Renal Organic Anion Transporter-Mediated Drug-Drug Interactions with Probenecid: A Systematic Review

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Writing Assignment

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Abstract

Objectives: Since drug-drug interactions (DDIs) substantially contribute to the incidence of adverse drug reactions, the management of polypharmacy and the preclinical identification of renal DDIs are becoming more-and-more important. To provide preclinical DDI screening, *in vitro* kidney models are being actively developed. Unfortunately, the translational value of the *in vitro* data of such models remains unclear. This study aims to create a comprehensive renal organic anion transporter (OAT) substrate database with OAT-mediated clinical DDIs. The database can be used as a validation set for *in vitro* kidney models to aid in the prediction of potential clinical DDIs.

Methods: A systematic literature review had been performed in EMBASE and PubMed/MEDLINE. Studies were eligible for inclusion if a renal drug interaction study with probenecid in human was described. Exclusion criteria were defined as *in vitro* studies, case-studies, and review articles. Study characteristics involving the study design and clinical pharmacokinetic outcomes were obtained from the studies. Articles describing *in vitro* experiments about the involved OAT of each clinical drug substrate were extracted using PubMed/MEDLINE and Google Scholar.

Results: A total of 384 articles were retrieved of which 62 clinical studies were included. The 62 studies included described 61 unique DDIs composed of 20 different drug classes. An effect of probenecid was shown for 61% of the identified compounds. The involvement of renal transporters was unidentified for 52% of the compounds, whereas the OAT-mediated renal clearance was identified for 38% of the compounds with OAT3 (45%) being the most prevalent.

Conclusions: This review is the first attempt to systematically develop a comprehensive database of renal drug interactions with probenecid. The identified compounds open up new avenues to construct OAT compound validation set to validate novel *in vitro* kidney models, which aid in the preclinical prediction of renal DDIs.

Layman's summary

Most of the drugs are removed from the human body by the kidneys. Before a drug can be eliminated from the body, it needs to be transported from the blood to the urine. This elimination process is carried out by the functional units of the kidney: the nephrons. The nephrons consist of multiple tubules including the proximal convoluted tubule, Loop of Henle, distal convoluted tubule (DCT), and the collecting duct.

The PCT is known to play an important role in the tubular secretion of many drugs. This tubular secretion occurs in the cells lining the PCT: the proximal tubular epithelial cells. These cells consist of renal drug transporters on both the basolateral, facing the blood vessels, and the apical side, facing the lumen of the PCT, which mediate the active transport of drugs.

The renal elimination of anionic drug compounds is known to be executed by basolateral organic anion transporters (OATs), which are paired with efflux via apical multidrug resistance associated proteins 2 and 4 (MRP2 and MRP4). Other basolateral renal transporters include the organic cationic transporters (OCTs) which are involved in the renal excretion of several cationic drugs. This study will focus on the renal clearance mediated by OAT1, OAT2, and OAT3, of which the relevance in drug elimination has been stressed for OAT1 and OAT3 by the Food Drug Administration and European Medicines Agency.

When two or more drugs are coadministered and are known to be excreted by the same renal transporter, a drug-drug interaction (DDI) can take place. This DDI can decrease or enhance the renal secretion or efficacy of both drugs. The changes in drug's renal clearance might cause changes in the drug action of the victim drug or can cause harmful adverse drug effects. It is therefore important that the potential of DDIs are identified before a pharmacist or a physician prescribes a multiple drug regimen. A well-known DDI as a consequence of OAT inhibition has been the interaction between penicillin and probenecid. Probenecid is a prototypical competitive inhibitor for OATs, which has often been clinically used as an adjunct to enhance the efficacy of drugs or to prevent adverse drug events. Moreover, it is widely used to investigate the OAT-mediated DDIs.

To provide the preclinical screening of newly developed drugs, *in vitro* models that mimick the physiological kidney environment are actively developed. However, it remains unclear how well the *in vitro* data of these models can be translated to the *in vivo* kidney setting. The translational value of the *in vitro* models can be assessed by performing a validation study using a subset of drug compounds. This

study aims to create a comprehensive renal OAT substrate database with OAT-mediated clinical DDIs with probenecid by performing a systematic literature review. The database can be used as a validation set for *in vitro* kidney models to aid in the prediction of potential clinical OAT-mediated DDIs.

The systematic literature review resulted in 384 articles of which 62 clinical studies were included. The 62 studies included described 61 unique DDIs with probenecid. An effect of probenecid on the clinical parameters of the drugs compounds was shown for 61% of the identified compounds. The involvement of renal transporters was unidentified for 52% of the compounds, whereas the OAT-mediated renal clearance was identified for 38% of the compounds, with OAT3 (45%) being the most prevalent. The identified compounds open up new avenues to construct OAT compound validation set to validate novel *in vitro* kidney models.

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Introduction

The number of new drugs approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) has been increasingly growing over the past decade. Parallel to this increase, the amount of reported interactions between medications has also risen (Batta, Kalra, & Khirasaria, 2020). The ageing population and therefore the high prevalence of polypharmacy increase the likelihood of such interactions. Drug-drug interactions (DDIs) contribute to a great extent to the occurrence of adverse drug reactions (ADR), which cause a large number of hospitalizations (Kohler et al., 2000). The management of polypharmacy by physicians and pharmacists is therefore getting more crucial but poses major challenges because of the increase of newly identified DDIs.

One of the human organs that is often faced with DDIs is the kidney. Thirty-two percent of the top 200 prescribed drugs in the United States were found to be cleared by renal mechanisms (Morrissey, Stocker, Wittwer, Xu, & Giacomini, 2013). Drugs are considered renally excreted when the extent of unchanged drug in urine is more than a fourth of the total absorbed dose (Meltzer, 2019). This renal elimination from the blood circulation to the urine is the net result of different processes: 1) glomerular filtration by the Bowman's capsule; 2) tubular secretion; and 3) tubular reabsorption (van Ginneken & Russel, 1989).

The physiologic units responsible for these processes, and therefore the disposition of drug compounds in the kidney, are the nephrons (Morrissey et al., 2013). Tubular secretion and reabsorption are bidirectional processes which occur at the proximal convoluted tubule (PCT), the loop of Henle, the distal convoluted tubule (DCT), and the collecting duct (Figure 1A). Active secretion across the PCT is mediated by the concerted action of multiple basolateral uptake and apical efflux drug transporters (Figure 1B) (Lee & Kim, 2004).

