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CKJ Review

CKJ REVIEW

Drugs with a negative impact on cognitive function (Part 1): chronic kidney disease as a risk factor

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ABSTRACT

People living with chronic kidney disease (CKD) frequently suffer from mild cognitive impairment and/or other neurocognitive disorders. This review in two parts will focus on adverse drug reactions resulting in cognitive impairment as a potentially modifiable risk factor in CKD patients. Many patients with CKD have a substantial burden of comorbidities leading to polypharmacy. A recent study found that patients seen by nephrologists were the most complex to treat because of their high number of comorbidities and medications. Due to polypharmacy, these patients may experience a wide range of adverse drug reactions. Along with CKD progression, the accumulation of uremic toxins may lead to blood–brain barrier (BBB) disruption and pharmacokinetic alterations, increasing the risk of adverse reactions affecting the central nervous system (CNS). In patients on dialysis, the excretion of drugs that depend on kidney function is severely reduced such that adverse and toxic levels of a drug or its metabolites may be reached at relatively low doses, unless dosing is adjusted. This first review will discuss how CKD represents a risk factor for adverse drug reactions affecting the CNS via (i) BBB disruption associated with CKD and (ii) the impact of reduced kidney function and dialysis itself on drug pharmacokinetics.

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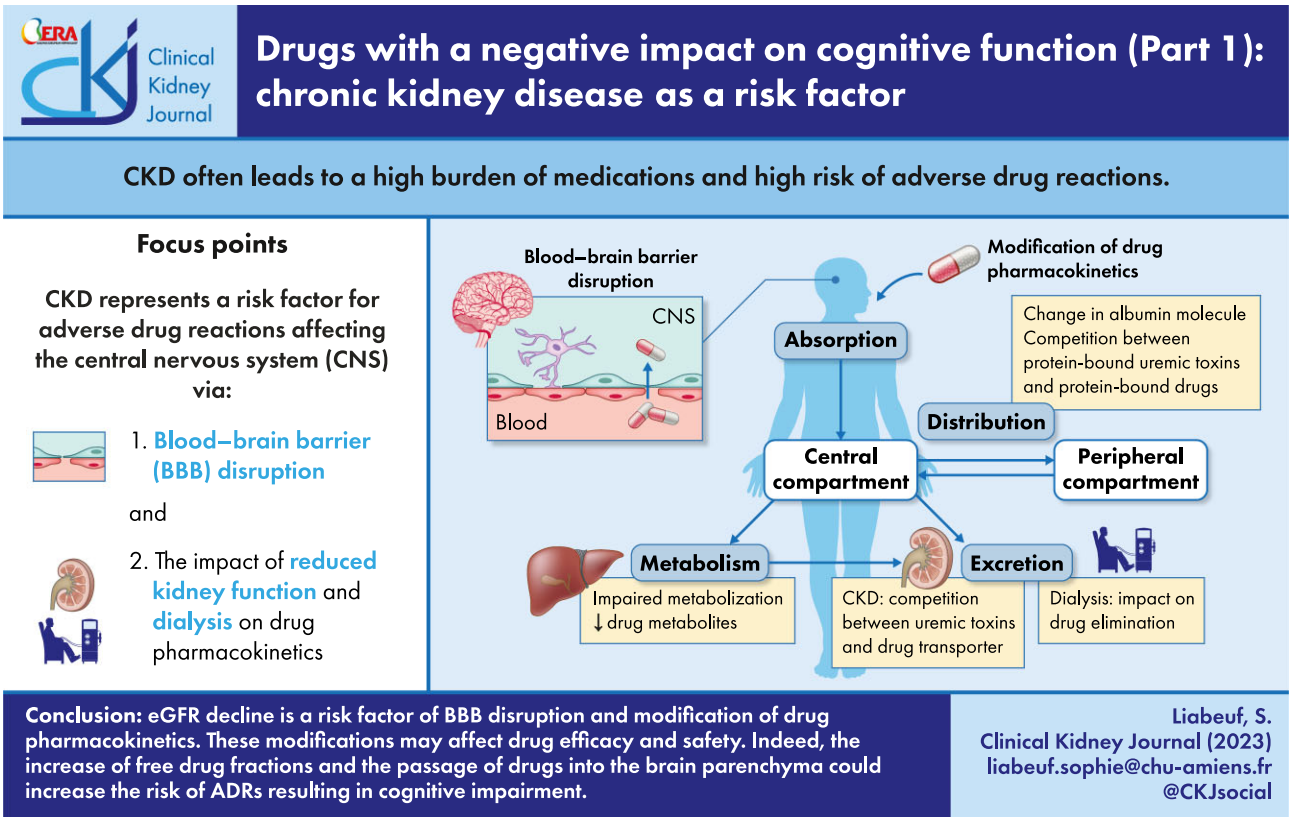
GRAPHICAL ABSTRACT



Keywords: adverse drug reactions, chronic kidney disease, cognitive impairment, drug prescription

INTRODUCTION

Neurocognitive disorders in the general population are associated with several risk factors including cardiovascular disease, inflammation and history of head injury. Cognitive impairment is the deterioration of cognitive function beyond what might be expected from normal aging. Deterioration can affect a single one or several of the following cognitive domains: attention span, planning, memory, reasoning, decision making, language and executive functioning. Neurocognitive disorder (NCD) is defined as primarily cognitive impairment, acquired and declining. The patient's cognitive pattern together with clinical examination, brain imaging and biology, allows the cause of the NCD to be determined (e.g. Alzheimer's disease, vascular NCD, frontotemporal degeneration, etc.), even though cognitive functions are interconnected and interdependent. Cognitively impaired CKD patients often exhibit executive dysfunction that would be expected in vascular neurocognitive disorder; however, CKD patients are also at higher risk of Alzheimer's disease compared with the general population [1, 2].

