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Review

MATE1-Mediated Drug–Drug Interactions: Emerging Relevance for Small-Molecule Cancer Therapies

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Simple Summary

Patients with cancer often receive several medicines at the same time, creating opportunities for drug–drug interactions that can change drug exposure, reduce treatment effectiveness, or increase toxicity. One potential but still poorly understood mechanism involves multidrug and toxin extrusion protein 1 (MATE1), a transporter that helps remove many positively charged drugs from cells and contributes to their elimination from the body. This review summarizes current knowledge of drugs that inhibit MATE1, with particular attention to small-molecule cancer therapies and other medicines concomitantly used in patients with cancer. We also discuss the limitations of current approaches used to predict clinically relevant MATE1-mediated interactions and identify important gaps in knowledge. A better understanding of these interactions may improve drug development, guide the interpretation of potential interaction risks, and support safer use of combination therapies in patients with cancer.

Abstract

Background/Objectives: Multidrug and toxin extrusion protein 1 (MATE1; *SLC47A1*) is an important renal and hepatic transporter involved in the disposition of numerous cationic drugs and endogenous compounds. Inhibition of MATE1 can alter drug exposure and renal clearance and may contribute to clinically relevant drug–drug interactions (DDIs). This review aimed to comprehensively evaluate the current evidence for MATE1 inhibition, with particular emphasis on small-molecule cancer therapies and the potential clinical relevance of MATE1-mediated DDIs. **Methods:** The published literature, regulatory documents, and available drug-interaction resources were evaluated to identify MATE1 inhibitors among approved drugs worldwide and to determine which compounds have reported or clinically supported evidence of MATE1-mediated DDIs. **Results:** MATE1 inhibition was widespread across therapeutic drug classes, with particularly high prevalence among oncology drugs and kinase inhibitors. Of the 99 FDA-approved kinase inhibitors evaluated, more than 80% inhibited MATE1 to some degree, and more than 40% had $C_{max,u}/IC_{50}$ ratios exceeding 0.02, a threshold incorporated into transporter DDI risk-assessment frameworks by major regulatory agencies, including the FDA, EMA, and PMDA. Comparison of in vitro inhibition data with available clinical evidence also highlighted limitations in predicting clinically relevant MATE1-mediated DDIs solely from plasma concentrations and in vitro IC_{50} values. **Conclusions:** MATE1 inhibition represents a potentially important but incompletely characterized mechanism of DDIs, particularly for small-molecule cancer therapies. Improved strategies integrating in vitro inhibition data with pharmacokinetic information, transporter-site exposure, and clinical biomarkers may facilitate more reliable identification

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of clinically relevant perpetrators and improve prediction of transporter-mediated DDIs during drug development and cancer pharmacotherapy.

Keywords: MATE1; drug transport; drug–drug interactions; kinase inhibitors

1. Introduction

Polypharmacy is increasingly common in modern clinical practice, particularly among older patients with multiple comorbidities and individuals with complex chronic diseases [1]. As the number of concurrently administered medications increases, so does the potential for clinically relevant pharmacokinetic drug–drug interactions (DDIs) [2], which can alter drug exposure, compromise therapeutic efficacy, and increase the risk of adverse effects [3]. Pharmacokinetic DDIs typically arise when a perpetrator drug alters the absorption, distribution, metabolism, and/or excretion of a victim drug. Although drug-metabolizing enzymes, particularly members of the cytochrome P450 family, have historically received the greatest attention in DDI assessment, membrane transporters are now recognized as important determinants of drug disposition and toxicity [4–6]. Polarized epithelial cells in the liver and kidney depend on coordinated networks of uptake and efflux transporters to mediate drug movement across biological membranes. Inhibition of these pathways can reduce systemic clearance, increase circulating drug exposure, or promote intracellular drug accumulation within specific tissues [7]. Accordingly, regulatory agencies now routinely require assessment of transporter-mediated DDI liability during drug development [8].

A substantial proportion of marketed small-molecule drugs are organic cations or weak bases that exist predominantly in a positively charged state at physiological pH [9]. These properties are common among therapeutically important compounds and can increase their dependence on transporter-mediated pathways for tissue distribution and systemic elimination [10–13].

Renal secretion of many organic cations involves coordinated transport across proximal tubule epithelial cells. Organic cation transporter 2 (OCT2) is a major basolateral uptake transporter for many cationic drugs in human kidney, although additional organic cation transport mechanisms may contribute depending on substrate affinity, capacity, and nephron segment. Apical efflux into the tubular lumen is subsequently mediated in part by multidrug and toxin extrusion proteins 1 (MATE1; *SLC47A1*) and 2-K (MATE2-K) [14]. MATE1 functions as a proton–organic cation antiporter, exchanging organic cations for protons, and contributes to the terminal step in the renal secretion of numerous cationic drugs [15,16].

Although MATE1 is best characterized in the kidney, it is also expressed in extrarenal tissues, including the heart, where it may influence intracellular exposure to cationic compounds. Thus, inhibition of MATE1 has the potential to alter both systemic drug disposition and tissue-specific drug accumulation [17]. This may be particularly relevant in oncology, where patients frequently receive multiple medications simultaneously, including small-molecule anticancer agents, anti-infective therapies, cardiovascular drugs, and other medications used to prevent or manage treatment-related complications. Many contemporary cancer therapies, including kinase inhibitors, interact with drug transporters and are administered chronically, creating opportunities for transporter-mediated DDIs that may not be readily predicted from conventional plasma pharmacokinetic measurements alone.

Despite its potential clinical importance, MATE1-mediated DDIs remain incompletely characterized. The inhibitory properties of many marketed drugs have not been systematically defined, and translation of in vitro inhibition data to clinically relevant interactions remains challenging. The aim of this review is therefore to comprehensively evaluate the current landscape of MATE1 inhibition, assess the potential clinical relevance of MATE1-mediated DDIs, and highlight their emerging importance for small-molecule cancer therapies.

