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Review Article

Drug-induced Fatty Liver Disease: Pathogenesis and Treatment

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Abstract

Metabolic dysfunction-associated fatty liver disease (commonly known as MAFLD) impacts global health in epidemic proportions, and the resulting morbidity, mortality and economic burden is enormous. While much attention has been given to metabolic syndrome and obesity as offending factors, a growing incidence of polypharmacy, especially in the elderly, has greatly increased the risk of drug-induced liver injury (DILI) in general, and drug-induced fatty liver disease (DIFLD) in particular. This review focuses on the contribution of DIFLD to DILI in terms of epidemiology, pathophysiology, the most common drugs associated with DIFLD, and treatment strategies.

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Introduction

Drug-induced liver injury (DILI) represents a significant health problem in the USA and many European countries.[1] In prospective and retrospective DILI studies,[2] the annual incidence has been reported as 2.7 per 100,000 people. Furthermore, in many countries, DILI has been associated with acute liver failure. The risk factors for DILI include numerous interrelated factors, such as advanced age, sex, drug dose, genetic factors, concomitant drugs, excessive alcohol consumption, nutrition, pre-existing liver disease, diabetes mellitus, human immunodeficiency virus infection, and kidney failure.[3] Historically, DILI has been divided into two types. Type 1 is dose-dependent and predictable, and type 2 results from idiosyncratic reaction. Type 2 is mostly dose-independent, and can be either allergic, immune-mediated, or non-allergic, nonimmune-mediated.[4] The diagnosis of DILI is determined by a temporal relationship between drug administration and increased levels of liver enzymes and/or alkaline phosphatase,[5,6] exclusion of other causes of liver damage, and rarely repeated drug challenge. There is no standardized clinical test for this condition.[5,7] Drug-induced cholestasis is induced when drugs disrupt bile acid transport by inhibiting liver transporters involved in bile flow.[6] Cholestasis can be also found in severe metabolic dysfunction-associated fatty liver disease (MAFLD) stages, alcoholic hepatitis and alcoholic cirrhosis.[8] Drug-induced cirrhosis is associated with drugs that cause fibrogenesis and production of extracellular matrix molecules.[9]

MAFLD is a new concept, proposed in 2020, that has been suggested to replace the term nonalcoholic fatty liver disease because it does not require the exclusion of alcoholic liver disease or viral hepatitis.[10,11] It is a more accurate term for people with fatty liver and those with dysmetabolism.[1,2] MAFLD is well known as a highly prevalent disease affecting a quarter of the world's adult population and is the main cause of chronic liver disease in Europe and USA.[11,12] Besides, with the very high prevalence of MAFLD and alcohol abuse worldwide, the relationship among any present study population and real-world populations is of concern.[10] The novel MAFLD criteria concentrate on the role of dysmetabolism in fat accumulation in the liver, that is the most frequent driver of fatty liver injury progression.[13,14] When fatty liver injury progresses due to preexisting MAFLD in combination with drug administration, it is defined as a dual-etiology fatty liver disease.[10] Recently, two studies have recommended that the MAFLD criteria are more efficient and better for perceiving patients with a higher risk of fibrosis, in contrast with nonalcoholic fatty liver disease criteria.[11,15] MAFLD is diagnosed in patients when they have the hepatic manifestation of metabolic syndrome, which is diagnosed when three or more of the following conditions are found: high glucose, hypertension, obesity, high triglyceride, and low high-density lipoprotein-cholesterol.[16] There are a growing number of clinical reports proposing that certain drugs can be more hepatotoxic in overweight patients with MAFLD, in contrast with lean patients.[17]

DILI in MAFLD appears in two particular clinical situations.[17,18] First, antibiotics such as piperacillin-tazobactam, telithromycin, and some analgesics and antipyretics, like

Keywords: Metabolic dysfunction-associated fatty liver disease; Drug-induced liver injury; Reactive oxygen species; Free fatty acids; Pharmacogenetics.

Abbreviations: DIFLD, drug-induced fatty liver disease; DILI, drug-induced liver injury; DILIN, Drug-Induced Liver Injury Network; DIS, drug-induced steatosis; DISH, drug-induced steatohepatitis; MAFLD, metabolic dysfunction-associated fatty liver disease; MASH, metabolic dysfunction-associated steatohepatitis; MRC, mitochondrial respiratory chain; mtFAO, mitochondrial fatty acid oxidation; PNPLA3, patatin-like phospholipase 3 gene; ROS, reactive oxygen species; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; VLDL, very-low density lipoprotein.