Since the PCT plays an important role in the excretion of many drug compounds, it is known as the main site of nephrotoxicity and transporter-mediated DDIs. The latter occurs when two or more co-administered drugs are transported, and therefore excreted, by the same renal drug transporter (Wang & Kestenbaum, 2018). Renal active transporters can transport drugs against their electrochemical gradient across the membrane of proximal tubular epithelial cells.

Transporter mediated DDIs have an impact on the pharmacokinetics and pharmacodynamics of the victim drug thereby causing adverse drug reactions. The inhibition of efflux drug transporters leads to

the accumulation of the victim drug in the proximal tubule cells resulting in drug-induced nephrotoxicity. Whereas the inhibition of basolateral drug transporter leads to an increased plasma drug concentration (Yin & Wang, 2016).
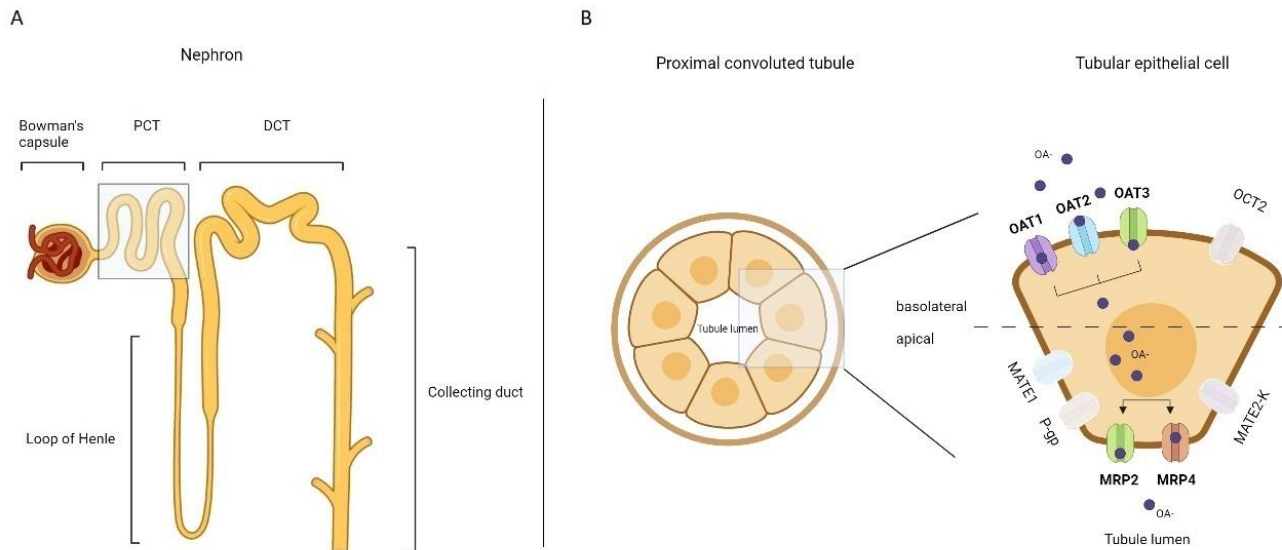

Figure 1: The anatomy of a nephron. A| Nephron. The functional unit of the kidney is composed of: the Bowman's capsule, the PCT, the DCT, and the collecting duct. **B|** Proximal convoluted tubule and tubular epithelial cells with renal transporters. Schematic presentation of basolateral and apical renal drug transporters in the proximal tubular epithelial cell. Anionic drug compounds are transported by basolateral OAT1, OAT2, and OAT3, paired with the efflux via MRP2 and MRP4. Cationic drug compounds are transported by basolateral OCT2, paired with the efflux via MATE1, MATE2-K, and P-gp. Abbreviations: DCT, distal convoluted tubule; MATE, multidrug and toxin extrusion protein 1; MRP, multidrug resistance associated protein; OA⁻, organic anionic drug compound; OAT, organic anion transporter; OCT2, organic cation transporter 2; PCT, proximal convoluted tubule; P-gp, P-glycoprotein. Created with BioRender

The tubular secretion of several cationic drug compounds is known to be executed by basolateral organic cationic transporters (OCTs), paired with efflux via multidrug and toxin extrusion proteins 1 and 2-K (MATE1 and MATE2-K), and P-glycoprotein (P-gp)(Figure 1B)(Launay-Vacher et al., 2006). As regards the renal elimination of anionic drug compounds, basolateral organic anion transporters (OATs) are the major transporters engaged in this process, which are paired with efflux via multidrug resistance associated proteins 2 and 4 (MRP2 and MRP4)(Figure 1B) (Yin & Wang, 2016). A more detailed overview of all present transporters in the proximal tubular cell is described by Schwenk & Pai, 2016.

This review will focus on the OATs of which four human variants exist in the renal proximal tubular cells: OAT1, OAT2, OAT3, and OAT4. However, the relevance in renal drug transport has been stressed for OAT1 and OAT3 specifically by the International Transporter Consortium (ITC), the FDA, and the EMA.

The relevance of OAT2 as basolateral renal drug transporter is currently unknown but has been indicated (International Transporter Consortium et al., 2010). As figure 1 illustrates, all OAT variants, except for OAT4 (not shown in figure 1B), are expressed on the basolateral membrane of proximal tubular cells. OATs are structurally similar to OCT because they originate from the same solute carrier 22 (SLC22) transporter family. As a consequence of their wide substrate selectivity, OATs are of high pharmacological significance and are a major target for clinically relevant DDIs (Sekine, Miyazaki, & Endou, 2006).

Due to the basolateral localization of OATs, OAT-mediated transport inhibition of the victim drug, caused by DDIs, will often result in elevated plasma concentration. Although DDIs are often unwanted when unpredicted, on occasion, renal transporter inhibitors can reduce the occurrence of adverse drug reactions, nephrotoxicity, or can even increase the drug efficacy by inhibiting the renal excretion of the affected drug (Yin & Wang, 2016).

