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Drug Exposure in Chronic Kidney Disease: It Is Not Just About the Glomerular Filtration Rate

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ABSTRACT

Chronic kidney disease (CKD) affects over 10% of the world's population and is associated with high morbidity and mortality rates. The management of CKD is complex; CKD alters drug pharmacokinetics and pharmacodynamics and further complicates therapeutic strategies regimens. Uremic toxins accumulate in patients with CKD and significantly impact drug pharmacokinetics and drug responses. These toxins modify drug pharmacokinetics. Indeed, uremic toxins can alter intestinal absorption by affecting drug transporters, such as P-glycoprotein and multidrug resistance-associated proteins. These changes modify the bioavailability of drugs and change drug absorption profiles in patients with CKD. Furthermore, uremic toxins interfere with drug distribution and metabolism. For instance, the urea-driven carbamylation of albumin can reduce drug-binding sites on this plasma protein and thus increase the free drug fraction. In the liver, CKD can reduce the expression of cytochrome P450 enzymes and thus impair drug biotransformation. Furthermore, uremic toxins can interact with cellular transporters, affecting drug clearance and leading to drug accumulation. In terms of pharmacodynamics, uremic toxins can alter receptor function and impair drug effectiveness. The blood–brain barrier may also be disrupted by the accumulation of toxins; this enhances drug penetration into the brain and increases the risk of adverse effects. After providing a brief summary of the various drug elimination pathways and the definitions and classification of uremic toxins, we shall use examples to illustrate the potential impact of a decrease in glomerular filtration rate (GFR) and/or an increase in uremic toxin levels on drug pharmacokinetics and pharmacodynamics.

1 | Introduction

Chronic kidney disease (CKD) is both common and associated with significant morbidity and mortality [1]. Accordingly, the Global Burden of Disease (GBD) initiative ranks CKD among the

top 30 risk factors in terms of years of healthy life lost [2]. CKD has consistently risen in GBD rankings: from 19th place in 1990 to 16th in 2006 overall, and to the 13th and 11th places among men and women, respectively, in 2016 [3]. As a progressive disease, CKD affects > 10% of the general population (amounting to

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> 800 million individuals worldwide) and becomes significantly more prevalent with age: One-third of people over the age of 70 are affected [4, 5].

In a recent study published in *JAMA*, nephrology was identified as the specialty in which the most complex patients are managed. Patients with CKD had the highest mean number of comorbidities (4.2), the highest mean number of prescription medications (14.2) and the highest mortality rate (6.6%) [6]. The management of patients with CKD is multimodal; the objectives are to slow the disease progression and to treat risk factors and complications. Drug treatments intend to correct hypertension, hyperlipidaemia, anaemia, metabolic acidosis, mineral and bone disorders and to slow the progression of CKD to kidney failure.

The kidney has a key pharmacological role that extends beyond the renal excretion of water-soluble drugs or metabolites into the urine. For example, CKD has a significant influence on non-renal elimination pathways. Indeed, uremic toxins (substances that accumulate in patients with CKD as a result of the impaired kidney function) significantly impact drug pharmacokinetics and drug responses. The present narrative review will focus on these aspects, which can potentially reduce a drug's effectiveness and/or increase its toxicity.

It is crucial to consider renal function when prescribing medications because CKD can impact both renal and non-renal elimination pathways—potentially leading to adverse drug reactions. In fact, even drugs predominantly eliminated via non-renal pathways (e.g., imatinib) can be affected by an impairment in renal function (Table 1). In patients with kidney failure, careful medication management and monitoring are crucial for preventing adverse drug reactions and optimizing treatment outcomes.

After providing a brief summary of the various drug elimination pathways and the definitions and classification of uremic toxins, we shall use examples to illustrate the potential impact of a decrease in glomerular filtration rate (GFR) and/or an increase in uremic toxin levels on drug pharmacokinetics and pharmacodynamics (Figure 1).

2 | Drug Elimination Pathways

Drug elimination is a critical pharmacokinetic process because it determines the duration and intensity of a drug's action in the body. The elimination pathway encompasses the processes by which a drug and its metabolites are removed—primarily through metabolism and excretion.