Chronic kidney disease (CKD) is an independent risk factor for the development of cognitive impairment [3]. Some general factors associated with cognitive performance in the general population are also linked to cognitive function in CKD such as demographic and psychosocial factors or depression, although specific data on CKD patients are limited [4]. A number of specific CKD-related factors are also associated with impaired cognitive performance such as anemia, hyperparathyroidism, uremic toxins and albuminuria [4–6]. The high proportion of cardiovascular risk factors in CKD patients makes it difficult to disentangle the effect of kidney function on cognitive function from the effect of coincident vascular damage [7].

CKD patients have a substantial comorbidity burden, which often results in polypharmacy [8]. A recent study found that the patients seen by nephrologists were the most complex to treat because of their high number of comorbidities and the high number of prescription medications taken [9]. Along with comorbidities and renal complications, the drug burden increases sharply as CKD progresses. Indeed, CKD patients not only have many comorbidities, but they also experience particular complications (such as anemia, hyperkalemia and bone mineral disorders) requiring specific medications. Various studies have found high levels of polypharmacy (from 10 to 12 drugs per day per individual, on average) in CKD patients [10–13]. Due to this polypharmacy, patients with CKD have also a high risk of developing adverse drug reactions (ADRs). In a large cohort of patients with moderate to advanced CKD, Laville *et al.* showed that ADRs are common, often serious and potentially preventable, and that the incidence was higher when CKD was severe [14]. Among ADRs, cognitive adverse effects are frequent in CKD patients and could be a modifiable factor targeting the different classes associated with cognitive impairment. Indeed, several medications frequently included in the treatment regimen of CKD

patients have been linked to negative effects on cognition such as drugs with anticholinergic properties, opioids agents, psychotropic agents, antibacterials, antiviral drugs and immunosuppressive drugs [15].

In addition, CKD is a very common clinical problem in older patients, thus older age is another important risk factor for ADRs, in particular drug-induced cognitive disorders [16]. In parallel with CKD progression, the accumulation of uremic toxins could lead to blood–brain barrier (BBB) disruption [17]. Alteration of the BBB could furthermore modify the efficacy of some drugs by increasing their penetration of the brain parenchyma and induce major central nervous system (CNS)-related ADRs. Prescribing to patients with CKD can be complex, because kidney disease and function has multiple effects on pharmacokinetics and these effects are dependent on both the drug and the clinical context [8]. In CKD patients, drug accumulation could lead to clinical symptoms augmenting the risk of ADRs affecting the CNS. Hence, dose adjustments may be required for selected drugs with pharmacokinetics that change significantly in kidney disease, especially for patients with end-stage kidney disease (ESKD) on dialysis.

In this narrative review, we will discuss how CKD represents a risk factor for ADRs affecting the CNS via (i) BBB disruption associated with CKD and (ii) the impact of reduced kidney function and dialysis on drug pharmacokinetics.

ALTERATION OF THE BBB ASSOCIATED WITH KIDNEY DISEASE

The BBB is vital for maintaining brain homeostasis by permitting fine control of the exchange of compounds and fluid between the blood and the brain parenchyma; moreover, the BBB prevents unwanted toxins, pathogens and drugs from entering the brain. The properties of the BBB are primarily determined by endothelial junctional complexes consisting of tight-junctions and adherens junctions, as well as by pericytes and astrocyte foot processes [18]. It is generally accepted that tight-junctions seal the interendothelial cleft forming a continuous blood vessel, while the adherens junctions are important for initiating and maintaining endothelial cell-to-cell contact. These junctions are composed of transmembrane proteins and cytoplasmic plaque proteins. Transmembrane proteins of the tight-junctions include occludin, claudins (claudin-5 being dominant in BBB endothelial cells), *zonula occludens* (ZO) proteins and junctional adhesion molecules (JAMs). Occludin has been shown to be increased in the peripheral circulation of animal models of cerebral ischemia [19], while JAM-1, located at the epithelial and endothelial tight-junctions, has been shown to be involved in regulation of endothelial cell migration. Adjacent cells also play a major role in the integrity of the BBB. Pericytes cover the outer surface of the capillaries along the basal lamina and play an important role in the integrity of the BBB by regulating the polarization of astrocytic foot processes in the BBB and endothelial transcytosis. In mice, knockout of the *PDGF-β* gene leads to a rarefaction of pericytes and a significantly increased permeability of the BBB [20]. Astrocytes are part of the glial cells of the CNS and have many functions that contribute to the protection of neurons. Astrocytes have long foot process–like extensions that allow connections to neurons and other astrocytes, but also to cerebral endothelial cells, and moreover participate in the architecture of the BBB and in the regulation of endothelial permeability and vascular tone [21]. After brain injury, astrocytes may hypertrophy and be recruited locally to form a barrier limiting the diffusion of leukocytes into the brain parenchyma [22].