A well-known DDI as a consequence of OAT inhibition has been the interaction between penicillin and probenecid. Probenecid is a prototypical competitive inhibitor for OATs, which has been initially developed as a treatment against chronic gout. However, during World War II, probenecid was widely administered concomitantly with penicillin as a mean to solve the problem of penicillin shortages by increasing its drug efficacy (Robbins, Koch, Tranter, & Rubinstein, 2012). Since then, probenecid has often been clinically used as an adjunct to enhance the serum levels of antibiotics or to prevent drug-induced kidney injury.

Before a new molecular entity (NME) enters the markets, the transporter-mediated DDI potential of a NME should be investigated according to the guidelines described by the FDA and the EMA, especially when the renal pathway is significantly involved in the excretion of a NME (European Medicines Agency, 2012; US Food and Drug Administration, 2020). To provide preclinical screening of the NME, kidney microphysological systems (MPS) are currently actively developed. These *in vitro* models can better mimick the physiological kidney environment, therefore anticipated to better predict preclinical renal drug transporter interactions. However, the translational value of the *in vitro* data derived from these systems to the *in vivo* setting remains unclear. The development of a compound set to validate MPS would therefore help to determine the translational value and assess the advantage of kidney MPS and traditional (2D) systems (Chen, Evangelista, Yang, Kelly, & Yeung, 2021).

This research aims to collate primary research presenting data on OAT-mediated DDIs with probenecid by performing a systematic review of literature. The results of this research could be used to validate the kidney MPS and will provide clear benchmarks to aid in the translation from *in vitro* MPS data to *in vivo* (van der Made et al., 2019). Well-validated *in vitro* kidney models provide the prediction of potential clinical OAT-mediated DDIs, whereby the clinical burden of DDIs and subsequent ADRs may be reduced in the long term.

Methods

Search strategy

A systematic literature review was performed to develop a comprehensive OAT substrate database with OAT-mediated clinical DDIs. This review was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Appendix 1)(Page et al., 2021). We aimed to address the following research question: 'What evidence is available on clinical organic anion transporter-mediated drug-drug interactions with probenecid?' The focus was on probenecid because of its characteristic as a chemical inhibitor for OAT transport.

Articles were retrieved from EMBASE and PubMed/MEDLINE until December 14, 2021. The literature search strategy was composed of the following components: ''kidney'', ''drug interactions'', and ''probenecid''. Steps taken to acquire the final research strategy of both databases can be found in the Supplementary material S1. Duplicates were removed from the search after assessed for eligibility. Any articles describing *in vitro* experiments about the involved OAT of each clinical drug substrate were extracted using PubMed/MEDLINE and Google Scholar.

Inclusion and exclusion criteria

Titles and abstracts of all articles obtained from the systematic search strategy were screened by D.S using predefined inclusion and exclusion criteria. In case of unavailable abstracts, the full text of corresponding articles was assessed for eligibility. When full-text articles were not available or accessible through the Utrecht University library, other libraries and sources were used to supply access. Articles were eligible for inclusion if they met the following inclusion criteria: (i) a primary study; (ii) a clinical trial or clinical study; and (iii) a drug-drug interaction study with probenecid used as an inhibitor. Exclusion criteria were defined as follows: (i) a review article; (ii) a case-study; (iii) the absence of clinical parameters, such as renal clearance; (iv) no drug substrate used; (v) the absence of probenecid as an inhibitor; and (vi) *in vitro* experiments using cell lines.

Data extraction and analysis

Articles that met all inclusion criteria had the following study characteristics extracted: the number and type of subjects, the drug regimen, and the drug administration route. The clinical pharmacokinetic outcomes related to renal DDIs with probenecid were gathered and were defined as follows: renal clearance (CL_R; mL/min), area-under-the-curve (AUC; $\mu g \cdot$ h/mL), peak serum concentration (C_{max}; μg/mL) and excreted fraction (f_e; %). The data were expressed as mean ± standard deviation. If the above-described clinical parameters were given in different units, then the attempt was made to

convert to the preferred units. The effect of probenecid on the victim drug has been analyzed by calculating the fold change of the clinical parameters. The fold change has been calculated by dividing the parameter value of a drug when coadministered with probenecid by the parameter value in the absence of probenecid.

In case an article was inaccessible, the abstract was used to collate the clinical pharmacokinetic outcomes. As regards the *in vitro* data, individual contribution of specific OAT to total active basolateral secretion and its intrinsic clearance (CL_{int}; µg/min/mg), if known, were collated from PubMed/MEDLINE literature.

