optimistic. Finally, selective outcome reporting and publication bias might have caused only positive results to have been published [30].

Diagnosis of major depression in patients with CKD is challenging since symptoms of uraemia might mimic those of clinical depression. Clearly, outcomes of interventional trials could be misleading if diagnostic tools fail to distinguish between uraemia and depressive symptoms. Both the randomized trials and six of the nine non-randomized studies required a diagnosis based on a clinical interview using DSM-III or -IV criteria, considered the gold standard to make the diagnosis of depression. Turk *et al.* used the BDI with a validated cut-off of 15 [72], the other two used screening tools with cut-offs, that had been less validated in patients with CKD.

The available study data point towards a different time lag needed for improvement after antidepressant therapy initiation for patients with CKD (up to 12 weeks) in comparison with the general population (3–6 weeks). Possibly, this is explained by inadequate dosing, drug availability or receptor-drug processing, non-adherence to treatment or somatic influences on treatment success, all of which is subject to further research.

For the present systematic review, studies were selected and data extracted by one person only. Although the findings were carefully checked, failing to include independent study selection and data extraction by a second author increases the risk of errors made in handling of the data.

Implications for further research. High-quality efficacy and safety data on the use of antidepressants in advanced CKD are lacking and a well-designed RCT to clarify the balance between benefits and harms is long overdue. We know of only one ongoing randomized trial, comparing sertraline to placebo with a 12-week follow-up, aiming to include 200 patients. Longer follow-up would be needed to demonstrate a sustained benefit of pharmacologic treatment and evaluate whether hard end-points such as hospitalization and mortality are affected without too many side-effects. Given the lack of adherence and the variability of pharmacokinetic and dynamic effects, larger sample sizes will probably be necessary to reliably show a beneficial treatment effect.

Supplementary data

Supplementary data are available online at http://ndt.oxfordjournals.org.

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