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acetaminophen, can induce more serious and common acute liver injury. It appears that some drugs, like amiodarone and statins, do not induce hepatotoxicity more often in MAFLD patients.[17] Other drugs like antiretroviral agents, corticosteroids, and methotrexate appear to cause the alteration of simple fatty liver to nonalcoholic steatohepatitis or exacerbate necroinflammation, pre-existing steatosis, and fibrosis.[19,20] Some drugs can cause more serious acute liver injury in MAFLD because this illness is connected with the various modified activities of metabolizing enzymes such as cytochromes P450. Regarding the above-mentioned information, MAFLD is frequently connected with increased CYP2E1 activity and decreased CYP3A4 activity as well as with higher glucuronide formation. These enzymes are responsible for metabolism of, e.g., lorazepam and acetaminophen. More *in vitro* and *in vivo* research is required because the mechanisms wherewith drugs and xenobiotics are more hepatotoxic in MAFLD are not well known and more studies are a necessary in ensuring success in dealing with this issue, especially considering the worldwide epidemic of obesity.[21,22]

Drugs represent an alternative cause of fatty liver disease and the term that corresponds to this injury is drug-induced fatty liver disease (DIFLD). It is a specific form of DILI, characterized by intracellular lipid accumulation in hepatocytes with steatotic changes as the predominant histopathological pattern.[23,24] Although this histopathological finding is required for the diagnosis, the finding is not specific.[11] DIFLD is often accompanied by inflammation and oxidative stress, which leads to the development of drug-induced steatohepatitis (DISH).[25] Chronic liver injury leads to hepatocyte death, followed by the activation of stellate cells which finally results in liver tissue fibrosis. In addition, there are numerous drugs which can cause progression of steatohepatitis.[26] In 2015, Satapathy *et al*.[27] have shown that tamoxifen, an anti-estrogenic drug used in the treatment and prevention of breast cancer, was frequently associated with hepatic steatosis, although rarely with cirrhosis or steatohepatitis. Moreover, the authors emphasized that chronic exposure to amiodarone, 4, 4′-diethylaminoethoxyhexestrol and perhexiline maleate rarely led to cirrhosis.[27,28] It is known that phospholipidosis develops after prolonged treatment with these drugs, in a dose-dependent manner. However, it does not lead to steatohepatitis. Further investigations are needed to elucidate mechanisms by which drug-induced steatosis leads to steatohepatitis and consequently to fibrosis.

Buggey *et al*.[29] reported that amiodarone-induced acute and chronic liver injury without steatosis leads to necrosis and bridging fibrosis with early-stage cirrhosis. It is well known that amiodarone-induced hepatotoxicity has been characterized by histologic steatosis, phospholipidosis and fibrosis. However, in that case report, the histopathology showed an absence of steatosis and phospholipidosis, despite years of amiodarone ingestion. This suggests that lack of formerly accepted histopathologic findings, such as steatosis and phospholipidosis, should not exclude the diagnosis. This conclusion, however, requires further study and confirmation. Various other studies have confirmed the role of amiodarone in the induction of liver cirrhosis, with possible fatal outcomes.[30–32] Nevertheless, these adverse effects were found to be rare, with an incidence of 1–3%. A long-term surveillance for liver toxicity in high-risk patients using amiodarone has been suggested by numerous researchers.[30,31,33]

Most drugs capable of causing steatosis and steatohepatitis are known to have cationic amphiphilic structure.[34] These drugs are divided into three groups, including drugs that cause steatosis and steatohepatitis independently, such as amiodarone and perhexiline, drugs that can accelerate latent metabolic dysfunction-associated steatohepatitis (MASH), such as tamoxifen, and drugs that may cause sporadic events of steatosis/steatohepatitis, such as carbamazepine.[23] More details over the effects of these drugs on liver tissue will be discussed in the sections below.