Metabolism involves the enzymatic modification of drugs. These modifications mainly take place in the liver but may also occur in other organs and body components, such as the kidneys, lungs and intestines. Regardless of the administration route, a drug will be excreted in an unchanged form or in a metabolized form. In some cases, drug metabolites are themselves pharmacologically active and/or toxic. Drug metabolites are primarily formed by enzymatic biotransformation reactions, which constitute one of the main mechanisms used by the body

to eliminate drugs. The main purpose of biotransformation is to increase the water solubility of lipophilic molecules. Indeed, high liposolubility prevents a drug from being eliminated in an unchanged form by the kidney. In the liver, two biotransformation phases occur sequentially: Phase 1 metabolism involves the cytochrome P (CYP) pathway, while Phase 2 metabolism mainly involves the glucuronidation mechanism catalyzed by UDP-glucuronosyltransferases (UGTs). Depending on the degree of solubility achieved after biotransformation, the metabolites are then excreted either by the kidney or via the bile into the faeces [24]. Any alteration in the function of the organ responsible for metabolism results in a decrease in elimination and induces a risk of accumulation.

Furthermore, the proportion of a drug available for elimination depends on its binding to proteins (albumin, alpha-1 glycoprotein, lipoproteins, globulins, etc.) and its distribution volume. A drug that is primarily protein bound and/or distributed widely throughout the body is less available for elimination [25].

Excretion is the terminal step in drug elimination and occurs primarily via the kidneys and the liver. The renal clearance of hydrophilic drugs and metabolites involves three key steps: (i) passive glomerular filtration of free, unbound drugs (molecular weight cut-off: <60 kDa), (ii) active tubular secretion mediated by transporters (e.g., organic anion transporters (OATs) for the elimination of acidic drugs like penicillin and organic cation transporters (OCTs) for the secretion of basic drugs like metformin) and (iii) tubular reabsorption into the circulation. Renal excretion is significantly influenced by the GFR—a key variable in conditions like CKD [26].

In conclusion, drug elimination is a complex, multifaceted process that includes metabolic and excretory components. Pharmacological knowledge of these pathways enables clinicians and researchers to predict drug behaviour, optimize therapeutic regimens, mitigate adverse effects and thus ultimately ensure safer and more effective drug use. However, CKD significantly impacts drug elimination pathways through the accumulation of uremic toxins and an overall decline in renal function. These changes reduce the clearance of drugs and their metabolites and increase the risk of accumulation and toxicity. Consequently, careful dose adjustments are often required to ensure safe, effective therapy in patients with CKD. Indeed, the current guidelines focus on drugs that are eliminated by the kidneys but often overlook others. It is noteworthy that when a drug's summary of product characteristics contraindicates or advises against use in patients with kidney impairment, this is often due to a lack of data in that population and not due to an identified, specific risk. To promote safe prescribing in patients with renal impairments, drug development programs must include studies in patients with CKD (particularly Stage 4/5 CKD). Lastly, it is essential to perform regular, comprehensive medication reviews that take into account renal function and the physiopathological specificities of CKD.

3 | Uremic Toxins

Uremic toxins are compounds that exert biological effects and are normally eliminated in the urine by healthy kidneys. Hence,

TABLE 1 | Drugs primarily eliminated by non-renal pathways and with changes in pharmacokinetic variables in non-dialyzed patients with Stages 4 and 5 CKD.