2. Historical Context and the Legacy of Incomplete MATE1 Characterization

Human MATE1 was identified relatively recently compared with many of the drug-metabolizing enzymes and transporters that have long been incorporated into pharmacokinetic evaluation. Its role in the final step of renal organic cation secretion was established in the mid-2000s, after numerous widely used medications had already entered clinical practice [16]. Consequently, many older drugs were developed before systematic assessment of MATE1-mediated transport or inhibition became part of contemporary DDI evaluation [18]. The subsequent incorporation of transporters into regulatory DDI assessment has created an important historical gap in the available data. For many long-established therapies, MATE1 substrate and inhibitor properties remain incompletely characterized, and potentially relevant transporter-mediated interactions have only been recognized retrospectively. This gap is particularly important when older medications are co-administered with newer therapies whose disposition depends on renal organic cation transport.

3. In Vitro Models for Evaluating MATE1 Inhibition

MATE1-mediated drug interactions are commonly evaluated using heterologous expression systems, including human embryonic kidney (HEK293) or Chinese hamster ovary (CHO) cells transfected with human *SLC47A1*, as well as membrane vesicles and other transporter-overexpression platforms. These systems allow relatively direct assessment of MATE1-mediated transport and concentration-dependent inhibition and are widely used to estimate inhibitory parameters such as IC_{50} and K_i [19].

A variety of probe substrates have been used in these assays, including [^{14}C]-metformin, [^{14}C]-tetraethylammonium (TEA), [^{3}H]-1-methyl-4-phenylpyridinium (MPP^+), and fluorescent substrates such as 4-(4-(dimethylamino)styryl)-*N*-methylpyridinium (ASP^+). However, apparent inhibitory potency can depend on the probe substrate, expression system, and experimental conditions, and substrate-dependent inhibition has been reported for MATE1 [20]. Differences in substrate–transporter interactions may therefore contribute to variability in reported IC_{50} values across assay systems. Polarized cell systems such as MDCKII cells provide an opportunity to assess directional transport, but interpretation can become more complex when multiple transporters contribute sequentially to transepithelial drug movement [21,22].

More physiologically relevant models, including primary human renal proximal tubule cells and kidney-derived cell systems, may better reproduce native transporter networks [23]. However, because these models often co-express multiple uptake and efflux transporters, changes in substrate disposition cannot always be attributed specifically to MATE1 [24,25]. This is particularly relevant for commonly used probes such as metformin, creatinine, and N^1-methylnicotinamide, whose renal handling reflects the integrated activity of OCT2, MATE1, MATE2-K, and other pathways [26–28]. Renal transporter expression and function may also vary according to nephron segment, sex, and physiological state [29]. Such heterogeneity, including reported sex-dependent differences in distal nephron transporter

expression, represents an additional limitation of simplified in vitro models when extrapolating to whole-kidney drug disposition.

Despite these limitations, transporter-overexpression systems remain the primary tools for screening MATE1 inhibition during drug development because they are rapid, scalable, and suitable for concentration–response analysis. However, translation of an in vitro IC_{50} or K_i value into clinical DDI risk requires consideration of unbound perpetrator concentrations, transporter localization and expression, substrate dependence, and competing routes of drug elimination. Thus, the ability of an in vitro system to detect MATE1 inhibition does not necessarily predict the magnitude or clinical relevance of an in vivo interaction.

4. Potential Clinical Consequences of MATE1 Inhibition

Inhibition of MATE1 can affect drug disposition through several mechanistically distinct pathways, including changes in systemic exposure, altered handling of endogenous compounds used as clinical biomarkers, intracellular accumulation within the kidney, and altered drug exposure in extra-renal tissues. The examples below illustrate these different consequences and are not intended to provide an exhaustive catalogue of MATE1-associated toxicities.

4.1. Altered Systemic Exposure and Drug Toxicity

Metformin is a well-established substrate of renal organic cation transport pathways and is commonly used as a clinical probe for MATE1-mediated drug interactions. Inhibition of MATE1 can reduce the renal secretion of metformin, increase systemic exposure, and thereby increase the likelihood of concentration-dependent adverse effects. In susceptible patients, excessive metformin accumulation can contribute to serious toxicity, including lactic acidosis [30]. Similar increases in systemic exposure have also been reported for other organic cation substrates, including procainamide [31], pilsicainide [32], and varenicline [33], following coadministration with cimetidine, a clinically relevant inhibitor of renal organic cation transport. These interactions have subsequently been linked to inhibition of MATE1 and/or MATE2-K, although the contribution of individual transporters cannot always be distinguished because these clinical studies predated the molecular characterization of MATE1.

4.2. Serum Creatinine Elevations and Apparent Renal Dysfunction

Inhibition of renal organic cation transport can also alter the tubular secretion of creatinine, leading to transient increases in serum creatinine that may be misinterpreted as a reduction in glomerular filtration. This phenomenon is particularly relevant for several small-molecule cancer therapies, including kinase inhibitors, many of which inhibit OCT2 and/or MATE transporters. MATE1 and MATE2-K inhibition is well documented to increase serum creatinine without necessarily causing a corresponding decline in glomerular filtration or renal function [34] despite creating the appearance of treatment-related renal dysfunction. Recognition of this mechanism is clinically important because inappropriate interpretation of creatinine elevations may lead to unnecessary dose modification or treatment interruption. More specific measures of kidney function, including alternative filtration markers or direct assessment of renal clearance, may help distinguish transporter-mediated changes in creatinine handling from true nephrotoxicity [35].

4.3. Renal Accumulation and Nephrotoxicity

MATE1 inhibition can also increase intracellular drug exposure within the kidney [36]. Cisplatin provides a well-characterized example: continued basolateral uptake into proximal tubular cells through OCT2, coupled with impaired apical efflux through MATE1, can pro-

mote intracellular accumulation and enhance tubular injury. This illustrates how transporter inhibition may increase tissue-specific toxicity even when changes in systemic exposure are modest [37]. More recently, inhibition of MATE1 by several flavonoids was shown to increase cisplatin cytotoxicity in vitro and exacerbate cisplatin-induced renal injury in vivo, further supporting a role for MATE1-mediated efflux in limiting renal accumulation of nephrotoxic drugs [38].