Epidemiology of DIFLD

Recently, reported annual incidences of DILI have varied widely in population-based studies, from 2.7 to 19.1 cases per 100,000.[35] Accordingly, the true incidence of DIFLD in the general population remains unknown.[35] However, drug-induced steatosis (DIS) or drug-induced steatohepatitis (DISH) are generally rare but well-documented forms of DILI. According to the Drug-Induced Liver Injury Network (DILIN), approximately 27% of DILI cases have some form of steatosis with histological injury.[36] In the study of Kleiner *et al*.,[36] only one case was diagnosed with the predominant pattern of microvesicular steatosis, while the remaining cases showed a combination of macrovesicular steatosis with inflammation. Previously published descriptions of pathologic changes in DILI were used as the basis for the diagnostic classification in DILIN in the prospective study by Kleiner *et al*.[36,37] To define patterns of injury, standard hepatopathological diagnostic criteria were used.[38] Although this included a large proportion of DIFLD in DILI cases, the DILIN prevalence may be biased by the pre-existing presence of a fatty liver. The true data on DIFLD epidemiology might become clearer after eliminating diagnostic difficulties and deficiencies in systematic reporting.

Histology of DIFLD

DIFLD can present as pure macrovesicular or microvesicular steatosis or as DISH. Histologically, in macrovesicular steatosis, the accumulation of large lipid vesicles (mostly triglycerides) occurs in the hepatocyte, with the nucleus becoming consequently dislocated to the periphery of the cell.[36,39] As in other causes of steatohepatitis, aminotransferases are usually moderately increased.[40] The presence of triglycerides is associated with deterioration of mitochondrial fatty acid oxidation (mtFAO), decreased very-low density lipoprotein (VLDL) secretion, stimulation of *de novo* lipogenesis, direct activation of transcription factors, such as SREBP1c and PPARγ, and development of insulin resistance.[17,27,41–43] In microvesicular steatosis, the cytoplasm of hepatocytes is filled with numerous small lipid vesicles, and the nucleus remains in the center of the cell.[44] The severe impairment of mtFAO leads to increased esterification into triglycerides, which are known to be histologically related to microvesicular steatosis.[27,45] Steatohepatitis is characterized by lobular inflammation, balloon degeneration, hyaline Mallory bodies, and sometimes perisinusoidal fibrosis.[23,39,46] Additionally, mitochondrial dysfunction plays a key role in DIFLD, through the direct or indirect action of oxidative stress and increased production of reactive oxygen species (ROS) that mainly occur due to modification of the mitochondrial respiratory chain (MRC).[17,47] Microvesicular steatosis (drug-induced) is frequently the result of drug-induced damage to mitochondria.[48,49] This type of steatosis can start with small droplets of fat in the cytoplasm and then increase to macrovesicular steatosis characterized by large fat droplets that shifted the nucleus to the periphery. Frequently, macrovesicular steatosis can present with mixed large and small droplets.[50,51] Depending on the particular pathogenic mechanism of each lipotoxic drug, DIS/DISH can present as micro- or macrovesicular steatosis/steatohepatitis, but most cases start acutely with microvesicular injury.[52] The latency of DIFLD before clinical manifestations may vary.[24]

For DIS/DISH diagnosis, liver biopsy is the standard means for confirmation of hepatic cell injury and liver inflammation.[52]

Risk factors for occurrence of DIFLD

Some drugs cause progression of MAFLD to MASH or cirrhosis, and may also worsen the prognosis in patients with fatty liver.[17] This conversion to MASH appears to involve genetic and environmental factors.[17] MAFLD and obesity may enhance the risk of hepatotoxicity of various drugs.[18] The possible mechanisms by which certain drugs are able to accelerate progression of MAFLD include induction of oxidative stress, diminished mtFAO, increased *de novo* lipogenesis, and damaged egress of VLDL from liver cells.[53]

Most often, DIFLD is a product of direct impact of drugs on the liver, mostly associated with the extended intake of medications. For example, long-term administration of drugs, such as amiodarone, perhexiline and diethylaminoethoxyhexestrol, can lead to DISH. Furthermore, patients with additional risk factors, like obesity and cardiometabolic risks, are more prone to exacerbation of steatosis or steatohepatitis when irinotecan, tamoxifen and methotrexate are added to their therapy. Insulin resistance and hypertriglyceridemia in combination with antiepileptic drugs and steroids can also lead to steatohepatitis, MASH or DIFLD.[27] Fatty liver injury progression is related to factors such as insulin resistance, adipose tissue dysfunction, lipid aggregation, and oxidative and endoplasmic reticulum stress. Also, increased gut permeability and increased plasma endotoxin levels can be associated with fatty liver.[54–56]