INN	UF-Tot (%)	UUF (%)	PB (%)	P-gp	Main metabolic pathway	PK variation Stages 4 and 5 CKD	Impact of the dose level
Afatinib [7]	4.3	< 1	95 (80% albumin)	Substrate	Non-cytochromic pathway	Cmax: ↑ 22% AUC: ↑ 50%	FDA: Initial dose ↓25% EMA: Monitoring and reduction if tolerated
Aripiprazole [8–10]	27	< 1	99 (primarily albumin)	Substrate	CYP3A4, CYP2D6	FF: ↑ × 1.45–1.75 (modelling)	—
Asciminib [11]	11	2.5	97.3	Substrate/ Inhibitor	CYP3A4, UGT2B7 and UGT2B17	Cmax: ↑ 8% AUCinf: ↑ 56%	Monitoring and reduction if tolerated
Bosutinib [12]	3.29	1	96	Substrate	CYP3A4	Cmax: 34% AUCinf: ↑ 60%	↓dose
Crizotinib [13]	22	2.3	91	Substrate	CYP3A4 and CYP3A5	Cmax: ↑ 34% AUCinf: ↑ 79%	↓dose
Fedratinib [14]	5	3	95% (primarily glycoprotein alpha)	Inhibitor	CYP3A4 and CYP2C19	Cmax: × 1.8 AUCinf: × 1.9 (modelling)	↓dose
Fexofenadine [15, 16]		10	60–70	Substrate	—	AUC: × 2.8	↓dose
Temsavir (Fostemsavir) [17, 18]	51	3	88 (primarily albumin)	Substrate	Esterases CYP3A4	FF: ↑ 58%	—
Imatinib [19–21]	13	5	95 (primarily albumin/ glycoprotein alpha)	Substrate	CYP 450	Cmax: ↑ 1.6 à 2	↓ initial dose
Lenacapavir [22]	< 1	< 1	99.8 (primarily albumin)	Substrate	CYP3A4 and UGT1A1	FF: ↔ Cmax: ↑ 162% AUCinf: ↑ 84%	—
Pemigatinib [23]	12.6	1	90.6 (primarily albumin)	Substrate	CYP3A4	PB: ↔ Cmax: ↓ 35.4% AUC: ↑ 59%	↓dose

Abbreviations: FF, free fraction; INN, international nonproprietary name; PB, protein binding; UF-Tot, urinary total fraction; UUF, unchanged urinary fraction.

