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REVIEW

Predicting disruptions to drug pharmacokinetics and the risk of adverse drug reactions in non-alcoholic steatohepatitis patients

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Drug−drug interaction;
Liver;
Adverse drug reaction

Abstract The liver plays a central role in the pharmacokinetics of drugs through drug metabolizing enzymes and transporters. Non-alcoholic steatohepatitis (NASH) causes disease-specific alterations to the absorption, distribution, metabolism, and excretion (ADME) processes, including a decrease in protein expression of basolateral uptake transporters, an increase in efflux transporters, and modifications to enzyme activity. This can result in increased drug exposure and adverse drug reactions (ADRs). Our goal was to predict drugs that pose increased risks for ADRs in NASH patients. Bibliographic research identified 71 drugs with reported ADRs in patients with liver disease, mainly non-alcoholic fatty liver disease (NAFLD), 54 of which are known substrates of transporters and/or metabolizing enzymes. Since NASH is the progressive form of NAFLD but is most frequently undiagnosed, we identified other drugs at risk based on NASH-specific alterations to ADME processes. Here, we present another list of 71 drugs at risk of pharmacokinetic disruption in NASH, based on their transport and/or metabolism processes. It encompasses drugs from various pharmacological classes for which ADRs may occur when used in NASH patients, especially when eliminated through multiple pathways altered by the disease. Therefore, these results may inform clinicians regarding the selection of drugs for use in NASH patients.

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1. Introduction

Non-alcoholic steatohepatitis (NASH) is a progressive and irreversible form of non-alcoholic fatty liver disease (NAFLD), a chronic liver disease characterized by steatosis and accumulation of fat in the liver unrelated to the consumption of alcohol[1]. NASH is associated with inflammation and hepatocyte ballooning, and with risk of fibrosis that increases the risk of comorbidities and other complications for the patient[2]. The most frequent complications are cardiac and metabolic disorders, which are accompanied with a risk of cirrhosis and hepatocellular carcinoma, placing NASH as one of the major qualifiers for liver transplants[3−6]. The prevalence of NASH is estimated at 1.5%−6.45% of the worldwide population, which represents several hundreds of millions of patients[7]. However, this rate is likely underestimated, since NASH can only be diagnosed using a liver biopsy, which is highly invasive and poses many risks to the patient[8]. A recent literature review reported the prevalence of biopsy-confirmed NASH to be about 15.9%−68.3% among NAFLD patients, which comprises about 11.2%−37.2% of the general population[9]. Thus, NASH is a major public health concern with severe health consequences.

The liver is one of the key players in drug metabolism and elimination, which are governed by metabolizing enzymes and membrane transporters[10]. The impairment of liver function due to chronic liver diseases results in impairment of the absorption, distribution, metabolism, and excretion (ADME) processes[11]. NASH is known to cause disease-specific alterations to the function of numerous ADME enzymes and transporters[12,13]. A previous study demonstrated the altered pharmacokinetics and hepatobiliary elimination of morphine by indicating an abnormally high level of its metabolites (morphine-3- and morphine-6-glucuronide, M3G and M6G) in the plasma of NASH patients compared to healthy patients[14]. Therefore, given the importance of drug metabolizing enzymes and transporters in the pharmacokinetic processes, these changes can place NASH patients at risk of adverse drug reactions (ADRs) by reducing the hepatobiliary elimination and consequently increasing plasma retention and tissue exposure to drugs. On the contrary, reduction in efficacy/potency by slowing the biotransformation of the drug in active metabolites is also a risk. Several of these metabolic pathways are well characterized and many drugs are known to be substrates of these enzymes and/or transporters[12,13]. Thus, the risk of drug toxicity associated with NASH can be predicted based on the underlying mechanisms governing their metabolism and elimination. The aim of this work is to provide an overview of potential NASH-induced ADRs by identifying drugs that may have altered ADME properties, thereby facilitating the educated administration of drugs in NASH patients.

2. Adverse drug reactions in liver disease

ADRs in NASH patients are widely understudied, and knowledge of the onset of ADRs is lacking. Preclinical studies with rodent models attempt to study drugs whose pharmacokinetic profiles may be modified by NASH[15]. However, preclinical models have limitations in reflecting and predicting clinical outcomes. Some preclinical models may provide insight into a single characteristic of NASH, but none can provide a comprehensive overview of all changes in enzyme and transporter expression or function[15]. A small number of studies have reported drugs that present risk of ADRs in patients with preexisting liver diseases (Table 1[16-165]). The diseases were mainly NAFLD and hepatitis C, and some cases of NASH and alcohol abuse[16−33]. The main risk was drug-induced liver injury (DILI) due to increased hepatic exposure to the drug[16,17,21,27]. A large observational and longitudinal study conducted in 889 patients with DILI in the United States showed that 10% of these patients had known pre-existing chronic liver injury, mainly hepatitis C and NAFLD[21]. The authors of this study concluded that severity of the DILI tended to be higher in patients with pre-existing liver disease, even though this result did not reach statistical significance. However, mortality was significantly higher in this group compared to the other patients[21]. Another prospective study conducted in Italy compared 174 patients with chronic hepatitis due to hepatitis C virus to 74 NAFLD patients and showed that abdominal obesity influenced acute drug-induced liver damage with NAFLD patients suffering from hepatotoxicity to different drugs (antihypertensives, antiplatelets, antimicrobials, non-steroidal anti-inflammatories, and proton pump inhibitors)[27].