4.4. Extra-Renal Tissue Exposure and Toxicity

MATE1 is also expressed in extra-renal tissues, including the liver and heart, where it may contribute to intracellular handling of cationic drugs. Drugs such as metformin enter hepatocytes through OCT1, where inhibition of canalicular MATE1 can increase intracellular hepatic accumulation [39,40]. Because biliary excretion is not a major route of metformin elimination, inhibition of canalicular MATE1 may have limited effects on plasma metformin concentrations while still increasing hepatic exposure and leading to lactic acidosis [30]. Inhibition or reduced activity of cardiac MATE1 can increase local drug exposure independently of changes in plasma concentrations. Dofetilide provides an illustrative example, because increased cardiac exposure to this cationic antiarrhythmic can enhance electrophysiologic toxicity, including QT prolongation and ventricular arrhythmias [41].

5. Regulatory Assessment of MATE1-Mediated DDI Risk

As transporter-mediated DDIs have become increasingly recognized, regulatory agencies have incorporated the evaluation of clinically important uptake and efflux transporters into routine drug development. Under the harmonized ICH M12 Guideline on Drug Interaction Studies, investigational drugs are evaluated for their potential to inhibit transporters including ABCB1 (P-glycoprotein), ABCG2 (BCRP), OATP1B1/1B3, OAT1/OAT3, OCT2, and MATE1/MATE2-K using validated in vitro systems [42–44]. These studies typically characterize concentration-dependent inhibition and derive parameters such as IC_{50} or K_i values that can be compared with clinically relevant drug exposures. Importantly, unlike substrate assessments, which consider the contribution of a transporter to a drug's disposition, transporter inhibition assessments are not dependent on the extent of the drug's elimination through that transporter. Thus, even drugs with minimal urinary excretion may inhibit MATE1 if they achieve sufficient concentrations at the transporter.

For MATE1 and MATE2-K, regulatory assessment relies on an exposure-based screening criterion that relates the unbound maximum plasma concentration of the perpetrator drug to its in vitro inhibitory potency [8]. When this ratio exceeds the recommended cutoff of 0.02, a clinically relevant interaction cannot be excluded and additional evaluation, including mechanistic modeling or a clinical DDI study, may be warranted. Importantly, this threshold is intended as a conservative screening tool rather than evidence that a clinically meaningful interaction will necessarily occur.

The predictive value of this approach depends on the quality and context of the underlying in vitro inhibition data. Apparent MATE1 inhibitory potency can vary depending on the probe substrate and experimental conditions, reflecting substrate-dependent interactions with the transporter [20]. In addition, inhibition of organic cation transporters by some compounds, including several kinase inhibitors, can be strongly influenced by pre-incubation time [45]. Preincubation-dependent changes in inhibitory potency may provide additional information beyond conventional IC_{50} measurements. However, an increase in inhibition following preincubation does not necessarily demonstrate prolonged inhibitor residence on MATE1, because slow association, membrane partitioning, intracellular accumulation, or other time-dependent processes may produce a similar phenotype. Inhibitor residence times have not been systematically characterized for putative inhibitors

of MATE1, and additional mechanistic studies will be required to determine whether this parameter improves prediction of clinical transporter inhibition. Although pre-incubation can increase the apparent inhibitory potency of certain drugs against MATE1, its effects appear less prevalent for MATE transporters than for OCT and OATP1B transporters, although compound-specific effects remain important [46,47].

Thus, conventional assay conditions may underestimate inhibitory potential for compounds that exhibit non-competitive inhibition or time-dependent transporter interactions. These considerations are particularly important when translating in vitro MATE1 inhibition data into quantitative predictions of clinical DDI risk.

6. Data Sources, Search Strategy, and Approach to Evidence Synthesis

To characterize the current landscape of MATE1 inhibition, information was compiled from peer-reviewed publications, abstracts, previously published reviews, publicly and non-publicly available databases, and regulatory documents (Figure 1). Data sources included UCSF-FDA TransPortal, UCSD/UCD-NIEHS TICBase, the Certara Drug Interaction Database (DIDB), FDA New Drug Applications (NDAs), EMA Marketing Authorization Applications (MAAs), and the FDA Orange Book. PubMed and Google Scholar searches were performed using terms including "MATE1 inhibitors," "MATE1 inhibition," "MATE1 antifungals," and "MATE1 TKI." The dataset was updated through mid-November 2026.