Besides environmental risk factors, genetics also plays a significant role in the progression of simple steatosis.[57] Among patients with similar risk factors, large interindividual variability in phenotypic penetrance exists.[57] Various genetic, epidemiological and twin studies have shown a strong heritability of predisposition to MAFLD.[57] Apart from drugs, intrinsic (sex, age, ethnicity, liver, and renal condition) and other extrinsic (environmental chemicals, alcohol, diet, and drug-drug interactions) risk factors must be considered in any clinical algorithm associated with the fatty liver.[58] There is growing evidence for a genetic contribution to the development of MASH, even though environmental risk factors play a main role in the development of simple steatosis. In various (twin, epidemiological, and familial) studies, a large variability exists in phenotypic penetrance among people with related risk factors, and a powerful heritability of sensitivity to MAFLD has been noticed.[57] Studies on the role of genetics in DIFLD are still in the early phases, and more studies are needed to augment understanding of genetic variants and other risk factors in the progression of DIFLD and MAFLD.

Influence of pharmacogenetics on the risk for developing DIFLD

Alterations in genes involved in pharmacokinetics and pharmacodynamics are partially responsible for variations in drug response.[58] Part of an individual's predisposition for the development of side effects with high doses of certain drugs, like methotrexate or tamoxifen, can be explained by the patient's genetic makeup as well as pharmacogenetics. As mentioned before, methotrexate and tamoxifen are some of the drugs that can cause macrovesicular hepatic steatosis linked to DIFLD. In the context of high-dose methotrexate toxicity, it is important to emphasize that it is unpredictable, and interindividual variability is significant. The results from the previous studies on the pharmacogenetics of high doses of methotrexate differ, and are sometimes contradictory. This can be partly explained by significant differences in the pharmacogenetics of various populations.[39,59] Several genotypes have been associated with a higher risk of methotrexate toxicity, such as MTHFR 677TT (reduced activity of methylenetetrahydrofolate reductase which leads to diminished elimination of methotrexate), RFC-1 80G>A (reduced folate carrier 1, which is responsible for methotrexate entrance into the cells), and ABCB1 C3435TT (ATP binding cassette subfamily B member 1; reduced action of MDR1 and, therefore, slower elimination of methotrexate).[60] The metabolisms of 5-fluorouracil depends on the enzymatic activity of dihydropyrimidine dehydrogenase. Indeed, variants *2A or *13 of this enzyme are related to reduced metabolism of 5-fluorouracil, which can lead to serious side effects.[61] Genetic alterations in the patatin-like phospholipase 3 gene (PNPLA3) affect the plasma levels of hepatic enzymes and risk for MAFLD development,[62,63] including predisposition for fibrosis progression.[64,65] The above-mentioned polymorphism is a powerful predictor of inflammation, steatosis and fibrosis[66] but the role of PNPLA3 in DIFLD pathogenesis remains obscure.[27] Polymorphisms of PNPLA3 are strongly associated with ethnic and interindividual variations in liver fat content.[57] Hispanics were found to have a higher tendency to develop liver steatosis, unlike African-Americans.[67] In addition, twin studies suggest that about 60% of alanine transaminase variability may be ascribed to genetic factors.[68] Slow metabolizers for perhexiline, such as Caucasians, are at the greater danger of neuropathy and steatohepatitis. Perhexiline is catabolized by cytochrome P450 isoform 2D6 and has a long half-life due to the slow liver clearance in slow metabolizers.[69]

In recent years, the genetic factors of steatosis have been studied utilizing genome-wide association techniques. Further research in the area of pharmacogenomics is needed to better understand numerous possible gene polymorphisms that might be responsible for increasing risk of DIFLD development.