Drugs that have been reported as a risk for causing ADRs in patients with liver diseases or described as involved in ADRs in at least one clinical case are summarized in Table 1. The analgesic acetaminophen, also known as paracetamol, used at therapeutic doses can induce mild to moderate hepatic cytolysis, and even fulminant hepatitis in a few patients[166,167]. These ADRs preferentially occur in patients with preexisting factors affecting the liver, especially in obese patients with NAFLD[17]. This toxicity is explained by the metabolic pathways of acetaminophen. The drug is primarily metabolized in the liver into glucuronide and sulfate conjugates, but a small part is oxidized to *N*-acetyl-*p*-benzoquinone imine, which is highly toxic, but normally detoxified by hepatic glutathione reduction[168]. Acetaminophen is oxidized into *N*-acetyl-*p*-benzoquinone imine by cytochrome 2E1 (CYP2E1), whose activity is increased in several pathologies including NAFLD[169]. Diseases producing these kinds of changes lead to a higher risk of toxicity to acetaminophen, even when used at common pharmacological doses.

Another drug frequently reported with liver toxicity is the folate antagonist methotrexate. Methotrexate-induced liver toxicity is linked to chronic forms of liver injury, such as NAFLD[17,26]. The exact mechanism underlying this toxicity is still unclear, although one hypothesis is that methotrexate causes mitochondrial dysfunction[16,17]. However, methotrexate is a substrate for a wide range of drug transporters (Table 1) and their expression and/or function is altered in NAFLD[170]. Another possible explanation for methotrexate toxicity is that there is a disruption in hepatobiliary elimination due to transporter activity alterations in chronic liver diseases. This assumption is supported by a preclinical study performed in a methionine-choline-deficient diet-induced rodent model of NASH that showed changes in the expression and localization of transporters responsible for the disposition of methotrexate[171]. The authors also observed increased hepatic and renal toxicity in NASH rats, as well as reduced gastrointestinal toxicity, which coincides with reduced fecal elimination of methotrexate[171].

Drug metabolism is governed mainly by the CYP (phase I), UDP-glucuronosyltransferase (UGT, phase II), and sulfotransferase (SULT, phase II) enzymes which convert lipophilic molecules into more water-soluble metabolites for urinary or biliary clearance[172]. Some of the metabolites are pharmacologically active and may also result in toxicity. A study demonstrated that 73% of the 200 most prescribed drugs were eliminated primarily through hepatic metabolism[172]. Many drugs and metabolites are also substrates of transporters that mediate their distribution across

Table 1 Drugs with adverse drug reactions reported in patients with liver disease and the transporters when involved in their pharmacokinetics. For each drug, the information was collected and verified from the database Drugbank, and the research was then extended by looking in Pubmed for the name of the drug and "transporter". Some transporters may be minor contributors to the pharmacokinetics of the drugs and the absence of data does not necessarily mean that the drug is not a substrate of the transporter, but merely that the information could not be collected or verified.

Drug	BCRP (*ABCG2*)	ENT1 (*SLC29A1*)	ENT4 (*SLC29A4*)	MATE1 (*SLC47A1*)	MATE2 (*SLC47A2*)	MRP1 (*ABCC1*)	MRP2 (*ABCC2*)	MRP3 (*ABCC3*)	MRP4 (*ABCC4*)	MRP5 (*ABCC5*)	MRP7 (*ABCC10*)	MRP8 (*ABCC11*)	OAT1 (*SLC22A6*)	OAT2 (*SLC22A7*)	OAT3 (*SLC22A8*)	OAT4 (*SLC22A11*)	OATP1A2 (*SLCO1A2*)	OATP1B1 (*SLCO1B1*)	OATP1B3 (*SLCO1B3*)	OATP2B1 (*SLCO2B1*)	OATP4C1 (*SLCO4C1*)	OCT1 (*SLC22A1*)	OCT2 (*SLC22A2*)	OCT3 (*SLC22A3*)	P-gp (*ABCB1*)	Ref. *In vitro* (v)	Ref. *In vivo* human (h)
Acetaminophen [16–20]																											
Amoxicillin – Clavulanate [21]																											
Azathioprine [21]																											
Azithromycin [21]																									h		34
Carbamazepine [21]							h																		h		35,36
Cefadroxil [21]																			v							37	
Cefalexin [21]				v																						38	
Cefazolin [21,39]									v						v			v	v							37,40,41	
Cefotaxime [21]									v																	41	
Ciprofloxacin [21]	v								v																	42–45	
Darunavir [21]																	v	v	v						v	46–48	
Deferasirox [21]	h						h																				49–52
Diclofenac [21]														v					v							53,54	
Disulfiram [21]																											
Duloxetine [21]																											
Efavirenz – Emtricitabine – Tenofovir Disoproxil Fumarate [21]				v			h		v		v	v														55 56,57	58
Erythromycin [21]							v, h		v					v			v	v, h	v, h						v	59–63	59,61,62
Escitalopram [21]																											
Ezetimibe [21]	v						v	v										v, h								64,65	65
Fenofibrate [21]																											
Fluconazole [21]																											
Fosinopril [16,17,27]																											
Glibenclamide [21]	v					v		v									v	v		v					v	66–72	
Hydralazine [21]																											
Infliximab [21]																											
Interferon [21]																											
Isoniazid [21]																											
Leflunomide [21]	v																									73	
Levofloxacin [21]																	v								v	74–76	
Lopinavir –						v	v										v	v	v						v	48,77–79	
Ritonavir [21]							v																		v	80,81	
Losartan [16,17,27]																									v	82	
Meloxicam [21]																											
Mercaptopurine [21]		v							v	v																83–85	
Metformin [16,21,22]	v		v	v	v, h																		v, h	v	v	v	72,86–92	93,94
Methotrexate [16,23–26]	v					v	v	v	v	v		v	v	v	v	v	v	v, h	v		v				v	95–118	119
Metoclopramide [21]																									v	120	
Micafungin [21]																											
Minocycline [21]																											
Moxifloxacin [21]																											
Nelfinavir [21]																									v, h	121	122
Nevirapine [21]																									h		123
Nicotinic acid [21]																											
Nitrofurantoin [21]	v																									124	
Omeprazole [16,17,27]																									v	125	
Oxacillin [21]																											
Oxaprozin [21]																											
Piperacillin –													v		v											126	
Tazobactam [16,17,21,27]													v		v											126	
Propylthiouracil [21]																											
Raloxifene [16,28]																		v, h	v						v	127–129	127