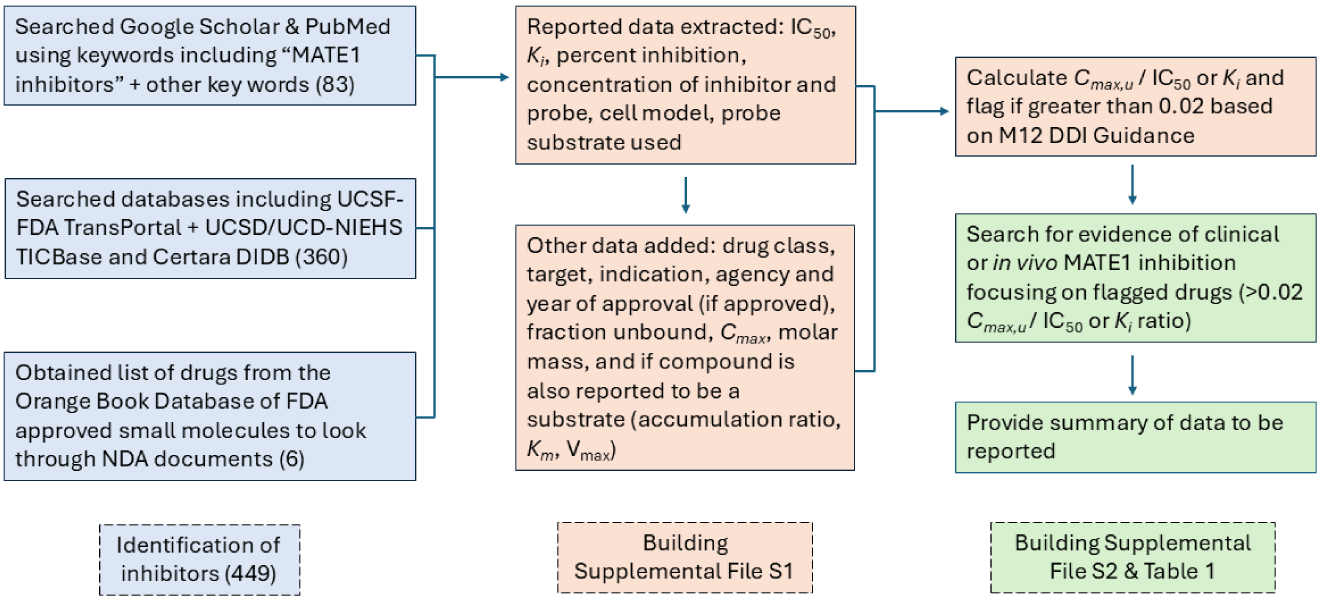


Figure 1. Applied methods for the acquisition of relevant MATE1 inhibition data included in Table 1 and Supplemental Files S1 and S2. The numbers in parentheses indicate the number of unique inhibitors initially identified through each method.

Drugs were included if they were approved by at least one regulatory agency worldwide, were currently in development, or had previously been approved and subsequently withdrawn or discontinued, and if measurable MATE1 inhibitory activity had been reported. Where available, compounds were also classified according to whether they were reported MATE1 substrates, defined as greater than 2-fold accumulation compared with vector control cells. Two authors (A.F.H. and C.W.J.) independently reviewed the collected data for validity and accuracy.

When multiple IC_{50} or K_i values were available for a given compound, the lowest reported value was selected. For estimation of potential clinical relevance, the dose and route associated with the highest reported systemic exposure and the highest reported fraction unbound were used to provide a conservative, worst-case estimate. When only percent inhibition was available, an approximate IC_{50} was derived using the reported inhibitor concentration and degree of inhibition, and this value was used to estimate the $C_{max,u}/IC_{50}$ ratio. This intentionally conservative approach was intended to minimize the likelihood of underestimating MATE1 transporter inhibition, although it introduces several limitations. Selection of the lowest reported IC_{50} or K_i together with the highest reported unbound clinical exposure may bias calculated exposure-to-potency ratios upward and was designed for hazard identification rather than quantitative prediction of clinical effect. In addition, IC_{50} values estimated from inhibition at a single concentration are less robust than values derived from complete concentration–response experiments and may be sensitive to experimental variability. Accordingly, calculated $C_{max,u}/IC_{50}$ values should be regarded as screening estimates of potential MATE1 DDI liability rather than precise predictors of the magnitude of an in vivo interaction.

The complete inhibitor dataset is provided in Supplemental File S1, whereas Supplemental File S2 summarizes compounds selected for further evaluation of potential clinical relevance. Selected compounds below the threshold were also included when relevant clinical studies or safety signals were identified in the literature or regulatory documents. The complete bibliography supporting the data presented in Supplemental Files S1 and S2 is available in a publicly accessible repository at https://doi.org/10.5061/dryad.cvdncjtmb (accessed on 17 November 2026).

Table 1. Selected drug summary of MATE1-mediated clinically relevant DDIs.

Drug	Class	IC_{50} or K_i (μM)	$C_{max,u}/IC_{50}$ or K_i	Study Results
Trilaciclib	Kinase Inhibitors	0.175	5.95	Coadministration with metformin caused metformin C_{max} to increase by 81%, AUC to increase by 65%, and a renal CL decrease of 37% [48]
Trimethoprim	Antibiotics	9.70	1.65	Coadministration with metformin caused metformin C_{max} increase of 38%, AUC increase of 37% and decrease in metformin CL of 20% [49]
Famotidine	Gastrointestinal Agents	0.25	1.33	Famotidine treatment increased plasma creatinine and decreased creatinine renal clearance [50]
Pyrimethamine	Antiparasitics	0.04	1.16	Coadministration with metformin caused metformin AUC 2.58-fold increase and reduced clearance [50,51]
Quinidine	Cardiovascular Agents	1.57	0.740	Quinidine reduced amantadine CL by 33% [52]
Ribociclib	Kinase Inhibitors	1.7	0.739	Grade-1 creatinine elevation in 28% of patients in 32-patient study [53]

Table 1. *Cont.*

Drug	Class	IC_{50} or K_i (μM)	$C_{max,u}/IC_{50}$ or K_i	Study Results
Levoketoconazole	Endocrine & Metabolic Agents	0.248	0.550	Coadministration with metformin caused metformin C_{max} increase of 82%, AUC increase of 120%, and decreased renal clearance 63% [54]
Cimetidine	Gastrointestinal Agents	6.6	0.344	In rats, coadministration with metformin caused metformin AUC to increase 3.2-fold, reduced renal clearance of MATE1 probes by 50% [55,56]
Ondansetron	Gastrointestinal Agents	0.1	0.244	Coadministration with metformin caused metformin C_{max} to increase by 17% and decreased renal clearance by 37% [57]
Vandetanib	(TKI) Kinase Inhibitors	1.23	0.162	Coadministration with metformin caused metformin C_{max} to increase by 50% and AUC to increase by 74% [58]
Tucatinib	(TKI) Kinase Inhibitors	0.34	0.112	Coadministration with metformin caused metformin AUC to increase 1.4-fold and a 41% decrease in CL. Creatinine CL decreased by 23% [59]
Abemaciclib	(TKI) Kinase Inhibitors	0.52	0.0419	Coadministration with metformin caused metformin AUC to increase by 37%, C_{max} to increase by 22%, and a renal CL decrease of 45% [60]
Isavuconazole	Antifungals	4.67	0.0367	Coadministration with metformin caused metformin AUC to increase by 52% and C_{max} to increase by 23% [61]
Pimicotinib	(TKI) Kinase Inhibitors	-	-	Coadministration with metformin caused metformin AUC to increase by 29% and C_{max} to increase by 42% [62]
Bictegravir	Antivirals	8	0.0163	Coadministration with metformin caused metformin AUC to increase by 39% and C_{max} to increase by 31% [63]
Dronedarone	Cardiovascular Agents	1.84	0.002167	After 400 mg dose, renal creatinine and NMN CL decreased by ~18% [64]