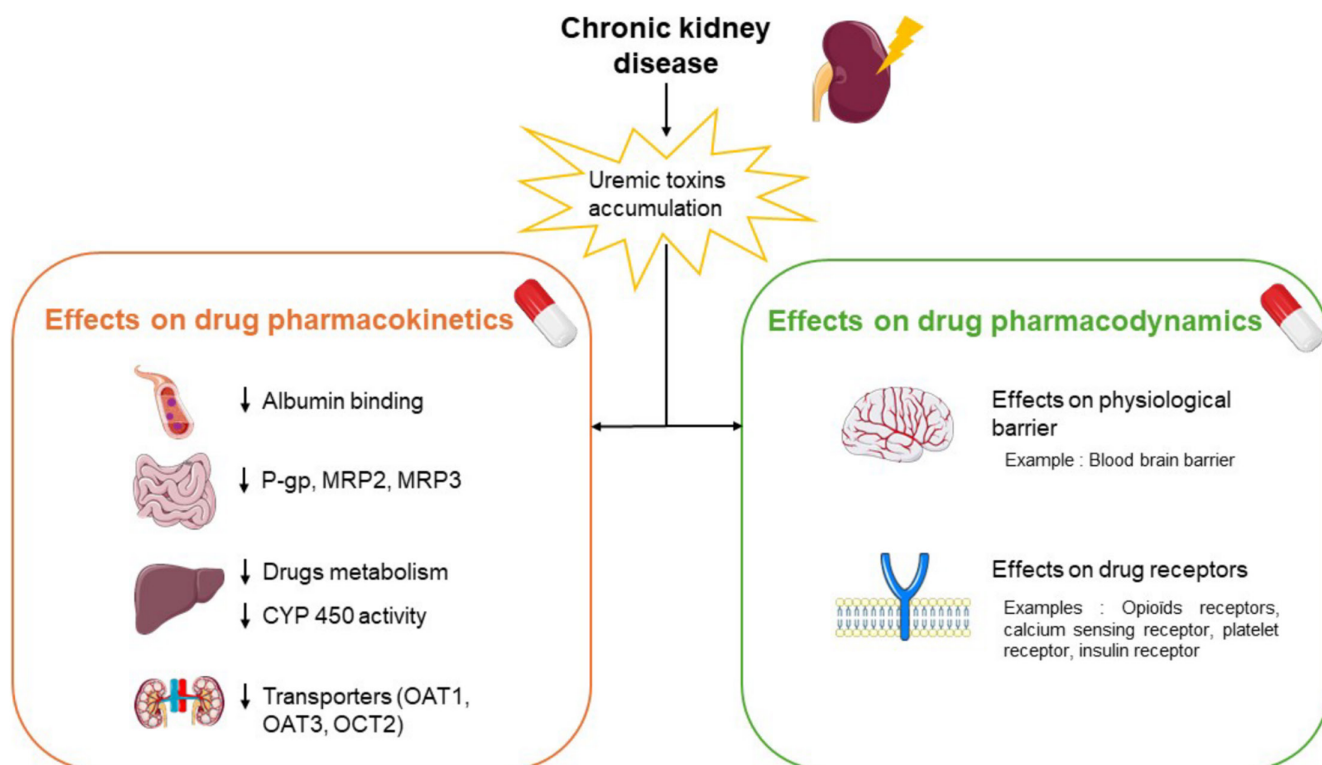


FIGURE 1 | Potential impact of a decrease in glomerular filtration rate and/or an increase in uremic toxin levels on drug pharmacokinetics and pharmacodynamics.

these toxins accumulate in patients with CKD. According to the EUtox consortium, a compound is a uremic toxin if it meets the following criteria [27]:

- The compound should be chemically identified, and accurate quantitative analysis in biologic fluids should be possible.
- The plasma level of the compound should be higher in uremic than in non-uremic patients.
- High concentrations should be related to specific uremic symptoms that decrease or disappear when the concentration is reduced.
- When studying toxicity of specific compounds in human subjects, experimental animals and/or in appropriate in vitro systems, the concentrations used should be comparable.

This definition has enabled the identification of more than 100 uremic toxins, which can be classified further based on their molecular weight and their ability to bind (or not) to plasma proteins [28]. Small water-soluble molecules have a molecular weight below 500Da (e.g., urea), and middle molecules have a molecular weight ranging from 500Da to 60kDa (e.g., β 2 microglobulin). Protein-bound molecules (e.g., indoxyl sulphate) are less effectively removed by conventional dialysis methods (Table 2). Some uremic toxins have an intestinal origin and result from the bacterial fermentation of dietary protein.

These uremic toxins are partly responsible for complications associated with uremic syndromes, including osteodystrophy,

vascular alterations, cognitive impairment and cardiopathies [29–31]. Moreover, a decline in renal function and the accumulation of uremic toxins can significantly influence drug pharmacokinetics and pharmacodynamics (Table 1).

4 | Uremic Toxins and Drug Pharmacokinetics

4.1 | Actions of Uremic Toxins in the Intestinal Tract

The absorption of a drug from the intestinal tract determines its bioavailability and so is a critical step in its pharmacokinetics. Uremic toxins can modify the expression and function of intestinal efflux or influx transporters, such as P-glycoprotein (P-gp) and multidrug resistance-associated proteins (MRPs), leading to impaired drug absorption.

P-gp is located on the apical side of epithelia; as an efflux transporter, it opposes the intestinal absorption of many drugs by acting as an efflux pump and expelling drugs into the intestinal lumen, bile and urine. Changes in P-gp level contribute to pharmacokinetic variability. The intestine can also metabolize drugs, albeit to a lesser extent than the liver. These various functions of the intestine can be affected by the accumulation of uremic toxins.

The MRP transport proteins are found in many tissues. MRP2 and MRP3 are involved in the absorption and excretion of drugs and metabolites and are localized at the apical or basolateral pole of intestinal epithelial cells. These transporters

TABLE 2 | Classification of uremic toxins: Examples of key molecules frequently described in the literature.

Free, water-soluble, and low-molecular-weight solutes	Middle molecules	Protein-bound solutes
Asymmetric dimethylarginine, symmetric dimethylarginine, urea and uric acid	β 2-microglobulin, parathyroid hormone, tumour necrosis factor and interleukin-6	Carboxyl methyl propyl furanpropionate, indole acetic acid, indoxyl sulphate, kynurenin and P-cresylsulphate

participate in detoxification and the efflux of drugs and drug metabolites into the intestinal lumen. Together, MRP2 and MRP3 help maintain the balance of drug and metabolite levels in the body, contribute to the overall detoxification process and protect intestinal cells from potentially harmful substances [32, 33].