(continued on next page)

Table 1 *(continued)*

Ranitidine [21]								v	v	v					v	v	v	130–132	
Rifampicin [21]											v	v						133	
Rosiglitazone [16,29,30]																	v	72	
Simvastatin [21]					h						v, h						h	134,135	136–138,138
Sorafenib [16,31]	v																v	139,140	
Sulfasalazine [21]	v				v													141	
Stavudine – Didanosine [16,17,32]																			
Tamoxifen [16,21,33]					h												v, h	142	143–145
Telithromycin [17,27]																			
Temozolomide [21]				v														146	
Ticlopidine [16,17,27]																			
Valaciclovir [21]										v								147	
Valproic acid [21]																			
Vincristine [21]				v	v		v										v	148–156	
Zidovudine – Lamivudine [21]	v					v		v	v	v	v						v	147,157–160	
		v												v, h	v	v		161–164	165

ABC, ATP-binding cassette; BCRP, breast cancer resistance protein; ENT, equilibrative nucleoside transporter; MATE, multidrug and toxin extrusion; MRP, multidrug resistance-associated protein; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P-gp, P-glycoprotein; SLC, solute carrier.

biological interfaces, including hepatic membranes for hepatobiliary elimination[173]. In the liver, efflux transporters from the ATP-binding cassette (ABC) family work together with the solute carrier (SLC) family, which is mostly composed of uptake transporters[173]. It is known that enzyme or transporter alterations that are frequent in liver diseases significantly impact drug metabolism and elimination[170,174,175]. Bibliographic research was performed to identify if the drugs reported as a risk in patients with liver diseases are substrates of drug transporters and/or metabolizing enzymes. We proceed in the same way for each drug: the research began by collecting and verifying the information presented in the database Drugbank, and then extended by looking in Pubmed for the name of each drug and "transporter" or "metabolism". Tables 1 and 2 present the information collected through this research. The absence of data does not necessarily mean that the drug is not a substrate of the transporter or enzyme, but merely that the information could not be collected or verified. These tables strive to be as exhaustive as possible in reporting any transport and/or metabolism described in the literature and aim at providing an overview of the drug transporters and/or metabolizing enzymes involved in the pharmacokinetics of these drugs. However, some of them may be minor contributors to disposition with limited relevance to overall role in pharmacokinetics.

Among the 71 drugs reported with ADRs in patients with hepatic impairment, 54 are substrates of major drug transporters (Table 1) and/or metabolizing enzymes (Tables 2[16–33,39,70,78,123,128,143,144,176-281]). Therefore, these pathological changes in the liver may play a role in the onset of ADRs. The liver disease underlying the onset of these ADRs was mainly NAFLD, and changes in ADME processes are identified in this disease[282]. Since NASH is the progressive form of NAFLD, it is reasonable that similar ADRs may occur due to changes in the ADME processes.

3. Predicting potential adverse drug reactions in NASH

Disease-specific alterations to the function of numerous enzymes and transporters have previously been characterized in NASH[12,13,170,283–286] (Fig. 1). Several studies have analyzed changes in the mRNA and protein expression of enzymes and transporters in NASH patients and some had functional impact on drug disposition[12,13,170,283–286]. An *in vitro* study using microsomes isolated from human liver samples determined the enzymatic activity of several cytochromes by means of specific drug substrates[285]. This experiment evidenced significant decreases in the phenacetin *O*-dealkylation by CYP1A2 and the mephenytoin 4′-hydroxylation by CYP2C19 as well as significant increases in the coumarin hydroxylation by CP2A6 and diclofenac 4′-hydroxylation and hydroxytolbutamide metabolite formation by CYP2C9[285]. A clinical study conducted in pediatric subjects with NASH showed that pharmacokinetic curves of caffeine, losartan, omeprazole, and midazolam—metabolized respectively by CYP1A2, CYP2C9, CYP2C19, and CYP3A4—were differentiated among the normal with a 71% decrease of the area under the curve (AUC) ratio (metabolite AUC divided by the parent AUC) for omeprazole in NASH patients compared with healthy subjects, indicating a significant loss of CYP2C19 function[283]. Another clinical study using midazolam as a probe of CYP3A4 enzymatic activity evidenced that mean concentrations of the drug were 2.4-fold greater in NASH patients compared with control subjects[286]. Regarding the phase II metabolism enzymes, a study conducted in human liver samples identified some changes in mRNA and protein levels of the two major phase II class of enzymes, UGTs and SULTs. However, measurement of the metabolism of acetaminophen revealed no significant change neither in glucuronidation by UGTs, nor in sulfonation by SULTs in the NASH samples compared to control samples[287].