The full list of drugs and supporting study information is provided in Supplemental File S2. The complete bibliography supporting Supplemental Files S1 and S2 is available in the accompanying public repository at https://doi.org/10.5061/dryad.cvdncjtmb (accessed on 17 November 2026).

7. Translating MATE1 Inhibition Potency to Clinical Relevance

In vitro parameters such as IC_{50} and K_i provide useful measures of inhibitor potency but, when considered in isolation, do not establish whether a clinically relevant MATE1-mediated DDI is likely to occur [65]. Clinical interpretation requires consideration of the concentration of unbound perpetrator drug available to interact with the transporter [66]. Accordingly, regulatory screening approaches relate unbound systemic exposure to in vitro inhibitory potency, commonly expressed as the $C_{max,u}/IC_{50}$ or $C_{max,u}/K_i$ ratio.

Although this static exposure-based approach is more informative than inhibitor potency alone, it has important limitations. The recommended screening threshold is intentionally conservative and may identify compounds for which clinically meaningful MATE1 inhibition is not subsequently observed. Conversely, clinically relevant changes in the disposition of MATE substrates may occur for compounds with exposure ratios near or below the screening threshold. These discrepancies likely reflect factors not captured by a simple plasma exposure-to-IC_{50} ratio, including transporter-site concentrations, substrate dependence, assay conditions, the contribution of parallel renal transport pathways, and differences between recombinant systems and native tissues.

An additional complication is that MATE1 inhibition frequently occurs in the context of broader transporter inhibition. Many compounds, particularly kinase inhibitors, interact with multiple uptake and efflux transporters, including OCT2 and MATE2-K [67,68]. Because renal secretion of commonly used probe substrates reflects coordinated transporter activity, a clinical DDI may represent inhibition of several components of the pathway rather than MATE1 alone. Differences in transporter selectivity among inhibitors may therefore contribute to the imperfect relationship between isolated in vitro MATE1 inhibition measurements and clinical outcomes.

Gabapentin has been reported to display potent interactions with renal organic cation transport pathways in vitro, yet the relationship between these findings and clinically meaningful MATE1 inhibition is not straightforward [69]. Conversely, bictegravir, despite a $C_{max,u}/IC_{50}$ ratio below the conventional screening threshold, increased metformin exposure and reduced metformin clearance in a clinical study, although the investigators concluded that the magnitude of the interaction did not warrant metformin dose adjustment [63]. Together, these observations emphasize that static screening ratios are best viewed as tools for identifying potential DDI liability rather than definitive predictors of clinical effect. Table 1 summarizes selected compounds for which clinical or in vivo evidence supports, or is suggestive of, MATE1-mediated interactions. Examples in the compiled dataset illustrate discordance between static exposure-to-potency ratios and reported clinical or in vivo effects. Because the available clinical evidence encompasses heterogeneous substrates, study designs, and pharmacokinetic or biomarker endpoints, these data do not permit a formal quantitative assessment of the predictive performance of $C_{max,u}/IC_{50}$ across compounds. The complete supporting information is provided in Supplemental File S2.

8. Therapeutic Classes Relevant to MATE1-Mediated DDIs

The compiled dataset demonstrates that MATE1 inhibition is distributed across a broad range of therapeutic classes (Figure 2A). Oncology therapies, particularly kinase inhibitors, are prominently represented, but clinically relevant interactions may also involve non-oncology drugs frequently co-administered to patients with cancer, including anti-infective, cardiovascular, gastrointestinal, and metabolic agents. The following sections highlight selected drug classes in which MATE1 inhibition may be especially relevant to polypharmacy and clinical DDI risk.