The BBB breaks down with age and further disruption is a hallmark of many age-related disorders such as Alzheimer's disease, which is also associated with pericyte dysfunction [23], and other chronic systemic diseases with a cerebral involvement. Thus, BBB disruption seems to be an important mechanism in diseases associated with cognitive impairment. In addition, certain pathophysiological factors like CKD may induce an impairment in BBB function (Fig. 1). This may lead to increased vascular permeability allowing entry of toxic substances into the CNS, resulting in damage that may manifest as cognitive impairments. There is accumulating evidence that CKD is associated with BBB disruption that may lead to cognitive impairment [17, 24]. One of the vascular mechanisms that may underly cognitive impairment in CKD patients involves "uremic toxins" causing BBB damage and dysfunction, since many of these toxins, including indoxyl sulfate, are known to induce endothelial dysfunction in CKD [25]. However, the acquisition of human brain tissues and subsequent isolation of brain micro-vessels is associated with complexities and there is limited research access to human brain endothelial cells. Therefore, studies aimed at modeling the BBB [26] have had limited success due to the complexity of its histological features. On the other hand, it was noted that small-vessel disease in the brain is mirrored by small-vessel pathologies in other organs [27]. Hernandez *et al.* [28] analyzed BBB dysfunction under uremic conditions assessing BBB permeability using serum CNS biomarkers and tight-junction integrity. They demonstrated that CNS biomarker neuron-specific enolase (NSE) was increased in hemodialysis patients, while brain-derived neurotrophic factor (BDNF) was reduced in the serum of hemodialysis patients compared with controls [29]. The expression of the tight-junction protein claudin-5, occludin and JAM-1 was lower in kidney transplant patients compared with controls. This study demonstrated that CKD is associated with biomarkers of BBB dysfunction, suggesting weakened tight-junction integrity.

In a rodent model of CKD induced by a high adenine diet, several neurological abnormalities (akinesia, catalepsy) as well as anxiety- and depressive-like behavior were demonstrated. In this model BBB disruption was shown by Evans Blue dye extravasation into brain parenchyma [24]. Furthermore, in three rodent models of CKD the BBB permeability was assessed by single-photon emission computerized tomography (SPECT-CT) imaging, demonstrating that accumulation of the uremic toxin indoxyl sulfate in the serum activates aryl hydrocarbon receptors (AhR) which leads to disruption of the BBB and consequent cognitive impairment, while AhR-knockout mice were protected from indoxyl sulfate–induced BBB disruption [17].

The endothelial tight-junction markers in the brain cortex were analyzed in Sprague–Dawly rats with CKD induced by 5/6 nephrectomy. There was a significant reduction of ZO-1 protein, occludin and JAM-1 levels, while there was no significant change in claudin-5 protein expression [30]. Using the same CKD model, Lau *et al.* [31] showed that elevated blood urea induced actin cytoskeleton derangements and decreased claudin-5 expression, resulting in BBB dysfunction.

Finally, when analyzing BBB function in patients with CKD, associated comorbidities must be considered, particularly those associated with systemic inflammation. Diabetes, dyslipidemia and arterial hypertension are all associated with reduced cerebral blood flow and could contribute to BBB dysfunction. Indeed, BBB disruption has been described in patients with diabetes and hypertension [32, 33]. Alteration of BBB could modify CNS