Given their interplay and the overlap of substrates, assessing the activity of hepatic transporters *in vivo* and their influence on drug pharmacokinetics is complex[288]. Moreover, the protein expression of several hepatic transporters is altered in NASH, which may further influence drug pharmacokinetics. A recent study assessed the NASH-induced changes on the expression of transporter proteins by means of targeted proteomic analysis on human liver tissue samples[282]. The results showed decreases in protein levels of several important SLC transporters involved in the uptake of drugs from blood to hepatocyte at the basolateral

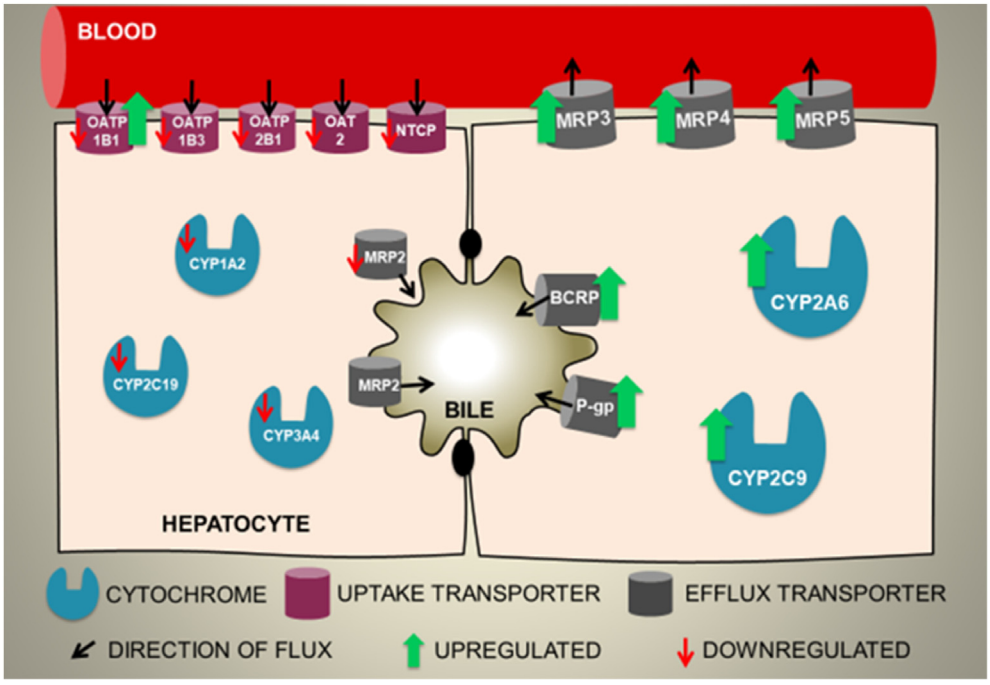

Figure 1 Hepatic metabolizing enzymes and drug transporters altered in NASH patients. BCRP, breast cancer resistance protein; CYP, cytochrome; MRP, multidrug resistance-associated protein; NTCP, Na^+-taurocholate cotransporting polypeptide; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; P-gp, P-glycoprotein; SLC, solute carrier.

side[282]. These changes were observed in NASH samples for the organic anion transporting polypeptides (OATPs), including the three major OATPs expressed in the liver (OATP1B1, OATP1B3, and OATP2B1), the organic anion transporter 2 (OAT2), and the sodium taurocholate protein (NTCP)[282]. However, the impact of the disease on the OATPs remains unclear since another study confirmed the decrease in OATP1B3 protein expression but the decrease in OATP2B1 was not statistically significant and the protein expression was increased for OATP1B1[289]. Another study conducted *in vitro* on human liver samples showed that most ABC transporters, expressed both on basolateral and canalicular membranes of hepatocytes, exhibited increased protein expressions in NASH[170]. The increase was observed for breast cancer resistance protein (BCRP) and for P-glycoprotein (P-gp), which mediate the biliary efflux of substrates from the liver into the bile at the canalicular side of the hepatocyte, and also for the multidrug resistance-associated proteins (MRP) 3, MRP4, and MRP5, which are involved in the basolateral efflux of their substrates from the liver into blood[170]. Conversely, MRP2 is the only ABC transporter that exhibits decreased efflux due to a mis-localization of the protein that appeared internalized into vesicles away from the canalicular membrane[170]. This observation was confirmed by a second *in vitro* study showing an inappropriate localization of the MRP2 transporter in NASH patients, as well as a significant increase in the protein expression of MRP3[284] also observed in the proteomic analysis[282].

Many drugs are substrates of these transporters and/or enzymes, which play a key role in drug/metabolite elimination. Some functional impacts of these modifications have been observed in clinical studies and physiologically-based pharmacokinetic (PBPK) modeling. A study conducted in a pediatric population confirmed that the disposition of acetaminophen was altered in NASH patients[284]. This observation appeared to be related to changes in metabolizing enzyme activity and changes to basolateral MRP activity[284]. In another study, PBPK modeling demonstrated that alterations in morphine metabolites were correlated with changes in the activity of hepatic transporters[282]. Morphine kinetics are primarily dependent on organic cation transporter (OCT) 1[290], whose activity is unaffected by NASH[282]. Studies have shown that the disease has no impact on the kinetics of the parent molecule, while the ADME kinetics for morphine glucuronide conjugates (M3G and M6G) were significantly affected[14,282]. For M3G and M6G, there was an increase in the area under the curve predicted by the PBPK model by approximately 27% in NASH patients compared to healthy patients[282]. This increase was explained by the disruption in hepatic disposition of these two metabolites, which relies on several transporters, including the OATPs and MRP3, which play a major role in their release from hepatocytes to the blood[14,282,291]. In the same study, the PBPK model was applied to ^{99m}Tc-mebrofenin, a radioactive drug used for hepatobiliary scintigraphy imaging, whose ADME kinetics are entirely dependent on transporters modified by NASH[282]. Indeed, the hepatic uptake of ^{99m}Tc-mebrofenin is mediated by OATP1B1 and OATP1B3, while its efflux involves MRP2 and MRP3 at the canalicular and basolateral sides, respectively[292]. The model predicted a 45% decrease in ^{99m}Tc-mebrofenin blood clearance in NASH patients compared with healthy subjects, which was similar to the change observed in a previous clinical study (49%)[293]. This modification appeared to be mainly driven by the decrease in the OATP1B1/3 uptake activity[282].