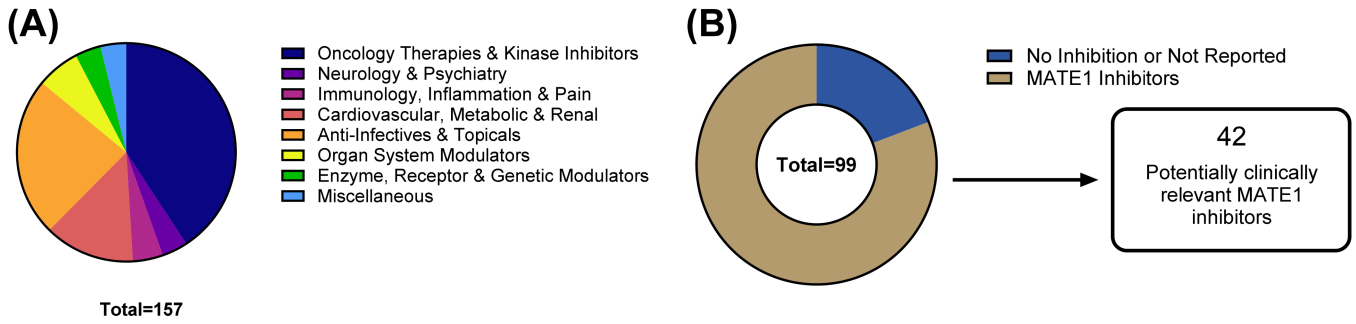


Figure 2. Distribution and clinical relevance of potential MATE1 inhibitors across drug classes, with a focused analysis of kinase inhibitors. (**A**) Drug class distribution of potentially clinically relevant MATE1 inhibitors. Potentially clinically relevant MATE1 inhibitors ($C_{max,u}/IC_{50} > 0.02$) were categorized according to their primary therapeutic drug class. Oncology therapies & kinase inhibitors includes kinase inhibitors, (TKI) kinase inhibitors, and antineoplastic/oncology agents. Neurology & psychiatry drugs includes CNS: psychotropics, CNS: neurodegenerative & other, and neuromuscular & nicotinic agents. Immunology, inflammation & pain include immunomodulators & anti-inflammatory, analgesics & anesthetics, antihistamines & allergy, and migraine therapies. Cardiovascular, metabolic & renal includes cardiovascular agents, endocrine & metabolic agents, uricosuric/renal agents, hepatoprotective agents, and mitochondrial targeted agents. Anti-infectives & topicals includes antimicrobials (antibiotics, antivirals, antifungals, antiparasitics), antiseptics, and topicals. Organ system modulators includes gastrointestinal agents, respiratory agents, ophthalmic agents, and autonomic/receptor modulators. Enzyme, receptor & genetic modulators includes GPCR modulators, neurotransmitter reuptake inhibitors, enzyme/protease inhibitors, ion channel modulators, oligonucleotide/genetic therapies, and scavenging agents. Miscellaneous includes miscellaneous, rare disease agents, and nutraceuticals & natural products. Metabolites were placed into the drug class of their parent drug. (**B**) FDA-approved kinase inhibitors that inhibit MATE1. Of the 99 FDA-approved kinase inhibitors, 80/99 inhibit MATE1 to some degree, and 42/99 are potentially clinically relevant.

8.1. Kinase Inhibitors

Kinase inhibitors represent a rapidly expanding class of targeted small-molecule cancer therapies and are frequently administered chronically in combination with other medications. Many kinase inhibitors interact with multiple drug transporters, including organic cation transporters [67], MATE proteins [45,67] OATs [70], OATPs [71], ABCB1 [72], and ABCG2 [72], contributing to a substantial potential for transporter-mediated DDIs.

Because most kinase inhibitors were developed after transporter assessment became an established component of regulatory drug development, their interaction profiles are generally better characterized than those of many older therapeutic classes. This provides an opportunity to examine the prevalence of MATE1 inhibition systematically. Among the 99 FDA-approved kinase inhibitors included in the present analysis, 80 showed measurable MATE1 inhibition and 42 exceeded the $C_{max,u}/IC_{50}$ screening threshold of 0.02 for potential clinical relevance (Figure 2B). These findings indicate that MATE1 inhibition is common within this drug class and may represent an underrecognized contributor to DDI liability.

The potential clinical importance of these interactions is heightened by the chronic oral administration of many kinase inhibitors and the frequent use of concomitant medications in patients with cancer. Inhibition of MATE1 may alter the renal clearance or tissue exposure of co-administered organic cation substrates, while kinase inhibitors that are themselves substrates may also be susceptible to interactions with other MATE1 inhibitors [73]. Thus, MATE1 should be considered alongside more established metabolic and transporter pathways when evaluating DDI risk associated with targeted cancer therapies.

8.2. Other Antineoplastic and Targeted Oncology Agents

Beyond kinase inhibitors, other anticancer agents may participate in MATE1-mediated DDIs either as substrates whose disposition depends on renal organic cation transport or as inhibitors that alter the handling of co-administered drugs. Platinum-based agents such as cisplatin and oxaliplatin are examples of drugs whose renal disposition involves coordinated basolateral uptake and apical efflux pathways, making them susceptible to changes in transporter activity. In such cases, altered MATE1 function may influence intracellular renal exposure and toxicity rather than simply changing systemic pharmacokinetics.

Conversely, some non-kinase targeted agents can act as MATE1 inhibitors and therefore function as DDI perpetrators. Olaparib, for example, has been reported to inhibit MATE1 and to increase metformin exposure in preclinical studies, illustrating the potential for targeted anticancer therapies to alter the disposition of co-administered organic cation drugs [74].

8.3. Central Nervous System and Psychotropic Agents

Several central nervous system and psychotropic drugs are organic cations and may interact with renal organic cation transport pathways. This is clinically relevant because many of these agents are used chronically and may be co-administered with other medications that inhibit MATE1 or share related renal secretory pathways.

Amantadine provides a clinically informative example. Its renal elimination depends substantially on active tubular secretion, and toxicity has been reported during co-administration with trimethoprim–sulfamethoxazole, a recognized inhibitor of renal organic cation transport [75]. Amantadine intoxication has also been described during concomitant treatment with donepezil in a patient with impaired renal function [76]. Although such case reports cannot establish that MATE1 inhibition alone was responsible, they illustrate how reduced renal secretory capacity, transporter inhibition, and patient-specific factors may combine to increase exposure to cationic CNS drugs.

8.4. Endocrine and Metabolic Agents

Endocrine and metabolic therapies are highly relevant to MATE1-mediated DDIs because metformin is both a widely used medication and the best-established clinical probe substrate for renal organic cation transport. Metformin undergoes little hepatic metabolism and is eliminated predominantly through the kidney, where basolateral uptake by OCT2 is followed by apical secretion through MATE1 and MATE2-K [77].

Because of this strong dependence on active renal secretion, metformin exposure can increase when these transport pathways are inhibited. Numerous clinical DDI studies therefore use metformin to evaluate the in vivo consequences of OCT2/MATE inhibition. Changes in metformin area under the concentration–time curve, peak concentration, or renal clearance can provide evidence of altered renal organic cation transport, although such changes cannot generally be attributed to MATE1 alone because OCT2 and MATE2-K contribute to the same pathway.

8.5. Cardiovascular Agents

Cardiovascular medications represent another clinically relevant class of potential MATE1 inhibitors, particularly because they are frequently co-administered with anticancer therapies in patients with cardiovascular comorbidities. Several cardiovascular drugs are organic cations and interact with renal organic cation transport pathways, creating the potential to alter the disposition of co-administered MATE substrates.