Drugs that cause DIFLD

Drugs shown to cause macrovesicular liver steatosis are glucocorticoids, amiodarone, methotrexate, estrogens, tamoxifen, nonsteroidal anti-inflammatory drugs, paracetamol, 5-fluorouracil, and metoprolol.[39,70–72] Drugs associated with microvesicular steatosis are valproic acid, tetracycline, aspirin, ibuprofen, zidovudine, and glucocorticoids.[24,44] Drugs associated with DISH are valproic acid, tamoxifen, perhexiline, amiodarone, and propranolol.[44,73] It is important to recognize the particular drugs that could cause acute liver damage on a fatty liver background or that could increase the danger of serious chronic liver disease. The hepatic accumulation of fat is not necessarily stable and DIS/DISH are reversible.[74] In many cases, it is difficult to elucidate whether the fatty liver disease is a direct result of an effect on hepatic cells or a consequence of a weight gain caused by the drugs such as antidepressants or antipsychotics. Pharmaceuticals that could induce the progression or exacerbate pre-existing fatty liver to MASH and fibrosis are shown in Table 1.[17]

Mechanisms of DIFLD development

The main mechanisms in the development of DIFLD are thought to include lipogenesis and generation of free radicals leading to oxidative stress induction in hepatocytes.[44,75] Kim *et al*.[76] showed that amiodarone caused an increase in short, medium- and long-chain acylcarnitines in the livers of

Table 1. Drugs specifically hepatotoxic in DIFLD, MAFLD and obesity

	Acute liver injury	Exacerbation of pre-existing fatty liver or MASH	Promoting the transition of pre-existing fatty liver into MASH, fibrosis, or cirrhosis
Drugs	Amiodaron, Aspirin, Acetaminophen, Ibuprofen, Isoflurane, Fosipronil, Halothane, Vitamin A, Valproat Acid, Tetracycline, Telithromycin, Piperacillin/tazobactam, NRTIs, Zalcitabin, Losartan, Omeprazole, Sorafenib, Ticlopidine, Troglitazone	Androgenic steroids, Benzbromarone, Corticosteroids, Irinotecan, Methotrexate, Tamoxifen, NRTIs, Pentoxifylline, Phenobarbital, Rosiglitazone, Tetracycline	Androgenic steroids, Benzbromarone, Corticosteroids, Irinotecan, Methotrexate, Tamoxifen

NRTIs, nucleoside reverse transcriptase inhibitors. Data from: Allard J *et al*.[17] Drug-induced liver injury in obesity and nonalcoholic fatty liver disease, EASL Clinical Practice Guidelines: Drug-induced liver injury.

rats, with the highest increases involving levels of acetylcarnitine. The most probable cause of these disturbances in liver tissue is the effect of amiodarone on mtFAO by blocking the activity of the carnitine palmitoyltransferase-1 enzyme, thereby directly inhibiting the mitochondrial β-oxidation of acyl-CoA to acetyl-CoA and by inhibiting complexes I and II of the MRC.[19,77] Another proven mechanism of amiodarone-induced DIFLD is triggering of *de novo* lipogenesis by augmenting the expression of genes sterol regulatory element-binding protein 1, thyroid hormone-inducible hepatic protein, ATP-citrate synthase, fatty acid synthase, and acyl-CoA desaturase, which are all involved in the process of lipogenesis.[78] Additionally, Anthérieu *et al*.[78] demonstrated *in vitro* that amiodarone administration led to overexpression of genes involved in formation of lipid droplets, namely perilipin-4 and adipose differentiation-related protein. Tamoxifen, like amiodarone, is a cationic amphiphilic compound that accumulates in liver tissue, causing liver injury.[34] Its toxic effect is also achieved by impairing the mtFAO and induction of *de novo* lipogenesis.[79] A possible mechanism for the induction of hepatic steatosis includes the upregulation of SREBP-1c and its downstream lipogenesis target genes.[24] Accumulation of triglycerides stimulates microsomal triglyceride transfer protein expression associated with VLDL assembly and secretion.[80] Several *in vivo* studies confirmed the role of oxidative stress in tamoxifen hepatotoxicity. Like amiodarone, it causes a reduction in liver glutathione levels, accumulation of oxidized form of glutathione, and lipid peroxidation.[75,81]