Results

Search results

The electronic search strategy in EMBASE and PubMed/MEDLINE identified 356 and 82 articles, respectively. Titles and abstracts of 429 unique articles were assessed after removal of duplicates (Figure 2). Subsequently, 83 articles were extracted for full-text assessment and of these 21 articles were excluded due to the following reasons: no clinical study was described (n = 10); no DDIs with probenecid were described; articles described a case-study (n = 2); articles consisted of irrelevant clinical parameters (n = 4); no full-text was available of some articles (n = 3) (Figure 2). A total of 62 articles were included in this review as they met all the selection criteria. The systematic review of the literature had an overall inclusion rate of 14%.
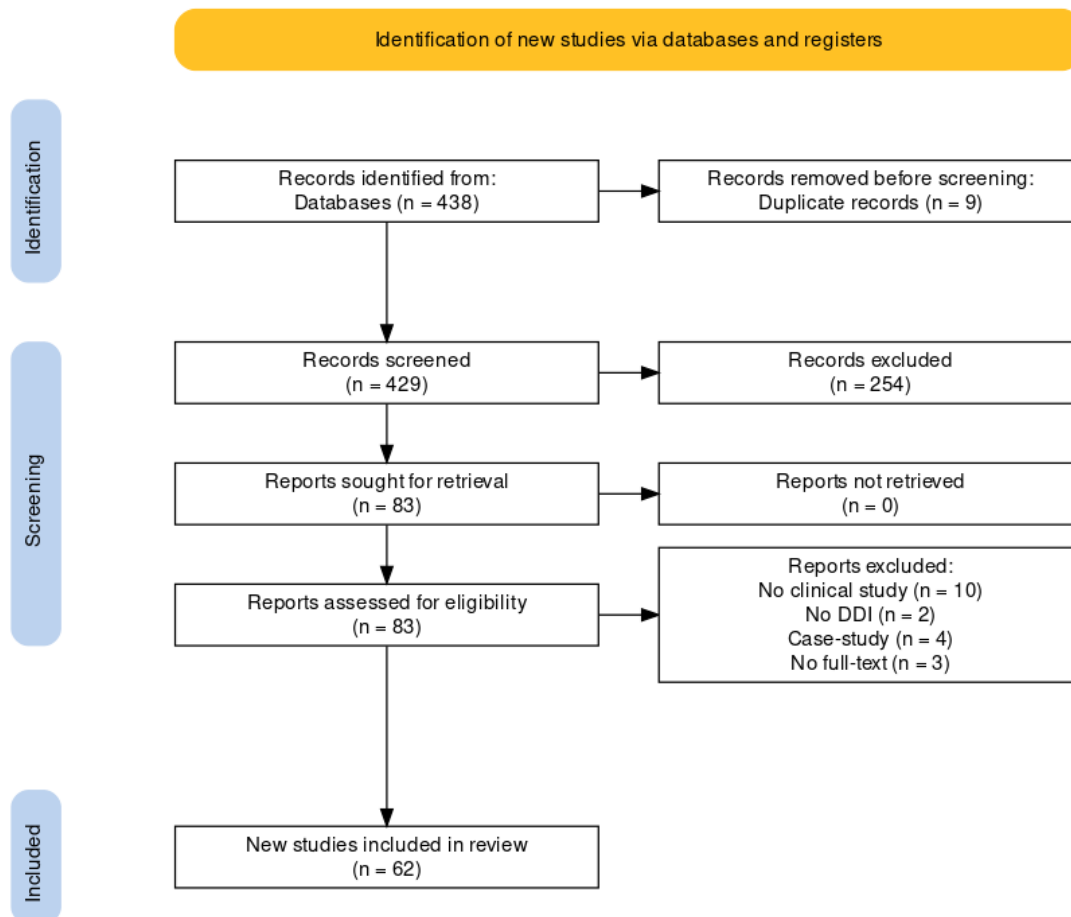

Figure 2: Flow diagram of the systematic review selection process (Haddaway, McGuinness, & Pritchard, 2021).

Study characteristics

Relevant study characteristic and pharmacokinetic outcomes that were collated from the 62 articles are listed in Table 1. The search strategy resulted in a total of 61 unique DDIs with probenecid of which 59 (97%) and 2 (3%) DDIs, respectively, involved drug compounds and endogenous markers (Figure 3A). The number of subjects enrolled in the clinical studies varied from 5 to 48 subjects. Forty-seven studies (76%) had been conducted in healthy volunteers. The remaining 15 studies enrolled patients including: studies with human immunodeficiency virus (HIV) patients (n = 6); studies with gouty arthritis patients (n = 4); and studies with other types of patients (n = 5). The full database can be found in Appendix 2 where the study characteristics are detailed in full.

B-lactam antibiotics were the most prevalent (25%), followed by antiviral antibiotics (15%), quinolone antibiotics (10%), diuretics (6%), and non-steroidal anti-inflammatories (NSAIDs; 6%)(Figure 3A). The remaining 23 drug compounds (38%) belonged to other drug classes including 1 adrenergic drug, 3 antiarrhythmics, 1 antidepressant, 1 antidiabetic, 1 antihistamine, 2 antineoplastics, 1 antitubercular drug, 2 atypical antipsychotics, 1 cardiac glycoside drug, 1 gabapentinoid anticonvulsant, 1 immunosuppressive drug, 2 lipid-lowering drugs, 2 sodium-glucose co-transporter-2 (SGLT2) inhibitors, 1 uricosuric, and 1 xanthine oxidase inhibitor (Table 1).

Table 1: Summary of relevant study characteristic and pharmacokinetic outcomes of 61 clinical studies

Compounds	Drug class	OAT	Subjects (n)	CL_R (fold change)	C_{max} (fold change)	AUC (fold change)	References
Acyclovir	Antivirals	1, 2	12	0.67 ↓	1.23	1.49 ↑	De Bony et al., 2002
Adefovir	Antivirals	1	5	0.85	NI	1.04	Maeda et al., 2014
Adinazolam	Antidepressants	NI	16	NI	1.37 ↑	1.13	Golden et al., 1994
Allopurinol	Xanthine oxidase inhibitors	NA	12	NI	0.56 ↓	0.59 ↓	Stocker, Williams, McLachlan, Graham, & Day, 2008
Allopurinol	Xanthine oxidase inhibitors	NA	19	1.27 ↑	NI	NI	Stocker et al., 2008
Aspirin	NSAIDs	NA	-	-	-	-	Harris, Bryant, Danaher, & Alloway, 2000
Benzylpenicillin	β-lactams	3	6	0.5 ↓	NI	1.39 ↑	Maeda et al., 2014

Table 1 *(continued)*

Compounds	Drug class	OAT	Subjects (n)	CL$_R$ (fold change)	C$_{max}$ (fold change)	AUC (fold change)	References
Bumetanide	Diuretics	3	-	-	-	-	Brater & Chennavasin, 1981
Bumetanide	Diuretics	3	6	0.15 ↓↓	2.92 ↑↑	NI	Odlind, Beermann, & Lindström, 1983
Canagliflozin	SGLT2 inhibitors	NI	14	0.66 ↓	1.15	1.20	Deviveni et al., 2015
Cefmenoxime	β-lactams	NI	10	0.42 ↓↓	1.11	2.05 ↑↑	Sennello, Quinn, Rollins, Tolman, & Sonders, 1983
Cefotaxime	β-lactams	1,3	6	0.48 ↓↓	NI	NI	Ings et al., 1985
Cefoxitin	β-lactams	3	12	NI	NI	NI	Goodwin et al., 1974
Cefprozil	β-lactams	NI	15	-	-	-	Shukla, Pittman, & Barbhaiya, 1992
Ceftazidime	β-lactams	NI	2	NI	NI	NI	Verhagen, Mattie, & Van Strijen, 1994
Ceftizoxime	β-lactams	1, 3	12	0.62 ↓	1.16	1.59 ↑	Lebel, Paone, & Lewis, 1983
Ceftriaxone	β-lactams	1, 3, 4	6	-	-	-	Patel et al., 1990
Cefuroxime	β-lactams	NI	5	NI	NI	NI	Verhagen et al., 1994
Cidofovir	Antivirals	1	42	0.48 ↓↓	2.27 ↑↑	1.78 ↑	Cundy et al., 1995
Ciprofloxacin	Quinolones	3	12	0.35 ↓↓	1.2	1.72 ↑	Landersdorfer et al., 2010
Ciprofloxacin	Quinolones	3	12	0.36 ↓↓	1.18	1.75 ↑	Jaehde et al., 1995
Dalcetrapib	Antineoplastics	NI	20	-	1.21 ↑	1.14	Baldó, Anzures-Cabrera, & Bentley, 2013
Digoxin	Cardiac glycoside drugs	NA	16	NI	0.87	1.07	Wiebe et al., 2020
Doripenem	β-lactams	NI	8	0.46 ↓↓	1.15	1.75 ↑	Shiba & Nakashima, 2005
DQ-2556	β-lactams	NI	5	-	-	-	Shiba et al., 1992