Quinidine provides one example: co-administration has been associated with reduced clearance of the cationic drug amantadine, consistent with inhibition of renal tubular secretion [52]. Dronedarone has likewise been associated with modest reductions in the renal clearance of creatinine and N^1-methylnicotinamide, suggesting inhibition of renal organic cation transport [64]. These examples illustrate how cardiovascular drugs may alter either the pharmacokinetics of co-administered substrates or endogenous biomarkers of transporter activity.

For patients receiving targeted cancer therapies, such interactions may be particularly relevant because cardiovascular medications are commonly used concomitantly and several kinase inhibitors themselves interact with MATE1 and related transporters.

8.6. Anti-Infective Agents

Anti-infective drugs are especially relevant to MATE1-mediated DDIs because they are frequently co-administered with other therapies in patients with cancer, including during treatment of infection or prophylaxis in immunocompromised patients. Although MATE1 preferentially handles organic cations, its substrate spectrum also includes certain zwitterionic compounds. For example, the cephalosporin antibiotics cephalexin and cephradine have been reported to interact with MATE1, and MATE1 deficiency reduces the renal clearance of cephalexin [14,78,79].

Trimethoprim is a particularly well-characterized inhibitor of renal organic cation transport and has been used extensively as a clinical and mechanistic example of OCT/MATE-mediated DDIs [80]. Its ability to reduce the renal secretion of cationic substrates illustrates how anti-infective therapy can alter the disposition of concomitant medications through transporter inhibition. This issue may be especially important in oncology, where antibacterial and antifungal agents are commonly administered together with targeted anticancer therapies. However, the MATE1 interaction profiles of many anti-infective drugs, particularly antifungal agents, remain incompletely characterized. More systematic evaluation of this class may therefore be important for identifying previously unrecognized transporter-mediated interactions in patients receiving combination cancer therapy.

9. Dual Substrate-Inhibitor Dynamics of MATE1

Transporter-mediated drug interactions are often described in terms of distinct “victim” and “perpetrator” drugs, but this distinction is not always straightforward for MATE1. As a polyspecific organic cation transporter, MATE1 recognizes a broad range of structurally diverse ligands, and many compounds can function both as transported substrates and as inhibitors of the transport of other substrates [14,81–83].

This dual behavior has important implications for DDI interpretation. A drug that is transported by MATE1 may also compete with a co-administered substrate for interaction with the transporter, particularly when local concentrations at the transporter are sufficiently high. Conversely, inhibition of MATE1 can alter the disposition of a compound that is itself a MATE1 substrate. Thus, the same drug may act as a victim, a perpetrator, or both, depending on the interacting drug pair, relative concentrations, and contribution of MATE1 to overall disposition. These properties further complicate translation of in vitro inhibition data to clinical DDI risk and underscore the importance of considering substrate status together with inhibitory potency when evaluating MATE1-mediated interactions.

10. In Vitro–In Vivo Extrapolation of MATE1-Mediated DDIs

In vitro–in vivo extrapolation (IVIVE) aims to translate in vitro inhibition parameters and clinically relevant drug exposures into predictions of transporter-mediated DDIs [84]. For MATE1 and related renal transporters, this translation is complicated by the fact that

systemic plasma concentrations may not accurately reflect drug concentrations at the transporter site.

For compounds that are substrates of OCT2, active basolateral uptake into proximal tubule cells can produce intracellular unbound concentrations that exceed unbound plasma concentrations [83,85]. Consequently, reliance on systemic exposure alone may underestimate the concentration of an inhibitor presented to MATE1 at the apical membrane and thereby underpredict the potential for clinically relevant inhibition [85,86]. This limitation is particularly relevant for compounds that function as both substrates and inhibitors of renal organic cation transport pathways.

A second challenge is that recombinant expression systems may not reproduce transporter abundance in human kidney. Quantitative proteomic measurements have demonstrated substantial differences in transporter expression between experimental systems and native tissues [87]. Scaling approaches based on relative expression or activity may therefore improve extrapolation of in vitro kinetic data to in vivo drug disposition.

Mechanistic physiologically based pharmacokinetic modeling provides a framework for integrating transporter kinetics, plasma protein binding, tissue exposure, renal function, and coordinated uptake and efflux transport. Although regulatory screening commonly relies on unbound plasma concentrations, plasma protein binding does not necessarily impose a simple proportional limitation on transporter-mediated clearance. For some highly protein-bound substrates, albumin-mediated delivery or facilitated dissociation can enhance transporter-mediated uptake and improve prediction of active renal secretion [88–91]. Such models may be particularly useful for oncology drugs, for which healthy-volunteer DDI studies may be impractical and initial clinical evaluation often occurs directly in patients receiving multiple concomitant medications. Incorporating intracellular kidney exposure and transporter abundance may therefore improve prediction of MATE1-mediated DDIs beyond static plasma exposure-based approaches.

11. Remaining Knowledge Gaps and Future Directions

A major limitation of current approaches to predicting MATE1-mediated DDIs is the reliance on static exposure-to-potency ratios such as $C_{max,u}/IC_{50}$. Although useful as regulatory screening tools, these ratios may not accurately represent the conditions at the transporter site. The systemic unbound plasma concentration used in the numerator may underestimate intracellular unbound drug concentrations in proximal tubule cells, particularly for compounds that undergo active basolateral uptake through OCT2. In such cases, transporter-site exposure at the apical MATE1 membrane may substantially exceed that inferred from plasma pharmacokinetics. Conversely, the IC_{50} used in the denominator is not necessarily a fixed property of the inhibitor and may vary according to probe substrate, expression system, incubation conditions, and assay parameters such as pH. Thus, both components of the screening ratio may incompletely reflect the actual interaction between a drug and MATE1 in vivo.