A study in a rat model of kidney failure found that drug transporter expression levels and activities were lower in CKD rats than in control rats. Specifically, the researchers observed a decrease in the expression and activity of P-gp, MRP2 and MRP3 proteins in the intestines of rats with CKD. This decrease might explain (for instance) the greater bioavailability of drug substrates for P-gp and MRP2 in CKD [29]. Indeed, Nolin et al. found a dramatically lower level of non-renal transporter function in patients with end-stage renal disease when compared with control individuals; this was evidenced by a 63% relative decrease in clearance and a 2.8-fold relative increase in the area under the plasma concentration-time curve for fexofenadine [15]. This observation was confirmed in patients with varying degrees of reduction in kidney function: non-dialysis patients with CKD, patients on peritoneal dialysis and patients on haemodialysis [34]. Indeed, fexofenadine does not undergo hepatic biotransformation and is a P-gp substrate: Only 10% is excreted in urine as the parent drug [15]. Thus, elevated exposure cannot be solely attributed to a decrease in renal clearance and should prompt a dose reduction in routine clinical practice

4.2 | Influence of Uremic Toxins on Drug Distribution

A drug's tissue distribution is essentially controlled by biotransformation and by transport across plasma membranes. How, then, can a uremic environment modify these processes? Machado et al. sought to determine whether indoxyl sulphate (IS, a protein-bound uremic toxin) modifies the expression of hepatic drug transporters [35]. Firstly, in vitro, the incubation of HepG2 hepatocellular carcinoma cells with uremic concentrations of indoxyl sulphate was associated with greater expression of the *ABCB1* gene (coding for P-gp) in a dose-dependent manner. Furthermore, indoxyl sulphate increased the protein expression and activity of P-gp. These findings were confirmed in two uremic mouse models: hepatic levels of *Abcb1a* mRNA were higher in uremic mice than in controls. Secondly, Machado et al. evaluated the potential clinical impact of indoxyl sulphate in a cohort of 109 patients with CKD treated with immunosuppressants after kidney or heart transplantation. The patients with elevated indoxyl sulphate concentrations required higher doses of cyclosporine to achieve the target plasma concentration.

Human serum albumin is the predominant protein in human plasma; it accounts for 50%–60% of the total protein content and has a key role in sustaining the blood's colloid osmotic pressure. Albumin has an exceptional binding ability and transports numerous endogenous and exogenous substances, including fatty acids, thyroxine, bilirubin and various drugs (e.g., warfarin, diazepam and ibuprofen). These compounds typically interact with one of the two primary binding sites

on the protein. The various metabolic disturbances associated with CKD may decrease albumin binding in a CKD context, with a potential impact on drug distribution [36]. Firstly, conformational changes in the albumin molecule (such as the carbamylation induced by urea accumulation) may affect the protein's drug-binding sites. Secondly, hypoalbuminemia may reduce the total binding capacity. Thirdly, the accumulation of uremic toxins may competitively displace drugs from their albumin binding sites, leading to an elevated free drug fraction. Indeed, the results of Erill et al.'s in vitro study demonstrated that salicylate protein binding decreased when protein carbamylation was induced [37]. The association between the progressive loss of albumin binding capacity and the accumulation of protein-bound uremic toxins has been demonstrated in vitro for various drugs, including phenytoin, phenobarbital and aripiprazole [8, 38]. A recent cross-sectional study had shown that low kidney function was associated with an elevation in the free Vitamin K antagonist drug fraction. This association was independent of blood albumin levels and appeared to be partly mediated by protein carbamylation [39].

4.3 | Impact of Uremic Toxins on Metabolization Function

The CYP450 system is the primary enzyme system in drug biotransformation. The results of several animal studies have shown that CKD is associated with lower activity and mRNA expression of hepatic CYP450 enzymes [40–44]. The main hypothesis is that inhibitors in the blood of uremic animals modulate CYP450 expression. Indeed, Guevin et al. demonstrated that when normal hepatocytes were incubated for 24 h with serum from rats with CKD, the levels of P450 isoforms were 45% lower than in control experiments [45]. Next, the researchers identified parathyroid hormone (PTH) as one of the factors in uremic blood that was associated with downregulation of CYP450 in CKD. The level of PTH is significantly elevated in patients with CKD because of secondary hyperparathyroidism [46]. Indeed, PTH can modulate the expression of Cyp3a in a dose-dependent manner, and parathyroidectomy before the induction of renal impairment in animals prevented the decrease in the expression and activity of Cyp3a. However, variables other than impaired kidney function and uremic toxins can modify drug metabolism in patients with CKD. For example, genetic polymorphisms in cytochrome enzymes are frequent, and so patients may need to undergo genetic testing if a drug has a narrow therapeutic index.