Table 1 *(continued)*

Compounds	Drug class	OAT	Subjects (n)	CL$_R$ (fold change)	C$_{max}$ (fold change)	AUC (fold change)	References
Empagliflozin	SGLT2 inhibitors	NI	18	NI	1.26 ↑	1.53↑	Macha et al., 2014
FCE 22101	β-lactams	NI	12	NI	2.08 ↑↑	0.99	Lovering et al., 1989
Fexofenadine	Antihistamines	1, 3	12	0.32 ↓↓	1.26 ↑	1.71 ↑	Yasui-Furukori, Uno, Sugawara, & Tateishi, 2005
Fexofenadine	Antihistamines	1, 3	18	0.26 ↓↓	1.31 ↑	1.59 ↑	Liu et al., 2008
FK037	β-lactams	NI	6	0.97	-	-	Shiba, Sakai, Obara, Sakamoto, & Terakawa, 1994
Foscarnet	Antivirals	NI	10	1.03	0.95	0.94	Noormohamed, Youle, Higgs, Gazzard, & Lant, 1997
Frusemide	Diuretics	1, 3	9	0.34 ↓↓	1.55 ↑	2.68 ↑	Vree, Van den Biggelaar-Martea, & Verwey-Van Wissen, 1995
Furosemide	Diuretics	1, 3	8	0.32 ↓↓	NI	NI	Chennavasin, Seiwell, Brater, & Liang, 1979
Furosemide	Diuretics	1, 3	16	NI	1.22	2.72 ↑	Wiebe et al., 2020
Ganciclovir	Antivirals	1, 2	26	0.69 ↓	1.41 ↑↑	1.55 ↑↑	Cimoch et al., 1998
GCDCA-S	Endogenous bile acid	1, 3	8	0.21 ↓↓	NI	1.00	Tsuruya et al., 2016
Gemifloxacin	Quinolones	NI	17	0.50 ↓	NI	NI	Landersdorfer et al., 2009
Indomethacin	NSAIDs	1, 3	17	NI	NI	1.64↑	Baber, Halliday, Sibeon, Littler, & Orme, 1978
Metformin	Anti-diabetics	NA	16	NI	1	1	Wiebe et al., 2020
Mirogabalin	Anticonvulsants	NI	30	0.59 ↓	1.28 ↑	1.76 ↑	Tachibana et al., 2018
Mizoribine	Immunosuppressives	NI	10	-	-	-	Utsunomiya et al., 2010

Table 1 *(continued)*

Compounds	Drug class	OAT	Subjects (n)	CL$_R$ (fold change)	C$_{max}$ (fold change)	AUC (fold change)	References
Moxalactam	β-lactams	NI	5	1.05	NI	0.87	DeSante, Israel, Brier, Wolny, & Hatcher, 1982
Moxifloxacin	Quinolones	NA	12	1.05	0.9	1.01	Stass & Sachse, 2001
Muzolimine	Diuretics	NI	8	-	-	-	Noormohamed & Lant, 1991
Naproxen	NSAIDs	3	6	NI	1.22	1.37 ↑	Runkel, Mroszczak, Chaplin, Sevelius, & Segre, 1978
NM441	Quinolones	NI	6	-	-	1.6 ↑	Totsuka, Kikuchi, & Shimizu, 1996
Ofloxacin	Quinolones	3	8	0.86	1.01	1.16	Nataraj, Rao Mamidi, & Krishna, 1998
Olanzapine	Atypical antipsychotics	NI	12	-	1.19	1.26 ↑	Markowitz, DeVane, Liston, Boulton, & Risch, 2002
Oseltamivir	Antivirals	3	48	NI	1	0.76 ↓	Holodniy et al., 2008
Oseltamivir	Antivirals	3	18	0.48↓↓	1.02	1.06	Hill et al., 2002
Pilsicainide	Antiarrhythmics	NI	9	0.93	0.92	1.05	Shiga, Hashiguchi, Urae, Kasanuki, & Rikihisa, 2000
Piretanide	Diuretics	NI	8	0.19 ↓↓	NI	NI	Noormohamed, McNabb, Dixey, & Lant, 1990
Piretanide	Diuretics	NI	7	0.12 ↓↓	2.16 ↑↑	4.37 ↑↑	Dixey, Noormohamed, Pawa, Lant, & Brewerton, 1988
Pradigastat	Lipid-lowering drugs	NI	22	NI	0.87	0.99	Mendonza et al., 2016
Procainamide	Antiarrhythmics	NI	6	0.98	-	-	Lam, Boyd, Chin, Chang, & Giacomini, 1991