Based on these data, the dysfunction in metabolizing enzyme and transporter activities can impact the pharmacokinetics of other drugs eliminated through the same pathways and can be involved in the onset of ADRs. According to this hypothesis, we aimed to identify a list of sensitive drugs whose ADME kinetics could be

Table 2 Drugs with adverse drug reactions reported in patients with liver disease and the enzymes when involved in their metabolism. For each drug, the information was collected and verified from the database Drugbank, and the research was then extended by looking in Pubmed for the name of the drug and "metabolism". Some enzymes may be minor contributors to the pharmacokinetics of the drugs and the absence of data does not necessarily mean that the drug is not a substrate of the enzyme, but merely that the information could not be collected or verified.

Drug	CYP1A1 (*CYP1A1*)	CYP1A2 (*CYP1A2*)	CYP1B1 (*CYP1B1*)	CYP2A6 (*CYP2A6*)	CYP2B6 (*CYP2B6*)	CYP2C8 (*CYP2C8*)	CYP2C9 (*CYP2C9*)	CYP2C18 (*CYP2C18*)	CYP2C19 (*CYP2C19*)	CYP2D6 (*CYP2D6*)	CYP2E1 (*CYP2E1*)	CYP3A4 (*CYP3A4*)	CYP3A5 (*CYP3A5*)	CYP3A7 (*CYP3A7*)	GST (*GST*)	SULT1A1 (*SULT1A1*)	SULT1A3 (*SULT1A3*)	SULT1C4 (*SULT1C4*)	SULT1E1 (*SULT1E1*)	SULT2A1 (*SULT2A1*)	UGT1A1 (*UGT1A1*)	UGT1A3 (*UGT1A3*)	UGT1A4 (*UGT1A4*)	UGT1A6 (*UGT1A6*)	UGT1A8 (*UGT1A8*)	UGT1A9 (*UGT1A9*)	UGT1A10 (*UGT1A10*)	UGT2B4 (*UGT2B4*)	UGT2B7 (*UGT2B7*)	UGT2B15 (*UGT2B15*)	UGT2B17 (*UGT2B17*)	Ref. *In vitro* (v)	Ref. *In vivo* human (h)
Acetaminophen [16–20]		v								v	v, h	v				v	v	v	v	v	v, h			v, h		v, h			v, h			176–184	185–189
Amoxicillin – Clavulanate [21]																																		
Azathioprine [21]															h																			190
Azithromycin [21]												v	v																	v			191	
Carbamazepine [21]		v		v	v						v	v, h	h																				192–194	36,195, 196
Cefadroxil [21]																																		
Cefalexin [21]																																		
Cefazolin [21,39]																																		
Cefotaxime [21]																																		
Ciprofloxacin [21]												v																					197	
Darunavir [21]																																		
Deferasirox [21]	h	h								h											h													
Diclofenac [21]		v			v	v	v	v	v			v										v				v		v				198–200	
Disulfiram [21]												v																					201	
Duloxetine [21]		v, h					v			v, h																							202,203	203,204
Efavirenz –				v	v																												205,206	
Emtricitabine – Tenofovir Disoproxil Fumarate [21]																																		
Erythromycin [21]												v		v																			207–209	
Escitalopram [21]									v, h	v, h		v																					210	211,212
Ezetimibe [21]																						v	v							v	v		213	
Fenofibrate [21]																										v							214	
Fluconazole [21]																																		
Fosinopril [16,17,27]																																		
Glibenclamide [21]						v	v, h	v				v	v	v																			70,215, 216	217
Hydralazine [21]																																		
Infliximab [21]																																		
Interferon [21]																																		
Isoniazid [21]																																		
Leflunomide [21]		h					h		h																									218–221
Levofloxacin [21]																																		
Lopinavir – Ritonavir [21]										v		v																					78,222	
Losartan [16,17,27]												v	v																				223	
Meloxicam [21]							v, h					v																					224,225	226,227
Mercaptopurine [21]																																	228,229	230,231
Metformin [16,21,22]																																		
Methotrexate [16,23–26]																																		
Metoclopramide [21]		v				v	v		v	v, h		v																					232,233	234
Micafungin [21]																																		
Minocycline [21]																																		
Moxifloxacin [21]																																		
Nelfinavir [21]									v, h																								235	236
Nevirapine [21]				v	h				v	v		v	h	v																			209,237	123,238
Nicotinic acid [21]																																		
Nitrofurantoin [21]																																		
Omeprazole [16,17,27]						v	v	v	v, h			v	v																				239–243	244
Oxacillin [21]																																		
Oxaprozin [21]																																		
Pipercillin – Tazobactam [16,17,21,27]																																		
Propylthiouracil [21]																																		
Raloxifene [16,28]																	v					v				v	v	v					128,245–247	

(continued on next page)

Table 2 *(continued)*

Ranitidine[21]																																	
Rifampicin[21]																																	
Rosiglitazone[16,29,30]						v, h	v				v	v																				248,249	249–251
Simvastatin[21]												v, h	h																			252	253–257
Sorafenib[16,31]												v, h														v						258	259
Sulfasalazine[21]																																	
Stavudine – Didanosine[16,17,32]																																	
Tamoxifen[16,21,33]	v	v	v	v	v		v		v	v, h	v	v	v, h			h									v		v		v			260–263	143,144,264–267
Telithromycin[17,27]												v, h																				258	269,270
Temozolomide[21]																																	
Ticlopidine[16,17,27]		v					v		v	v		v																				271	
Valaciclovir[21]																																	
Valproic acid[21]				v	v		v																v	v	v		v		v			272–275	
Vincristine[21]												v	v, h																			276,277	278
Zidovudine – Lamivudine[21]							v																					v	v		v	279–281	