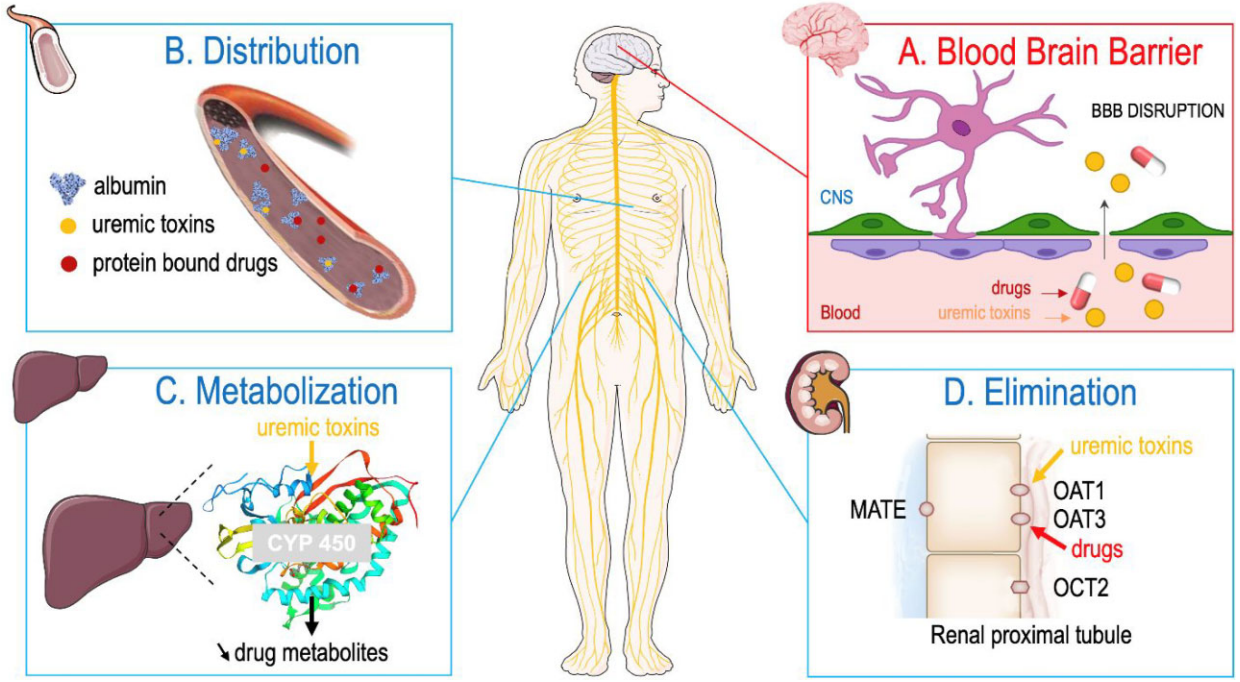


Figure 1: Impact of CKD on drug pharmacokinetics and the BBB. **(A)** BBB disruption. CKD is associated with alterations of the BBB leading to high number of CNS ADRs. **(B)** Distribution. A subject with late-stage CKD presented with low albumin levels, conformational changes in albumin molecule (such as carbamylation), competition between protein-associated uremic toxins and protein-bound drugs for albumin binding resulting in elevated free drugs fractions. **(C)** Metabolization. Severe CKD will result in decrease of expression and activity of drug-metabolizing enzymes such as CYP450 leading to unpredictable pharmacokinetics. **(D)** Elimination. CKD is associated with alteration of drug transporters. Example of competition between toxins and drugs as substrates of the OAT in renal proximal tubule leading to potential accumulation of drugs.

drug efficacy by increasing the passage of drugs into the brain parenchyma and induce ADRs resulting in cognitive impairment (Fig. 1A).

In addition to alteration of BBB, reduced kidney function could have an impact on drug pharmacokinetics inducing drug accumulation, leading to increased CNS ADRs.

REDUCED KIDNEY FUNCTION AND IMPACT ON DRUG PHARMACOKINETICS

Although most health professionals know that patients with a reduced estimated glomerular filtration rate (eGFR) have impaired clearance of drugs excreted primarily by the kidneys, the effect of CKD on non-kidney drug clearance is underappreciated. Indeed, there is evidence indicating that the drug distribution, the function of drug-metabolizing enzymes and transporters, which collectively determine net non-kidney drug clearance, is altered in CKD. Drug pharmacokinetics can be simply categorized as absorption, distribution, metabolization and elimination of the drug of interest. Pharmacokinetic properties are important determinants of the amount of drug reaching its site of action. In parallel with CKD progression, accumulation of uremic toxins could lead to drug pharmacokinetic alterations [34], especially distribution, metabolization and elimination phases (Fig. 1B–D). In clinical practice, eGFR equal to 40 mL/min/1.73 m^2 corresponds to the threshold where the blood concentrations of uremic toxins increase.

Indeed, various CKD-associated metabolic disturbances might alter drug distribution and potentially trigger a CKD stage decrease in albumin drug binding [35]. Hence, (i) hypoalbuminemia might reduce the number of drug-binding dependent sites, (ii) conformational changes in the albumin molecule (such as carbamylation induced by urea accumulation) might have a similar effect, and (iii) the accumulation of endogenous substances (named uremic toxins) might competitively displace drugs from their albumin binding sites [35], resulting in an elevated free drug fraction.

Besides other factors such as genetics, animal studies suggest that expression and activity of drug-metabolizing enzymes such as hepatic cytochrome P450 (CYP450) are decreased in moderate and severe CKD. Hence, drug metabolism is significantly decreased in CKD which implies that patients with moderate to late CKD may be subject to unpredictable pharmacokinetics [36].

In addition to decreased renal elimination of drugs, CKD is associated with alterations in various drug transporters. Moreover, several uremic toxins can interact with membrane transporters (mediating their entry or exit from the cell) and may cause deleterious biological effects. Membrane transporters such as organic anion transporters (OAT) are particularly important for renal clearance and elimination by other routes of drugs and uremic toxins. Hence, there may be competition between toxins and drugs as substrates of the transporter or even inhibition of their activities. Consequently, tissue disposition and the elimination of drugs as well as uremic toxins may be affected [34].

In summary, CKD changes the pharmacokinetics of many drugs, both those with renal and those with non-renal clearance, leading to the need for dose adjustments. As a result both supra- and subtherapeutic dosing can occur in a CKD setting unless appropriate dose adjustments are made, and both have negative effects on patient outcomes (ADRs, hospital admissions and

Table 1: Factors affecting dialysability of drugs [37].

Physicochemical and pharmacokinetic properties of the drug favoring dialyzability	
Water solubility	• Insoluble or fat-soluble drugs are not dialyzed—e.g. diazepam which is water insoluble
Low protein binding	• Tightly bound drugs are not dialyzed because dialysis is a passive process of diffusion—e.g. propranolol is 94% bound
Low MW	• Molecules with MW of <500 Da are easily dialyzed—e.g. vancomycin is poorly dialyzed via diffusion and has a MW of 1450 Da
Small Vd	• Widely distributed drugs are dialyzed more slowly because the rate limiting factor is the volume of blood entering the machine—e.g. digoxin, Vd = 250–300 L • Drugs concentrated in the tissues are usually difficult to remove by dialysis
Characteristics of the dialysis modality favoring dialyzability	
Blood flow rate	• Higher blood flows give higher clearance rates
Dialysate	• Higher dialysate flows give higher clearance rates
Dialysis membrane	• Higher permeability characteristics and surface area give higher clearance rates
Transmembrane pressure	• Ultrafiltration increases with transmembrane pressure increase • Higher substitutive solution flows give higher clearance rates
Duration and frequency of dialysis	• Longer duration and more frequent dialysis sessions give higher clearance rates

MW: molecular weight; Vd: volume of distribution.