Table 1 *(continued)*

Compounds	Drug class	OAT	Subjects (n)	CL$_R$ (fold change)	C$_{max}$ (fold change)	AUC (fold change)	References
Pyrazinamide	Antitubercular drugs	NI	12	NI	NI	NI	Yü et al., 1977
Risperidone	Atypical antipsychotics	NI	12	NI	0.97	1	Markowitz et al., 2002
Ritobegron	Adrenergic drugs	3	12	0.26 ↓↓	1.37 ↑	2.96	Abe et al., 2016
Rosuvastatin	Lipid-lowering drugs	NI	16	NI	4.28 ↑↑	2.23 ↑↑	Wiebe et al., 2020
Sorafenib	Antineoplastics	NI	16	NI	0.75 ↓	0.73 ↓	Hussaarts et al., 2020
Sulfinpyrazone	Uricosurics	NI	8	0.24 ↓↓	NI	NI	Perel, Dayton, Snell, Yu, & Gutman, 1969
Taurine	Endogenous	1, 3	8	0.40 ↓↓	NI	0.98	Tsuruya et al., 2016
Temafloxacin	Quinolones	NI	6	NI	1	1.39 ↑	Maezawa, Yosida, Shiba, Sakai, & Saito, 1993
Tenoxicam	NSAIDs	NI	6	0.93	1.25 ↑	1.05	Day, Geisslinger, Paull, & Williams, 1994
Ticarcillin	β-lactams	3	18	NI	1.43 ↑	1.49 ↑	Corvaia et al., 1992
Valacyclovir	Antivirals	NA	12	NI	1.23 ↑	1.22	De Bony et al., 2002
Zalcitabine	Antivirals	3	12	-	-	-	Massarella, Nazareno, Passe, & Min, 1996
Zidovudine	Antivirals	1, 2, 3	7	NI	1.43 ↑	2.06 ↑↑	De Miranda et al., 1989
Zidovudine	Antivirals	1, 2, 3	8	1.18	NI	1.57 ↑	Kornhauser et al., 1989

NI = no information available, **NA** = not applicable, **-** = no access article

↓↓ = fold change of 0.0 up to 0.5; and ↓ = fold change of 0.5 up to 0.75.

↑ = fold change of 1.25 up to 2.0; and ↑↑ = fold change of 2.0 and higher.

OAT-mediated renal clearance

The renal transport of the majority of the compounds (n = 32; 52%) remained unidentified due to lack of relevant information in literature (Figure 3B). The involvement of specific renal transporters had been identified for 29 compounds (48%) whereof the renal clearance is non-OAT-mediated for 6 compounds (10%) and OAT-mediated for 23 compounds (38%)(Figure 3B). Our results show that OAT3 was the most

frequently involved in the renal clearance of 19 out of 23 compounds (53%), followed by 38% OAT1 involvement (n = 13), and 9% OAT2 involvement (n = 3)(Figure 3C). Most of the compounds are identified with an aspecific OAT involvement, i.e., compounds can be transported by multiple OAT isoforms (Figure 3D). The most prevalent combination is the drug excretion mediated by OAT3 (n = 10; 45%), followed by the combination OAT1+OAT3 (n = 7; 32%)(Figure 3D).

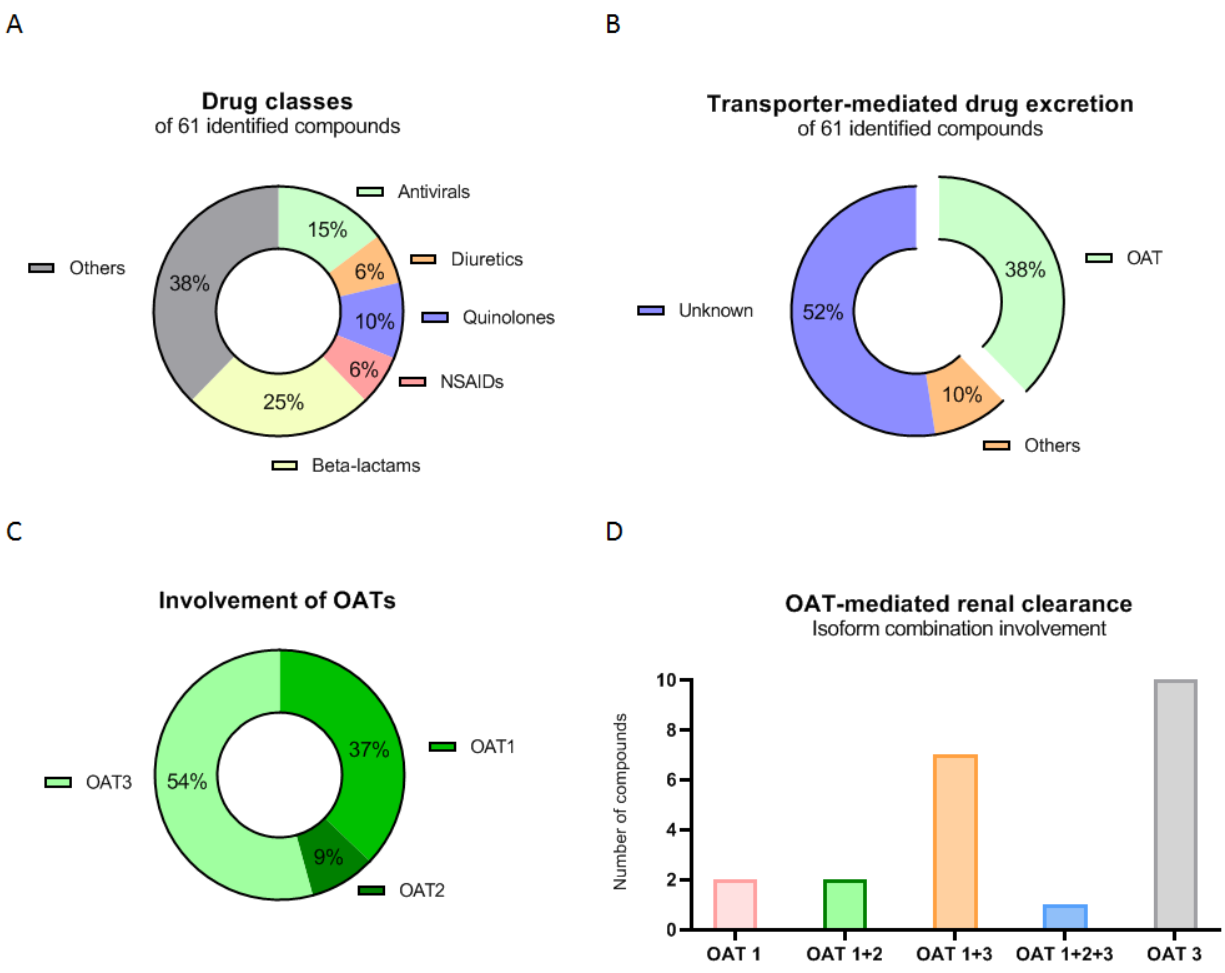**Figure 3: A|** Drug classification. A total of 61 unique DDIs can be classified in the following drug classes: antivirals, diuretics, quinolones, NSAIDs, beta-lactams, and others. **B| T**ransporter-mediated drug excretion. The graph illustrates an overview of renal transporters of the 61 unique identified DDIs. **C|** The involvement of OAT isoforms. **D|** The OAT-mediated renal clearance. The combinations of OAT isoforms involved in the renal clearance combinations of the 22 identified drug compounds, that are known to be renally excreted by OATs, are illustrated. Abbreviations: DDI, drug-drug interaction; NSAID, non-steroidal anti-inflammatory drug; OAT, organic anion transporter.