CYP, cytochrome; GST, glutathione *S*-transferase; SULT, sulfotransferase; UGT, UDP-glucuronosyltransferase.

disrupted (Table 3[37,48,80,96,101–103,114,134–136,152,154,288,292-586]). We applied the same methodology as for Tables 1 and 2 to perform bibliographic research to identify the drugs that have been described as substrates for transporters or metabolizing enzymes modified in NASH. Given the enormous number of drug substrates of these transporters and/or enzymes, we decided to limit this list to the drugs with at least four transporters and/or enzymes involved in their pharmacokinetics. This threshold is arbitrary but we considered that multiple mechanisms must be involved because of the overlapping substrate specificities, and the specific number of four represents a list of less than 100 drugs that might be the most likely at risk in NASH disease. We also decided to include animal data for transporters with appropriate orthologs in this research, which can be predictive of clinical outcomes. Table 3 presents the 71 drugs identified with kinetics highly dependent on transporters and/or enzymes modified in NASH and associated with an important risk of disruption in their pharmacokinetic process.

NASH is an underdiagnosed disease due to the invasiveness of a liver biopsy for confirmation, and to the lack of treatments[587]. Few patients go through the full diagnostic procedure, thus, it is difficult to identify statistically significant ADRs in small populations. Consequently, although there is little to no evidence to indicate a risk of ADRs for these drugs in NASH patients, their ADME properties may easily be affected. Changes in drug disposition and/or elimination in NASH may result in the onset of ADRs with potential DILI or other toxicities or, on the contrary, decreased drug efficacy/potency. If these pharmacokinetic changes are identified and their intensity quantified, an adjustment of their dose could be considered in NASH patients. However, the more transporters and enzymes that are impacted, the more unpredictable the changes in kinetics will be. The drugs presented in Table 3 are substrates for four or more transporters/enzymes that may be modified in NASH, placing them at higher risk of kinetic disruption.

Several considerations should be made for each drug to assess the risk of kinetic disruption. First, the potency of the drug should be considered to determine the activity and potential toxicity of the drug. Drugs with a narrow therapeutic index (NTI) should be used with caution. Drugs with NTIs are known to have high intra- and inter-individual pharmacokinetic variability with greater risk of overdosing if not administered with caution for each patient[588]. Their doses must be adjusted for each patient to prevent ADRs[588]. NTI drugs include several different classes such as immunosuppressive, antiepileptic, or anticoagulant drugs[589,590]. Our list includes some of these drugs that may display modified ADME in NASH, such as mycophenolic acid, phenytoin, and warfarin (Table 3). Therefore, clinicians should use these drugs with greater care in NASH patients given their potential risk for toxicity. The consequences of inaccurate dosing may also have indirect effects, for example if a disease disrupts metabolism and elimination. The anticancer drug irinotecan is a prodrug that is metabolized into its active metabolite SN-38. This reaction is catalyzed by carboxylesterase, whose activity is not known to be modified by NASH disease[447]. However, irinotecan is metabolized through other pathways that involve enzymes, such as CYP3A4 and CYP3A5[447]. A decrease in CYP3A4 activity could decrease the biotransformation of irinotecan into its inactive metabolites and increase its bioavailability to carboxylesterase. Consequently, higher irinotecan levels will lead to higher SN-38 levels in the plasma. Moreover, SN-38 is a substrate of transporters that are affected by NASH, including OATP1B1, OATP1B3, MRP2, P-gp, and BCRP[591–597]. This may also result in changes in SN-38 pharmacokinetics even though UGT1A1, the main enzyme in charge of SN-28 metabolism[598–601], does not seem to be affected by NASH disease[287]. Conversely, the anticancer prodrug ifosfamide needs to be bioactivated by specific cytochromes to form therapeutically active cytotoxic metabolites[602]. CYP3A4 seems to be the driving force of this bioactivation[354] and the decrease in CYP3A4 activity observed in NASH may result in a loss of efficiency of the chemotherapeutic treatment. As a matter of fact, some of the drugs presented in this list may also have low toxicity with minimal-to-no ADRs, even when plasma retention is increased. However, consequences other than ADRs may also occur, such as a reduction in the efficacy/potency of the treatment in NASH patients. Warfarin for example is almost fully eliminated

Table 3 Drugs with risk of pharmacokinetic disruptions in non-alcoholic steatohepatitis. For each drug, the information was collected and verified from the database Drugbank, and the research was then extended by looking in Pubmed for the name of the drug and "transporter" or "metabolism". Some transporters and/or enzymes may be minor contributors to the pharmacokinetics of the drugs and the absence of data does not necessarily mean that the drug is not a substrate of the transporter or enzyme, but merely that the information could not be collected or verified.