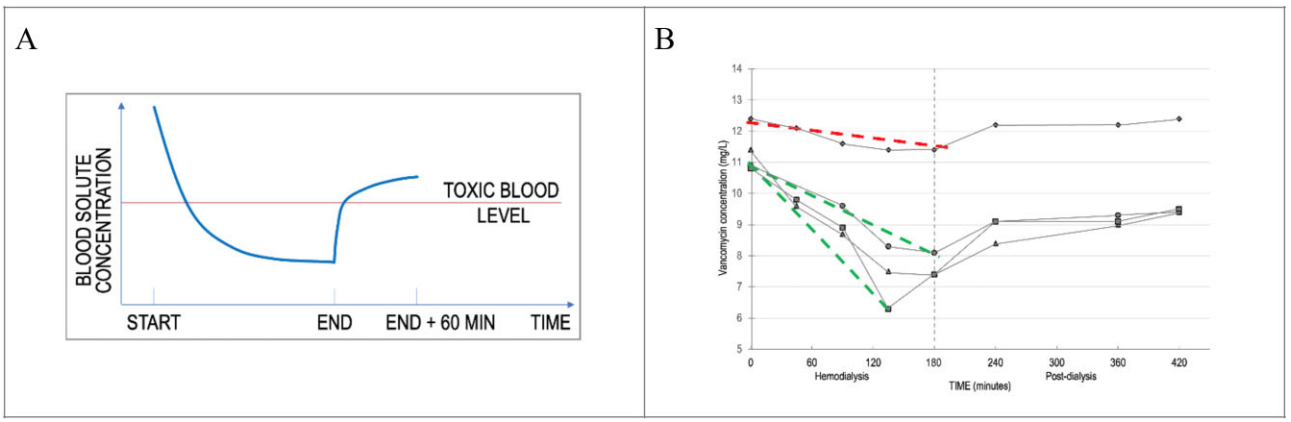


Figure 2: The effect of hemodialysis on blood concentrations of drugs that are removable by convective or diffusive processes [38, 40]. (**A**) Example of small solute removal during dialysis and (**B**) removal of vancomycin (high molecular weight) through low-flux (red) vs high-flux (green) membranes.

mortality). The risk of supratherapeutic exposure from drugs (or their toxic or active metabolites) that rely on renal elimination is amplified when the drug has a narrow therapeutic index, e.g. lithium or digoxin. Subtherapeutic dosing increases the risk of treatment failure that may be life-threatening (e.g. with some antibiotics) or organ threatening (e.g. with immunosuppressive drugs).

Patients with ESKD on dialysis are subject to extracorporeal clearance of small molecules, including many drugs. This aspect will be discussed in the next section.

CONSEQUENCES OF DIALYSIS ON DRUGS PHARMACOKINETICS

In patients with ESKD on dialysis, excretion of drugs that depend on kidney function is severely impaired. Hence, adverse and toxic levels of a drug or its metabolites may be reached at even low doses unless the dose is adjusted but also that a drug's concentration may be affected by dialysis itself.

In general, "dialyzability" through hemodialysis relates to a drug's excretion via the kidneys and its magnitude depends on a patient's preserved or residual kidney function. There are several key factors affecting the dialyzability of drugs [37] (Table 1). The extent to which hemodialysis removes a particular drug from plasma is dependent on its molecular weight, water solubility, protein binding capacity and volume of distribution. In addition, drug dialyzability is affected by the characteristics of modality of dialysis such as blood flow rate, dialysate solution, dialysis membrane, transmembrane pressure and duration/frequency of dialysis.

In peritoneal dialysis, where the convective and diffusive processes are continuous and slower, it may not be very significant [38].

Drug clearance by dialysis must be considered for appropriate timing of administration and dosing. For those drugs in which a substantial fraction is removed by hemodialysis they should be administered after dialysis to avoid drug removal and loss of efficacy. On the other hand, for drugs that are not significantly removed by dialysis, their administration does not need to be related to the timing of dialysis.

Figure 2 represents two examples of blood drug concentration after starting hemodialysis in drugs that are removed by convective or diffusive processes. Figure 2A represents general kinetics of dialyzable solute in blood during and immediately

Table 2: Common drugs and their relation to dialysis [41–47].