4.4 | Actions of Uremic Toxins on Transporters

Membrane transporters regulate the influx and efflux of compounds into cells and interact with uremic toxins. Once inside the cell, uremic toxins can trigger signalling pathways, alter cellular responses and thereby contribute to the pathology of CKD. The transport of uremic toxins across cell membranes involves the solute carrier and ATP-binding cassette transporter superfamilies, which are known to handle various endogenous and xenobiotic substances and have a critical role in drug therapy. Moreover, membrane transporters are crucial for the renal elimination of these toxins through tubular secretion. In a rat model, Naud et al. have shown that in comparison to control rats, rats

with 5/6 nephrectomy presented a reduction in the expression of several kidney drug transporters; this led to the intrarenal accumulation of drugs and reduced renal clearance [47]. Toxins and drugs might therefore compete as substrates of the transporter or as inhibitors of its activity.

Uremic toxins are predominantly eliminated through specific efflux channels in the proximal renal tubules, such as the OAT1 and OAT3. The results of in vivo and in vitro studies have shown that indoxyl sulphate, kynurenine, p-cresyl sulphate and indole-3-acetic acid are excreted by both OAT1 and OAT3 [48–57]. The OATs are mainly expressed in the liver, brain and kidney and are known to be involved in the transport of proton-pump inhibitors, diuretics, non-steroidal anti-inflammatory drugs, antiviral drugs and antibiotics [58–61]. It has been shown that the active, secretory clearance of drugs is known to be substrates of OAT1/3 declines in parallel with the GFR in CKD [61]. Further studies are needed to clarify these findings; uremic solutes that accumulate in CKD and inhibit OAT1 and OAT3 may provide an explanation.

Furthermore, other renal transporters (such as OCT2) have a key role in the renal secretion of many basic drugs. Several uremic toxins are known to inhibit OCT2. A pharmacokinetic study of several OCT2 drug substrates in patients with CKD demonstrated that the secretory clearance mediated by OCT2 decreased in parallel with the decline in GFR—potentially because of the inhibitory effects of uremic toxins on this transporter [48].

5 | Uremic Toxins and Drug Pharmacodynamics

A drug's effect may be modified in the context of CKD, notably because of the impact of the uremic milieu on receptors and physiological barriers.

5.1 | Action on Drug Receptors

As mentioned previously, CKD is characterized by the up- or downregulation of the expression of various receptors. An imbalance in the endogenous opioid system (characterized by the upregulation of mu-opioid receptor signalling and the downregulation of kappa-opioid receptor signalling) has been reported in patients with CKD and might be involved in the pathogenesis of itch in uremic pruritus [62]. This question is particularly important because a significant proportion of patients with CKD experience pain, especially as the disease progresses. In fact, 82% of patients with late-stage CKD suffer from moderate-to-severe pain [63].

CKD is associated with resistance to PTH's hypercalcaemic action. Indeed, a marked decrease in the expression of the PTH receptor in the kidney and bone of uremic rats has been reported [64, 65]. The expression of other receptors (such as calcium-sensing receptor (CaSR)) has also been studied in a uremic context. Indeed, CKD seems associated with a decrease in monocyte CaSR expression [66]. Moreover, CaSR mRNA and protein expression in large and small arteries was significantly lower in patients with end-stage renal disease than in control individuals

[67]. As CaSR is targeted by calcimimetic drugs, this change in expression might have an impact on treatment efficacy.

Furthermore, the chronic urea overload associated with CKD progression leads to an increase in cyanate concentrations, which in turn results in the irreversible carbamylation of proteins [68, 69]. In addition to albumin carbamylation (which might affect drug distribution), recent studies have highlighted the potential impact of the carbamylation of receptors on platelets. Specifically, haemodialysis patients exhibited significantly low activation of $\alpha\text{IIb}\beta 3$ and marked carbamylation of both α and β subunits of $\alpha\text{IIb}\beta 3$ on platelets, compared with healthy controls. These changes led to a loss of receptor activity and impaired fibrinogen binding [70]. The platelet dysfunction associated with carbamylation might affect the response to anti-platelet agents.