The effect of probenecid

To see whether probenecid coadministration results in DDI interactions, the clinical parameters of substrates are measured and compared when administered alone and co-administered with probenecid. The effect of probenecid on the fold change of CL_R, C_{max}, and AUC are classified as either weak or moderate-to-strong. The weak decrease of a fold change is depicted as one down-arrow in Table 1, whereas a moderate-to-strong decrease is depicted as two down-arrows. A weak and moderate-to-strong increased fold changes are depicted as one up-arrow and two up-arrows, respectively (Table 1).

Based on the included studies, the renal clearance has shown to be decreased by probenecid in 26 studies, in which 19 studies observed a moderate-to-strong inhibition. Only one study showed an increase in renal clearance of upon administration of probenecid. Probenecid has shown to increase the C_{max} in 18 clinical studies, whereby for bumetanide, cidofovir, FCE 22101, ganciclovir, piretanide, and rosuvastatin a moderate-to-strong increase is described (Table 1). As for the AUC, 26 studies showed that a DDI with probenecid resulted in a fold change higher than 1.25. Six out of the 24 studies describe a fold change which can be classified as moderate-to-strong: cefmenoxime, ganciclovir, piretanide, rosuvastatin, S44121, and zidovudine.

The pharmacokinetic parameters of 37 compounds (61%) were known to be affected by the coadministration of probenecid. In contrast to these compounds, the clinical parameters of a total of 9 compounds (15%) seem to be unaffected by co-administration of probenecid, and therefore do not show evidence for DDIs. Furthermore, 2 studies that both investigated the DDI between oseltamivir and probenecid seem to be inconsistent when comparing their observed AUCs (Table 1).

Discussion

This systematic literature review presents a comprehensive database of clinical drug interactions with probenecid via the kidney. The 62 studies included reported a total of 61 unique renal DDIs derived from PubMed/MEDLINE and EMBASE. The aim of this study is to create a database of DDIs with probenecid which subsequently can be used to choose a validation set for future *in vitro* validation studies of 2D and 3D kidney models. This validation tool will aid in the improvement of preclinical drug development in the future.

The contributions made in this systematic review are of wide interest and applicability due to several reasons. First, the database can be used for various research purposes, among them the validation of the kidney MPS. The primary goal of this microfluidic device is to preclinically enable the evaluation of drug safety, efficacy, and toxicity, and the prediction of potential DDIs (Chen et al., 2021). The clinical parameters described in this review could therefore be used to see whether similar values can be replicated by the kidney MPS after *in vitro* to *in vivo* extrapolation of MPS data. In order to use the database as a validation tool, the list of drug compounds needs to be prioritized first to ensure generalizability of the 3D kidney model to new molecular entities. Suggestions to prioritize are: (1) the extent of protein plasma binding; (2) the detectability of the compound by Liquid Chromatography-Mass Spectrometry (LS-MS) and radioactivity; (3) the hydrophobicity of the compound (i.e., LogP and LogD); (4) the fraction excreted unchanged higher than 25%; (5) the OAT-specificity of the compound; and (6) the extent of inhibition by probenecid. These criteria are envisioned to capture transporter and system specific processes.

Second, as mentioned earlier, the increase of newly identified drug interactions poses major challenges for physicians and pharmacists. The data retrieved from the studies included provides specialists an overview of what is known to interact with probenecid in the kidney. This can be helpful to guide decision making for drug dosing in patient populations, e.g. chronic kidney disease, or for polypharmacy. Unfortunately, there are no clearly defined criteria or rules on how to interpret clinical significance of identified drug interactions. It is therefore an important issue for future research to explore what clinical parameters, and to what extent, need to be changed for a drug interaction to be defined as clinically significant.

The most important clinical parameters are the ones that are the most sensitive for drug competition of active tubular transport. Since the AUC and renal clearance of a drug are inversely

proportional and the clearance is dependent on renal tubular transport, a DDI could be considered as clinically significant once changes in these clinical parameters are observed (Ratain & William K. Plunkett, 2003). For a clinically significant DDI to be then recognized as clinically relevant, further assessment of pharmacodynamic-, risk-, and patient-related factors needs to be conducted (Callahan, Marangell, & Ketter, 1996)**.**

The search results interestingly demonstrate a large difference in hits between both databases, whereby EMBASE resulted in four times as many articles (356 *versus* 82 articles). This difference can be explained by which type of journals the medical databases are indexed. In contrast to PubMed/MEDLINE, EMBASE has a great coverage of journals describing studies in the field of pharmacology including drug safety, toxicology, pharmacy, and drug interaction (Wong, Wilczynski, & Haynes, 2006). Due to the scope of this literature review, it is therefore expected that more eligible studies will be derived from EMBASE with the defined search strategy.

The collated data from the *in vitro* studies clearly demonstrates that the renal drug disposition of the found identified drug substrates is to a substantial extent explained by OAT1 and OAT3 involvement, with OAT3 being the most dominant transporter. The emerging importance of these renal transporters in renal drug disposition is highlighted by the ITC, FDA, and EMA (International Transporter Consortium et al., 2010). Contrary to OAT1 and OAT3, a low number of drug substrates ($n = 3$) were shown to be transported by OAT2. The results of this study further highlight that the exact role on drug disposition and elimination of this transporter is less extensively studied and remains to be elucidated (Shen, Lai, & Rodrigues, 2017).