Drug	Dialyzable[a]	Recommended dose adjustment[b]
Anticholinergic drugs		
Antiepileptics		
Carbamazepine	Controversial (dialyzable or Not)	NDA (75%–100% dose as in normal renal function + supplementary dose as in GFR <15 mL/min
Oxcarbazepine	Unknown	NDA + supplementary dose as for GFR <10 mL/min
Antiparkinsonians		
Amantadine	Not dialyzable	No additional dose, dose as in GFR <15 mL/min
Trihexyphenidyl	Unknown	No known effects but should be used with caution
Anxiolytic		
Hydroxyzine	Not dialyzable	NDA, supplement for IHD dose as in GFR <10 mL/min, consider risk of M(+), cetirizine
Antidepressants		
Tricyclic		
Amitriptyline	Not dialyzable	NDA, monitor ADRs, especially anticholinergic and QT interval prolonging ones, potentially due to accumulation of glucuronide metabolites
Amoxapine	Unknown	No dose recommendations; avoid use, due to risk of overdosage of parent and M(+) with antidopaminergic ADRs
Clomipramine	Not dialyzable	NDA, monitor for amitriptyline-like ADRs
Doxepin	Not dialyzable	NDA, monitor for amitriptyline-like ADRs
Imipramine	Not dialyzable	NDA, monitor for amitriptyline-like ADRs
Nortriptyline	Not dialyzable	As for amitriptyline
Trimipramine	Not dialyzable	NDA, monitor for amitriptyline-like ADR
SSRI		
Citalopram	Not dialyzable	NDA, note high QT-prolonging potential vs lower potential SSRIs
Escitalopram	Not dialyzable	As for citalopram
Fluoxetine	Not dialyzable	NDA
Fluvoxamine	Not dialyzable	NDA
Paroxetine	Not dialyzable	NDA
Sertraline	Not dialyzable	NDA
Other serotonin and norepinephrine acting		
Duloxetine (SNRI)	Not dialyzable	NDA, consider regulatory contraindication if GFR <30 mL/min
Mianserine (tetracyclic, NE-MM)	Not dialyzable	NDA, consider risks stemming from variable PK and ADRs from M(+)
Mirtazapine (tetracyclic, SN-Ran)	Unlikely to be dialyzable	NDA, based on high PB and large Vd, consider risks of ADRs from M(+)
Moclobemide (RIMA—SND-RevEI)	Likely to be dialyzable	Dose as in normal renal function
Venlafaxine (SNRI)	Not dialyzable?	NDA, consider risks stemming from variable PK ADRs from M(+)
Antihistaminics		
Brompheniramine	Unlikely	Dose as in normal renal function, no supplementary dose required
Chlorpheniramine	Not dialyzable	Dose as in normal renal function, no supplementary dose required
Cyproheptadine	Unknown	Add 50%–100% dose supplement for IHD, consider overdosage risk
Diphenhydramine	Unlikely	Dose as in normal renal function, no supplementary dose required
Promethazine	Unlikely	Some experts recommend supplementary dose

Table 2: Continued

Drug	Dialyzable[a]	Recommended dose adjustment[b]
Drugs related to cardiovascular system		
Alverine	Unknown	Unknown
Atropine	Not dialyzable	No specific recommendations are available, but the need for dose adjustment is unlikely
Dimenhydrinate	Unknown	NDA + supplementary dose as in GFR <10 mL/min
Parasympatholytics		
Scopolamine (hyoscine)	Unknown	Unknown
Urinary antispasmodics		
Flavoxate	Unknown	Risk of overdosage due to renal excretion (57%) and presence of M(+), if dose is not adjusted, thus avoid use
Oxybutynin	Unlikely	Dose as in normal renal function, consider risk of QT prolongation and M(+) accumulation, transdermal use is less risky
Tolterodine	Unlikely	NDA, consider risk of QT prolongation and M(+) accumulation, not recommended use of extended formulations
Opioids		
Buprenorphine	Yes	NDA; transdermal: dose as in normal renal function
Codeine	Not dialyzed	Avoid its use in ESKD and dialysis
Dihydrocodeine	Unknown	ND
Fentanyl	Not dialyzed	NDA
Hydrocodone	Unknown	Use alternative medicines
Meperidine/pethidine	Not dialyzed	NDA, risk for CNS and respiratory depression due to M(+) ADRs
Methadone	Poorly dialyzed	NDA
Hydromorphone	Unknown	NDA, metabolites may cause neuroexcitation and cognitive impairment
Morphine	Yes	NDA, some centres avoid use slow release preparations due to M(+)
Oxycodone	Unknown	NDA, limited accumulation of metabolites in renal failure compared with morphine
Oxymorphone	Unknown	Use alternative medicines
Propoxyphene	Poorly dialyzed	NDA
Tapentadol	Unknown	Not recommended in ESKD
Tramadol	Yes	NDA
Benzodiazepines and similar agents		
Alprazolam	Not dialyzable	NDA
Bromazepam	Unlikely	NDA, risk of overdosage should be considered during long-term use due to several M(+)
Clobazam	Not dialyzable	NDA, effect is less predictable due to M(+)
Diazepam	Not dialyzable	NDA, effect is less predictable due to presence of several M(+)—nordazepam, oxazepam and temazepam
Estazolam	Not dialyzable	NDA
Lorazepam	Not dialyzable	NDA, caution should be exercised for repeated i.v. formulation use due to risk of propylene glycol toxicity; monitor osmol gap closely
Lormetazepam	Not dialyzable	NDA
Midazolam	Not dialyzable	NDA (oral), use with caution and monitor closely for excessive sedation; consider longer dosing intervals for intermittent dosing and slower titration of continuous infusions
Nitrazepam	Not dialyzable	NDA
Nordazepam	Unknown	Unknown
Oxazepam	Not dialyzable	NDA, risk of overdosage should be monitored
Prazepam	Not dialyzable	NDA, effect is less predictable due to presence of several M(+)—nordazepam and oxazepam