Drugs	BCRP (*ABCG2*)	MRP2 (*ABCC2*)	MRP3 (*ABCC3*)	MRP4 (*ABCC4*)	MRP5 (*ABCC5*)	NTCP (*SLC10A1*)	OAT2 (*SLC22A7*)	OATP1B1	OATP1B3	OATP2B1	P-gp (*ABCB1*)	CYP1A2 (*CYP1A2*)	CYP2A6 (*CYP2A6*)	CYP2C9 (*CYP2C9*)	CYP2C19	CYP3A4 (*CYP3A4*)	Ref.		
																	In vitro (v)	*In vivo* animal (a)	*In vivo* human (h)
Acenocoumarol											h	v		v, h	v		294		295,296
Ambrisentan		v						v	v		v					h	297,298		299
Amitriptyline											v, a	v		v	v	v	300–303	304–306	307
Antipyrine												v	v	v	v	v	308,309		
Apixaban	v										v, h	v				v, h	310–312		313
Asunaprevir								v, h		v, h	a					v	314,315	315	314
Atorvastatin	v	v		v		v		v	v	v	v					v, h	134,316–322		136,323
Axitinib								v	v		v	v			v	v, h	324,325		326
Bortezomib											v	v		v	v	v, h	327,328		329
Bosentan								v	v		v			h		h	297,330		331,332
Canaglifozin	v	v									v			v		v	333		
Celecoxib	v										v			v, h		v	334–337		335,338
Cefoperazone	v	a						v	v								37,339,340	339	
Clopidogrel											v	v		v	v, h	v, h	341–343		344–348
Clozapine												v	h	v	v	v	349,350		351
Cyclophosphamide				v										v	h	v	352–354		355
Docetaxel	v							a	v, a		v					v, h	356–361	362	363
Doxepin											a	v		v, h	v, h		364	365	366
Doxorubicin	v	v									v					v	102,114,367–370		
Erlotinib	v, a									v, h	v, a	v				v, h	371–375	371,372,376	375,377
Estradiol		v, a										v		v	v	v	378–382	383	
Estrone											v	v, a		v		v	378,381,384–389	390	
Ethinylestradiol											v	v		v	v	v	389,391		
Etoposide	v	v	v								v, a	v				v, a	392–399	392,400	
Fexofenadine	a	a	a						v		v, a						401–403	401,404,405	
Flunitrazepam													v	v	v, h	v	406		407
Fluorouracil	v				v	v						v	v				408–411		
Fluoxetine												v		v	v, h	v	412		413

(continued on next page)

Table 3 *(continued)*

Fluvastatin		v				v		v	v	v				v		v	414–418	
Folic acid	v		v	v	v												96,101,113,419	
Gadoxetic acid		v, a	v			v		v, h	v, h								420,421	421	422,423
Haloperidol											v			v	v	v	424–427	
Ifosfamide													v	v	v	v	354,428	
Imatinib	v, a								v		v, a					h	429–436	431,437,438	439
Imipramine											v, a	v			v, h	v	440–443	444	445,446
Irinotecan	v						v				v, a					v	447–451	452,453	
Lonafarnib												v	v	v	v	v	454,455		
Loratadine											v, a	v		v	v	v, a	456–459	460	
Lorcaserin												v	v		v	v	461		
Lovastatin	h	v						v, h								h	417,462		463,464
Mebrofenin		v, a	v					v, a, h	v, a								292,465–468	288,292,469,470	293
Methadone												v		v	v, h	v, h	471–476		477–479
Montelukast										v				v	v	v	480,481		
Mycophenolic acid		a, h							h		a					v	482	483	484
Nicotine												v	v	v		v	485		
Nortriptylline											a, h	v			v	v	303,486	487	488
Olmesartan		v, a		v				v	v								489,490	490	
Paclitaxel		v					v	v, a	v, a		v, h					v	102,152,154, 361,408,491–503	491	153
Paritaprevir	v							v	v		v, h					v, h	504		505
Perphenazine												v		v	v	v	506		
Phenytoin		a, h									v, h			v, h	v	v	507–509	510	511,512
Pitavastatin	v, a					v		v, h	v, h								513–516	514	517
Pravastatin		v						v		v	v						134,135,417, 516,518–522		
Promazine												v		v	v	v	523,524		
Propranolol											v	v			v	v	525–529		
Rosuvastatin	h	v		v	v	v		v, h	v	v				v		v	320,417,530–533		534
Rucaparib	v, a										v, a	v				v	535,536		
Saquinavir		v							v	v	v, a					v	48,80,537–544	543,545	
Selumetinib	v,										v,				h	h	546		547,548

(continued on next page)

Table 3 *(continued)*

	a					a													
Sildenafil	v					v			v	v	v	549–553							
Tenofovir alafenamide	h			v	v	h						554					555		
Terbinafine							v		v	v	v	556							
Testosterone	v				v, h				v	v	v	557–561					562		
Trastuzumab deruxtecan	v			v	v	v						563							
Triclabendazole							v		v	v	v	564							
Trimethoprim						v	v		v		v	565,566							
Valsartan		v, a		v	v				v, h			567–569	569				570		
Verapamil						v, a	v		v		v	571–573	573–575						
Vortioxetine								v	v	v	v	576							
Warfarin							v		v, h	v	v	577–581					582–585		
Zolpidem							v		v	v	v	586							

ABC, ATP-binding cassette; BCRP, breast cancer resistance protein; CYP, cytochrome; MRP, multidrug resistance-associated protein; NTCP, Na^+-taurocholate cotransporting polypeptide; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; P-gp, P-glycoprotein; SLC, solute carrier.

through the urine in the form of metabolites[603–605]. The enzymes responsible for this metabolism are cytochromes affected by NASH (CYP1A2, CYP2C9, CYP2C19, and CYP3A4)[577]. CYP2C9 is likely to be the principal form of human liver cytochromes which modulates the *in vivo* anticoagulant activity of the drug[583]. Since *in vitro* and *in vivo* studies demonstrated increases in CPY2C9-mediated metabolism of several drugs in NASH[283,285], therapeutic failure may occur and especially with NTI drugs as warfarin. Other interactions could also happen with diagnostic agents as mebrofenin, which is used in special applications to study gallbladder and its ejection fraction to diagnose cholecystitis in patients with biliary pain[606,607]. Because blood clearance of mebrofenin could be decreased significantly in NASH patients (45%−49%), this might result in reduced biliary excretion and a decrease in the release from the blood to the gallbladder[282,293,608]. Consequently, this may interfere with the examination of gallbladder ejection fraction and lead to an incorrect diagnosis.