The results of the OAT involvement on the identified drug substrates are due to observed inconsistencies in literature are equivocal, hence offering inconclusive results. To overcome this problem, a parallel renal tubular transporter study on the identified drugs is suggested to be conducted by using either a 2D or a 3D bioengineered kidney model. Examples of 2D kidney models include proximal tubular epithelial cell lines (PTECs) transfected with human OATs, such as conditionally immortalized PTECs (ciPTECs) and Madin-Darby canine kidney (MDCK) cells, whereas examples for 3D models are kidney-on-a-chips or a kidney proximal tubule model (Shin, Lee, Park, Shin, & Song, 2010; Wilmer et al., 2016). In this way, current discrepancies, and gaps in the knowledge of renal OAT-mediated drug transport can be clarified. Moreover, it gives the possibility to either confirm or disprove the *in vitro* data of OAT involvement reported in this review.

While this study successfully identified a wide variety of clinical interactions of probenecid, several limitations may have influenced the collated data naturally. First of all, the included studies were marked by a high heterogeneity, especially in terms of dose regimen, sample size, and how the parameters are quantified and measured in urine and blood plasma. This heterogeneity is worth noting as it might hamper the interpretation of the significance and relevance of the found DDIs in this review. In future work, refinement of the eligibility criteria by implementing age class, gender, and type of subject to the search may reduce the heterogeneity of the studies.

Another critical point to take into consideration is that most of the clinical studies included in this review are performed in healthy, middle-aged adults. This approach suffers from the limitation that many population subgroups remain underrepresented which might influence the generalizability of the described effect of probenecid on found drug substrates (He et al., 2020). For that reason, the results of this review should be interpreted with caution and cannot be directly extrapolated to other types of subjects such as patients, pregnant women, and the elderly.

Finally, due to time constraints, the evidence contained in this systematic review has not been assessed for quality. Since distinct types of clinical studies are included in this systematic review, the assessment and interpretation of the potential bias in these studies should ideally be conducted separately. A distinction can be made between randomized, non-randomized, and cross-sectional clinical studies for which, respectively, the Cochrane Risk of Bias (RoB) tool, the Risk Of Bias In Non-randomized Studies- of Interventions (ROBINS-I) tool, and the Joanna Briggs Institute (JBI) critical appraisal is commonly used (Ma et al., 2020). Follow-up study should aim to implement the use of these tools to examine and ensure the confidence of the review findings.

Despite the limitations, the data gathered in this systematic review merits further research in the discovery of clinical DDIs. On top of that, this review contributes to the understanding of the mechanism and transport involvement on renal clearance of how and by which OATs the identified drug compounds are renally cleared.

Conclusion

In conclusion, at time of writing, this review is the first attempt to systematically develop a comprehensive database of renal drug interactions with probenecid. 61 DDIs with probenecid have been identified in the database. The identified compounds open up new avenues to construct OAT compound validation set to validate novel *in vitro* kidney models, such as the kidney MPS model. As there is an increasing need for stable and reproducible kidney models, the validation of these models is essential. Properly validated *in vitro* models establish the usage of these models as reliable preclinical drug screening and disease modelling tools, with the potential to reduce the clinical burden of DDIs and improve the efficacy of drug development in the long term.

Supplementary material

Supplementary material S1: Full Search Strategy

Table 1: Steps of search strategy of EMBASE

Strategy	Components	Hits	Relevant hits
'probenecid'/exp/dd_it AND [clinical study]/lim		335	55
('probenecid'/exp/'drug interaction' OR 'probenecid-induced':de,ab,ti) AND [clinical study]/lim	**Add** probenecid-induced	356	56
('probenecid'/exp/'drug interaction' OR 'probenecid-induced':de,ab,ti) AND [clinical study]/lim AND 'pharmacokinetics'	**Add** pharmacokinetics	281	48

Table 2: Steps of search strategy for PubMed/MEDLINE

Strategy	Components	Hits	Relevant hits
(("Kidney Tubules, Proximal"[Mesh]) AND "Drug Interactions"[Mesh]) AND "Clinical Study" [Publication Type]		4	1
(("Kidney Tubules, Proximal"[Mesh]) AND "Drug Interactions"[Mesh])	Remove clinical study	175	-
(("Kidney Tubules, Proximal"[Mesh]) AND "Drug Interactions"[Mesh]) AND "Humans"[Mesh]	Add human	61	6
((("Kidney Tubules, Proximal"[Mesh]) AND "Drug Interactions"[Mesh]) AND "Humans"[Mesh]) AND "Organic Anion Transporters"[Mesh]	Add OAT	9	7
(("Kidney Tubules, Proximal"[Mesh]) AND "Drug Interactions"[Mesh]) AND "Organic Anion Transporters"[Mesh]	Remove human	9	4
((("Kidney Tubules, Proximal/drug effects"[Mesh] OR "Kidney	Expand kidney tubules	9	4

Tubules, Proximal/metabolism"[Mesh])) AND "Drug Interactions"[Mesh]) AND "Organic Anion Transporters"[Mesh]			
(("Kidney Tubules, Proximal"[Mesh]) AND "Drug Interactions"[Mesh]) AND "Probenecid"[Mesh]	Remove OAT Add probenecid	5	2
(("Kidney"[Mesh]) AND "Drug Interactions"[Mesh]) AND "Probenecid"[Mesh]	Replace proximal tubule for kidney	82	38
(("Kidney"[Mesh]) AND "Drug Interactions"[Mesh])	Remove probenecid	3542	-
((("Kidney"[Mesh]) AND "Drug Interactions"[Mesh]) AND "Probenecid"[Mesh]) AND "Organic Anion Transporters"[Mesh]	Add OAT	19	10

Table 3: Final search strategy for EMBASE and PubMed/MEDLINE.

Electronic database	Search terms	Hits
EMBASE	('probenecid'/exp/'drug interaction' OR 'probenecid-induced':de,ab,ti) AND [clinical study]/lim	356
PubMed/MEDLINE	(("Kidney"[Mesh]) AND "Drug Interactions"[Mesh]) AND "Probenecid"[Mesh]	82

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