Table 2: Continued

Drug	Dialyzable[a]	Recommended dose adjustment[b]
Z-Drugs		
Zolpidem	Not dialyzable	NDA: option of dosage reductions is advised by some experts due to increased protein binding
Zopiclone	Controversial data	NDA, despite moderate PB (45%)
Psycholeptics (neuroleptics)		
Aripiprazole	Unlikely	NDA, based on high PB of parent and M(+)
Clozapine	Not dialyzable	NDA, based on high PB and complete metabolism with limited or no activity metabolites, but consider regulatory contraindication to use in case of severe renal disorder
Chlorpromazine	Not dialyzable	NDA, caution should be exercised due to unknown level of M(+)
Levomepromazine (methotrimeprazine)	Unknown	NDA, although caution should be exercised due to unknown presence or absence of activity of metabolites
Loxapine	Controversial data	NDA, based on high PB and complete metabolism with limited or no activity metabolites
Olanzapine	Not dialyzable	NDA, based on high PB, large Vd and complete metabolism to M(–)
Perphenazine	Unknown	Unknown, caution should be exercised due to M(+)
Pimozide	Unknown	NDA, although caution should be exercised due to unknown presence or absence of M(+) and its PK
Quetiapine	Unlikely	NDA, based on relatively high PB (83%) and large Vd, although caution should be exercised due to M(+) and non-negligible renal elimination
Risperidone	Not significantly dialyzed	Oral: use with caution, doses up to 2 mg have been tolerated, i.m. or s.c.: avoid use; risk due to extensive hepatic metabolism to M(+); both risperidone and M(+) are mainly excreted by the kidney and may increase risk of ADRs (e.g. orthostatic hypotension, QT prolongation)
Other antipsychotics		
Lithium	Dialyzable (80%)	Avoid use when possible, consider risk of lithium induced kidney damage in patients with significant residual kidney function; if necessary, initiate therapy at 300 mg 3 times weekly after dialysis; gradually titrate based on clinical response, tolerability, and serum lithium levels
Antibiotics		
Penicillins		
Amoxicillin and amoxicillin/clavulanate	Dialyzable	NDA, dose after IHD
Ampicillin and ampicillin/sulbactam	Dialyzable	NDA, dose after IHD
Benzylpenicillin	Dialyzable	NDA, dose after IHD
Cloxacillin	Not dialyzable	NDA
Oxacillin	Poorly dialyzable	Due to risk of neurotoxicity, the maximum daily dose of 8 g/day may be considered, otherwise—NDA
Phenoxymethylpenicillin	Dialyzable	NDA
Piperacillin	Dialyzable	2 g every 8 h + 1 g after IHD
Piperacillin and tazobactam	Dialyzable	2.25 g less frequently (every 8–12 h) + 0.75 g after IHD
Sultamicillin	Dialyzable	NDA, dose after IHD
Temocillin	Dialyzable	NDA, dose after IHD
Ticarcillin	Dialyzable	NDA, dose after IHD

Table 2: Continued

Drug	Dialyzable[a]	Recommended dose adjustment[b]
Cephalosporines		
Cefadroxil	Dialyzable	1 g first dose; 500–1000 mg 3 times a week, or every 36 h, dose after IHD
Cefalexin	Dialyzable	NDA, dose after IHD
Cefazolin	Dialyzable	NDA, dose after IHD
Cefepime	Dialyzed	1 g on day 1 followed by 0.5–1 g every 24 h, dose after IHD
Cefixime	Not dialyzable	NDA
Cefotaxime	Dialyzable	NDA, dose after IHD
Cefoxitin	Dialyzable	NDA, dose after IHD
Cefuroxime	Dialyzable	NDA, dose after IHD
Cefpodoxime	Dialyzable	100–200 mg every 24 h, dose after IHD
Ceftazidime	Dialyzable	NDA, dose after IHD
Ceftazidime/avibactam	Dialyzable	0.94 g every 24 h, dose after IHD
Ceftozolane/tazobactam	Dialyzable	0.75–2.25 g loading dose, followed by 1250–450 mg every 8 h, dose after IHD
Ceftriaxone	Poorly dialyzable	NDA
Astreonam	Dialyzable	NDA, dose after IHD
Carbapenem		
Ertapenem	Dialyzable	NDA, dose after IHD
Imipenem/cilastatin	Dialyzable	Due to neurotoxicity, consider alternative therapy; otherwise—NDA, dose after IHD
Meropenem	Dialyzable	NDA, dose after IHD
Fluoroquinolones		
Ciprofloxacin	Minimally dialyzable (<10%)	NDA, dose after IHD
Levofloxacin	Dialyzable (up to 21% in HF)	NDA, dose after IHD
Moxifloxacin	Poorly dialyzable	NDA, dose after IHD
Norfloxacin	Not dialyzable	NDA, dose after IHD
Ofloxacin	Dialyzable	NDA, dose after IHD
Sulfonamides		
Sulfadiazine	Dialyzable	In some countries the administration is contraindicated in case of severe renal insufficiency; if used NDA, dose after IHD
Sulfamethoxazole	Dialyzable	In some countries the administration is contraindicated in case of severe renal insufficiency where repeated plasma measurements cannot be performed; if used NDA, dose after IHD
Trimethoprim	Dialyzable	NDA, dose after IHD
Macrolides		
Azithromycin	Not dialyzable	NDA
Clarithromycin	Not dialyzable	In ESKD: for IR formulation—prolong interval for the same single dose (from twice daily to once daily), for ER formulation—50% dose
Erythromycin	Not dialyzable	NDA, consider limiting dose to 2 g/day due to risk of ototoxicity
Josamycin (rovamycin)	Unlikely to be dialyzable	Consider use alternative macrolide
Spiramycin	Unlikely to be dialyzable	Consider use alternative macrolide
Roxithromycin	Unlikely to be dialyzable	Consider use alternative macrolide