The drugs listed in Table 3 may be at risk for ADRs in NASH patients, but the level of risk for each of the drugs may be different for several reasons. Here, we reported drugs that are substrates of transporters and/or enzymes affected in NASH; however, some studies only used *in vitro* models and may not be clinically relevant. For example, *in vitro* studies conducted in human liver microsomes described the involvement of several cytochromes in the metabolism of the tricyclic antidepressant imipramine, mainly CYP1A2 and CYP3A4[441,443]. However, a clinical study carrying out phenotypic tests did not find any evidence of either CYPlA2 or CYP3A4 activity in the *N*-demethylation of imipramine[446]. Another discrepancy to consider in the results presented in Table 3 is the level of contribution of each transporter and/or enzyme to the pharmacokinetic process. The phenothiazine neuroleptic promazine for example appears in Table 3 to be metabolized by four cytochromes whose activity could be modified in NASH, with potentially opposite consequences. The activity of CYP2C9 is expected increased in NASH and could offset the decrease in the activity of the other enzymes. However, the *in vitro* data showed that CYP2C9 contributed only to a lesser degree to promazine metabolism[523], suggesting that the decrease in the other enzymes activities (CPY1A2, CYP3A4, and CYP2C19) is probably the driving force toward a decrease in promazine metabolism and possibly increase in plasma concentrations.

Another point to consider is that some of these transporters are expressed in many tissues and the impact of transporters on the drugs listed in Table 3 may not be the same at different locations. As an example, P-gp is expressed in the intestinal barrier where it plays an important role in absorption by limiting or restricting the oral bioavailability of many of drugs[609]. The role of P-gp and its pharmacokinetic impact on the absorption of drug substrates of this transporter is well known. P-gp is also expressed at the canalicular side of the hepatocyte, where its expression is slightly increased in NASH. However, the functional impact of NASH on P-gp activity and the pharmacokinetic consequences on the biliary excretion of drugs remains elusive. Thus, most of the drugs listed in Table 3 as P-gp substrates were investigated in studies exploring the intestinal role of P-gp. Assessing the hepatic role of P-gp is complex since the protein is expressed on the canalicular membrane distal from the blood in this tissue and there is little information about its function in NASH[610]. As a result, the changes observed in protein expression due to NASH may not necessarily result in pharmacological changes that are clinically relevant for each drug, especially considering the interplay between transporters. Nevertheless, these drugs should be used with strict vigilance in NASH patients given the increased risk of dysregulation in their ADME processes.

Lastly, another danger to consider is the increased risk of drug−drug interactions. NASH is considered a complex and chronic disease with several comorbidities such as dyslipidemia, diabetes or heart disease[611]. As such, polypharmacy is a concern among NASH patients and will necessitate further studies. The dysregulation in drug and enzyme activities that can occur in NASH may also precipitate the onset of drug−drug interactions between these different drugs and might result in unexpected ADRs associated with these drugs, even when used at pharmaceutical doses. Recently, several preclinical studies also demonstrated drug−herb interactions in preclinical models of

NASH[612−615]. The botanical natural product silymarin for example can be used for the treatment of NASH disease and contains flavonolignans that are both substrates and inhibitors of the OATP hepatic transporters[612,613]. Preclinical studies showed that the use of silymarin in a NASH model of rats caused an additive increase in pitavastatin plasma concentrations associated to a decrease of its biliary excretion, due to the silymarin−pitavastatin interaction at the OATP level, whose protein expression is also affected by the disease[612,613]. Another study demonstrated that evodiamine, a quinolone alkaloid extracted from a traditional Chinese herb that may be used in NASH for anti-obesity, anti-inflammatory, and anti-cardiovascular properties, affected the pharmacokinetics of pravastatin only in NASH rats by enhancing the OATP hepatic distribution of the drug, probably previously decreased by the disease[615]. Finally, a rodent study showed that the risk of hepatotoxicity related to coadministration of simvastatin and *Gardenia jasminoides* J. Ellis (frequently used together in patients with multi-morbidity, such as stroke rehabilitation patients with NASH) was lowered in the NASH group compared to the control group that might be partially explained by the upregulation of P-gp in the NASH animals[614]. These interactions may also occur in patients and especially patients with NASH who are often inclined to take botanical dietary supplements because of their chronic liver disease and the related comorbidities. This study is focused on NASH disease, but these kinds of interactions and drug disruptions are not specific to this disease. This approach may be enlarged to any other liver disease impacting the function of metabolism enzymes and drug transporters. Some of these changes have already been reported in hepatitis C virus infection and alcohol-associated liver disease for example[174,175,616] but this topic is not fully investigated yet and many vulnerabilities may apply to other liver diseases.

4. Conclusions

NASH patients are at an increased risk of ADRs due to the pharmacokinetic alterations associated with this liver disease. Understanding the mechanisms underlying the ADME processes may help prevent the onset of ADRs in NASH patients and promote the use of personalized treatments. Here, we present a list of drugs whose metabolism and/or elimination are dependent on these processes and that may pose an increased risk of ADRs in NASH patients. This list is a preliminary step that requires further investigation and these drugs should be studied on a larger scale to assess the individual risk of each one. However, this comprehensive list of drugs is a tool to help clinicians identify drugs with a potential for altered pharmacokinetics that may result in the onset of ADRs in NASH patients. When confirmed, the drugs should then be carefully used in this population and the dose selection adjusted to the disease. This is a first step toward precision medicine in NASH patients.

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Author contributions

Solène Marie performed the study and wrote the article. Kayla L. Frost, Raymond K. Hau, Cassandra M. Myers, Jailyn Izu, Lucy Martinez-Guerrero, Stephen H. Wright, and Nathan J. Cherrington contributed to the writing of the article. All authors approved the final article.

Conflicts of interest

The authors declare no conflicts of interest.

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