Insulin resistance worsens with CKD progression and is associated with the development of uremic syndrome. In a preclinical study, Koppe et al. demonstrated that p-cresylsulphate administered to mice with normal renal function induces insulin resistance and metabolic disturbances mimicking those reported in CKD. Indeed, in patients with a low GFR, it is necessary to modify the dosage of certain antidiabetic drugs (such as metformin and exogenous insulin) and to avoid others because of renal elimination of a large part of antidiabetic drugs and to the impact of uremic toxins [71].

5.2 | Action in the Brain

The blood–brain barrier (BBB) has a crucial role in brain stability by regulating the exchange of substances and fluids between the bloodstream and brain tissue. Furthermore, the BBB protects the brain against harmful toxins, pathogens and exogenous compounds.

In a rodent model of CKD induced by a high-adenine diet, several neurological abnormalities (akinesia and catalepsy) and anxiety- and depressive-like behaviours were found to be associated with disruption of the BBB [72]. Furthermore, the permeability of the BBB in various rodent models of CKD has been evaluated using single-photon-emission computed tomography. The studies revealed that the accumulation of the uremic toxin indoxyl sulphate in the bloodstream activates the aryl hydrocarbon receptor (AhR) and results in BBB disruption and subsequent cognitive decline. Conversely, AhR-knockout mice were protected against indoxyl sulphate-induced damage to the BBB [73]. CKD-associated impairments of the BBB might modify the effectiveness of central nervous system drugs by enhancing the latter's entry into brain tissue; this can lead to central adverse drug reactions and contribute to cognitive impairment [63, 74].

6 | Conclusion

Personalized medicine (especially therapeutic drug monitoring) provides valuable support in managing patients with CKD; treatments can be adjusted according to the individual's level of kidney function. Therapeutic drug monitoring

optimizes drug efficacy, minimizes adverse events and thus improves patient outcomes. Adjusting medication dose levels is essential in patients with CKD, in particular because of the impaired elimination of drugs usually cleared predominantly by the kidneys. The literature data show that the accumulation of uremic toxins in progressive CKD can significantly impact nearly all stages of drug pharmacokinetics and pharmacodynamics and thus increase the risk of adverse drug events in these patients [7, 75]. Even for drugs eliminated primarily by non-renal pathways, increased drug exposure is also possible. This drug overexposure might be particularly significant for patients with Stages 4 and 5 CKD, when uremic toxins accumulate substantially. There is a need for pharmacokinetic and modelling studies of drugs that are substrates of P-gp, strongly bound to albumin and metabolized by the liver, even when their primary elimination pathway is non-renal. These studies could help justify dose-level adjustments, particularly for drugs with a narrow therapeutic index, even when renal elimination is minimal. The care of patients with CKD is particularly complex; meticulous medication management is required to prevent adverse drug reactions and optimize therapeutic outcomes. Guidelines on the use of treatments in the CKD population are often limited in scope. Computer-based clinical decision support systems that take into account all the physiological aspects of advanced CKD appear to be promising. These tools must help healthcare professionals adapt drug dose levels as a function of the patient's CKD stage, regardless of whether or not the drug is eliminated by the kidneys.

Author Contributions

S.L., J.B.T., L.A. and A.M. wrote the first draft of the manuscript. Z.A.M., G.D. and M.J. revised the manuscript for critical content. All the authors approved the final version.

Conflicts of Interest

Z.A.M. reports having received grants for CKD REIN and other research projects from Amgen, Baxter, Fresenius Medical Care, GlaxoSmithKline, Merck Sharp and Dohme-Chibret, Sanofi-Genzyme, Lilly, Otsuka, Astra Zeneca, Vifor and the French government, as well as fees and grants to charities from Astra Zeneca, Boehringer Ingelheim and GlaxoSmithKline. G.D. reports fees and grants to charities for research projects from Astra Zeneca and Bayer HealthCare. S.L., J.B.T., L.A. and A.M. declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during this study.

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