Table 2: Continued

Drug	Dialyzable[a]	Recommended dose adjustment[b]
Aminoglycosides		
Amikacin	Dialyzable	I.v. (administered after IHD): 5–12.5 mg/kg/dose 3 times weekly; according to levels; postdialysis concentrations should be drawn ≥2 and up to 4 h after hemodialysis to allow for redistribution
Gentamicin	Dialyzable	I.v. (administered after IHD): after reduced loading dose (e.g. 2–3 mg/kg), in case of conventional dosage regimen—1 mg/kg/dose 3 times weekly; in case of consolidated dosage regimen—2–3 mg/kg/dose 3 times weekly; according to levels; postdialysis concentrations should be drawn ≥2 and up to 4 h after hemodialysis to allow for redistribution
Tobramycin	Dialyzable	I.v. (administered after IHD): after loading dose (e.g. 2–3 mg/kg), 1–2 mg/kg/dose 3 times weekly; according to levels; postdialysis concentrations should be drawn ≥2 and up to 4 h after hemodialysis to allow for redistribution
Other antibiotics		
Metronidazole	Dialyzable in IHD, 10% removal in PD	Metabolized in the liver; M(+) have long half-life in renal impairment; NDA, dose after IHD
Vancomycin	Not dialyzable, but adsorbable in case of high-flux membrane	Oral: NDA; i.v. (administered after IHD): after normal loading dose (e.g. 25 mg/kg), in case of low-flux membrane—7.5 mg/kg after 48 h and every 48 h; in case of high-flux membrane—10 mg/kg after 48 h and every 48 h
Linezolid	Dialyzable	NDA, dose after dialysis
Polymyxins (Colistin)	Dialyzable	Increased dose: after normal loading dose (e.g. 9 MIU), 4.3 MIU per day in 2 divided doses on nondialysis days, adding 1.2 MIU after 3 h of IHD or 1.6 MIU after 4 h IHD
Isoniazid	Dialyzable	Dose as in normal renal function, dose after dialysis
Antivirals		
Acyclovir	Dialyzable	NDA, dose after dialysis
Darunavir	Unlikely	Dose as in normal renal function
Famciclovir	Dialyzable	NDA, dose after dialysis
Foscarnet	Dialyzable	NDA, dose after dialysis
Ganciclovir	Dialyzable	Oral: 500 mg 3 weekly post IHD; i.v.: NDA, dose after dialysis; for IHD, the fraction of ganciclovir removed in a single dialysis session varied from 50% to 63%
Indinavir	Not dialyzable	Dose as in normal renal function
Ritonavir	Not dialyzable	Dose as in normal renal function
Nirmatrelvir	NA	Nirmatrelvir is contraindicated in case of severe renal impairment
Tenofovir	Dialyzable	Avoid use; if no alternative therapy is available—NDA, dose after dialysis
Valaciclovir	Dialyzable	NDA, dose after dialysis

[a]Based on intermittent haemodialysis; not dialyzable category includes limited (0% to 5%) dialyzability.

[b]The dosing recommendations are based upon the dosage level of CKD 5 (not on dialysis) with CrCL <10 mL/min (if not otherwise stated), best available evidence and clinical expertise, but not considering obesity, cachexia and/or other risk factors for PK.

ER: extended release (formulation); HF: high-flux (dialyzer); ID: insufficient data; IHD: intermittent haemodialysis; i.m.: intramuscular; IR: immediate release (formulation); i.v.: intravenous; NA: not applicable; NDA: no dose adjustments in case of IHD of CKD patients, dose as in case of GFR <10 mL/min; MIU: million international units; M(+): active metabolites; M(–): inactive metabolites; NE-MM: norepinephrine multimodal; PB: protein binding; PD: peritoneal dialysis; PK: pharmacokinetic; RIMA: reversible inhibitor of monamino oxidase A; s.c.: subcutaneous; SN-Ran: serotonin, norepinephrine receptor antagonist; SND-RevEI: serotonin, norepinephrine, dopamine reversible enzyme inhibitor; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; Vd: volume of distribution.

after the dialysis session. After the start of dialysis, the solute concentration in blood decreases during a dialysis session and recovers to some extent after the cessation of dialysis. This happens due to solute redistribution which takes place after the dialysis session has stopped. Figure 2B represents different large molecule (vancomycin) pharmacokinetics depending on different permeabilities of membranes. Non-dialyzable drug through low-flux membrane becomes dialyzable, when a high-flux membrane is used.

In a clinical setting, it is important to know whether the drug is dialyzable or not. Variations in blood concentration of drugs may influence the effect of prescribed treatments that may have CNS effects and alter cognitive function. Table 2 represents common drugs with potential negative impact on the CNS and their relationship to dialysis [37–39].

CONCLUSION

This narrative review presents eGFR decline as a risk factor of BBB disruption and modification of drug pharmacokinetics. These modifications may affect drug efficacy and safety. Indeed, the increase of free drug fractions and the passage of drugs into the brain parenchyma could increase the risk of ADRs, resulting in cognitive impairment. In an associated review [15] we describe drugs that are commonly recognized as a risk for causing cognitive impairment.

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AUTHORS' CONTRIBUTIONS

S.L. and G.H. were responsible for the research idea and supervision of review writing. V.P., G.C., R.M., M.B., A.F. and I.A.B. contributed to writing parts of the manuscript. C.A.W., R.J.U. and G.C. critically revised the manuscript. All authors reviewed and approved the manuscript for publication.

DATA AVAILABILITY STATEMENT

Not applicable.

CONFLICT OF INTEREST STATEMENT

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APPENDIX

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