Improved experimental systems are therefore needed to better characterize drug concentrations and transporter activity at the site of interaction. Conventional recombinant models do not fully reproduce the polarized architecture, transporter abundance, intracellular environment, or coordinated OCT2/MATE1 transport of the human proximal tubule. Emerging proximal-tubule-on-chip and micro-physiological models may provide more physiologically relevant platforms for studying vectorial renal transport and intracellular drug exposure [92–95]. Spatial analytical approaches, including mass spectrometry imaging, may further improve characterization of localized intrarenal drug concentrations [96]. Together with mechanistic PBPK modeling, these approaches may enable more accurate es-

timation of intracellular inhibitor exposure and improve IVIVE beyond static plasma-based screening metrics.

Greater standardization of MATE1 inhibition assays is also needed. MATE1 exhibits broad substrate specificity, and reported inhibitory potency can vary substantially according to the probe substrate, expression system, incubation conditions, and assay design. For some compounds, including itraconazole, reported IC_{50} values differ by orders of magnitude across experimental systems [41,97]. Harmonization of probe selection, assay conditions, and reporting standards would improve comparison across studies and increase confidence in the interpretation of MATE1 inhibition data.

Interindividual variability represents an additional challenge. Genetic variation in *SLC47A1* can alter transporter activity [98,99], and renal function, disease state, transporter abundance, intracellular pH, and other patient-specific factors may further influence susceptibility to MATE1-mediated DDIs. Incorporating these sources of variability into mechanistic models may improve prediction of transporter-mediated drug disposition in individual patients and in populations that are underrepresented in conventional DDI studies.

Endogenous biomarkers may provide less invasive approaches for assessing renal organic cation transport in clinical studies. Serum creatinine, N^1-methylnicotinamide, and N^1-methyladenosine have been investigated as biomarkers of OCT2/MATE pathway activity, although none are specific for MATE1 [46,100]. Because these biomarkers reflect integrated renal transport and additional physiological processes, paired plasma and urine measurements and the use of complementary biomarkers may provide a more informative assessment of transporter function [26]. The clinical evaluation of revumenib illustrates both the potential and limitations of such indirect approaches, in which changes in serum creatinine and metformin pharmacodynamics were used to explore possible MATE1-mediated effects rather than a dedicated assessment of metformin renal clearance [101]. This method alone is not sufficient to determine MATE1-mediated inhibition, and the FDA still requires dedicated PK DDI studies to establish if a drug inhibits MATE1 in a clinically relevant manner.

Finally, many commonly prescribed drugs remain incompletely characterized as MATE1 inhibitors, particularly agents developed before routine transporter screening became part of regulatory drug development. This gap may be especially important in oncology, where targeted cancer therapies are frequently combined with anti-infective and supportive-care medications. Antifungal drugs represent a particularly relevant example because they are routinely administered to immunocompromised patients, including individuals with acute leukemia, yet the MATE1 interaction profiles of many agents remain poorly defined [102]. Systematic characterization of these co-medications may identify currently unrecognized transporter-mediated DDIs and improve the safety of combination cancer therapy.

12. Conclusions

MATE1 inhibition represents a potentially important but still incompletely characterized mechanism of DDIs. Although current regulatory screening approaches provide a useful first step, static plasma exposure-to-inhibition metrics may not reliably predict the extent of MATE1 inhibition in vivo because they do not fully account for transporter-site exposure or variability in experimentally determined inhibitory potency.

This uncertainty is particularly relevant in oncology. Many small-molecule cancer therapies, especially kinase inhibitors, interact with MATE1, while patients with cancer frequently receive multiple concomitant medications that may themselves be substrates or inhibitors of renal organic cation transport. At the same time, the MATE1 interaction profiles of many older and commonly used co-medications remain poorly defined.

Improved prediction of clinically relevant MATE1-mediated DDIs will therefore require integration of more physiologically relevant experimental systems, quantitative modeling, and clinical biomarkers with systematic characterization of both anticancer drugs and commonly co-administered therapies. Such approaches should improve interpretation of transporter-mediated DDI risk and support safer use of combination therapies in patients with cancer.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/cancers18233821/s1. File S1: Comprehensive Dataset of Drug-Mediated MATE1 Inhibition Characteristics; File S2: Clinical MATE1 Inhibition Evidence. File S1 contains all information collected during the MATE1 inhibitor literature search, including drug name, drug class, indication, approval status, reported MATE1 inhibition data, relevant experimental conditions, C_{max} in humans, F_u, molecular mass, $C_{max,u}/IC_{50}$ or $C_{max,u}/K_i$ values, substrate data when available, source links, and all abbreviations used. File S2 assesses available clinical evidence for potentially clinically relevant MATE1 inhibitors, including whether clinical or in vivo inhibition has been evaluated and the type of evidence available.

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Abbreviations

The following abbreviations are used in this manuscript:

MATE1	Multidrug and toxin extrusion protein 1
MATE2-K	Multidrug and toxin extrusion protein 2-kidney isoform
SLC47A1	Solute carrier family 47 member 1
DDI	Drug–drug interaction
OCT1	Organic cation transporter 1
OCT2	Organic cation transporter 2

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
HEK293	Human embryonic kidney 293
CHO	Chinese hamster ovary
TEA	Tetraethylammonium
MPP^+	1-methyl-4-phenylpyridinium
ASP^+	4-(4-dimethylaminostyryl)-N-methylpyridinium
BCRP	Breast cancer resistance protein
DIDB	Drug interaction database
NDA	New drug application
MAA	Marketing authorization application
TKI	Tyrosine kinase inhibitor
CL	Clearance
AUC	Area under the plasma concentration–time curve
C_{max}	Maximum plasma concentration
$C_{max,u}$	Maximum unbound plasma concentration
IC_{50}	Half-maximal inhibitory concentration
K_i	Inhibition constant
F_u	Fraction unbound
NMN	N^1-methylnicotinamide
IVIVE	In vitro–in vivo extrapolation
CNS	Central nervous system
FDA	U.S. Food and Drug Administration
EMA	European Medicines Agency
PMDA	Pharmaceuticals and Medical Devices Agency
PBPK	Physiologically based pharmacokinetic

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