Methotrexate and especially its polyglutamated metabolite are both stored in hepatocytes and exert hepatotoxic effects.[82] Several mechanisms are proposed for the hepatotoxic effect of methotrexate, including hampering of folate entry to mitochondria, which leads to mitochondrial dysfunction and generation of ROS and finally induction of caspase-dependent apoptosis.[54,83,84] Another possible mechanism of hepatotoxicity is disruption of the intestinal epithelial barrier by methotrexate, which then leads to leaky gut syndrome, and the progression of fatty liver injury.[34,54] 5-Fluorouracil, irinotecan, and l-asparaginase, all exert their hepatosteatotic effects by impairing mtFAO and enhancing ROS accumulation in hepatocytes.[20,85] Valproate, a branched-chain fatty acid, disrupts the mtFAO, leading to the accumulation of triglycerides and steatosis.[44] Valproate in its free acid form can serve as a substrate for mtFAO pathways, competing with other free fatty acids. After entering the hepatic mitochondria, it conjugates with coenzyme A and causes a deficiency in that enzyme.[44] Chronic valproate administration increases the progression of a pre-existing fatty liver disease by inducing systemic insulin resistance and weight gain.[86,87] Tetracycline is well known for causing DIFLD. Mechanisms for this toxic effect include inhibition of mtFAO, inhibition of MTP enzyme (which results in accumulation of VLDL), decrease in the expression of several genes involved in mtFAO (peroxisome proliferator-activated receptor alpha, carnitine palmitoyltransferase I, and fatty acid-binding protein 1), and enhancement of ROS generation by activation of the transcription factor ATF4 (which up-regulates CYP2E1; specifically, by doxycycline and minocycline).[34,41,88,89] Nucleoside reverse transcriptase inhibitors, such as zidovudine, didanosine, stavudine, tenofovir and abacavir, are capable of inhibiting human DNA polymerase γ, leading to the decrease in mitochondrial DNA replication.[90,91] Consequently, oxidative stress and accumulation of fat occur.[90,91] All the above-mentioned mechanisms involved in DIFLD development are summarized in Table 2.

Current and future directions in the treatment of DIFLD

A fairly common recommendation for the management of DILI and potential manifestation of DIFLD is the withdrawal of the potential offending agent. Timely exclusion of the problematic drugs can lead to full recovery; up to 95% of patients show improvement but a few will still develop chronic liver disease.[92] Criteria of withdrawal of the drugs causing DILI were published in 2009 by the Food and Drug Administration[93] and are summarized in the following guidelines as follows: alanine aminotransferase or aspartate aminotransferase are >8 upper limit of normal (ULN), >5 ULN (for the period of 2 weeks), >3 ULN combined with international normalized ratio >1.5 and total bilirubin >2 ULN or levels of alanine aminotransferase/aspartate aminotransferase higher than 3, but followed with nausea, fever, fatigue, vomiting, rash, tenderness or pain (right upper abdominal quadrant) and potential eosinophilia.[92] If there is no adequate replacement for the hepatotoxic drug, then the dose should be adjusted in order to manage the primary disease, especially in intrinsic DILI.[92]

Glucocorticoids are used sometimes to treat DILI and DIFLD, but only after a serious risk-benefit assessment. They are beneficial in patients who show notable signs of autoimmunity or hypersensitivity, even after drug withdrawal.[92] Ursodeoxycholic acid (UDCA) has a hepatoprotective effect (including for cholangiocytes), stimulatory effect on hepatobiliary secretion, and prevents cellular apoptosis, as described in 15 DILI patients.[94] The effectiveness of UDCA in DILI cases lies in its improvement of the liver function abnormalities and relieving symptoms such as fatigue, pruritus and jaundice,[95–97] significantly improving liver tests[98] and possibly delaying liver transplantation.[99,100] Beneficial effects of UDCA have been shown in cohort studies and case reports after administration of the following drugs that cause liver injury, namely chlorpromazine, cyclosporine, amoxicillin-clavulanate, ticlopidine, flucloxacillin, paraquat, and methotrexate.[97,101–105] Rarely, individual case reports have supported the therapeutic properties of UDCA. One of those is a pediatric report of amoxicillin/clavulanic acid toxicity 4 years after the liver transplantation. Amelioration

Table 2. Drugs that cause DIFLD and proposed mechanisms responsible for their toxicity

Drugs that cause DIFLD	Proposed mechanisms
Amiodarone	Blockage of CPT1 enzyme activity, blockage of mtFAO, increase in acetylcarnitine levels, inhibition of MRC I and II complexes. Trigger of *de novo* lipogenesis by augmenting SREBP1, THRSP, ACLY, FASN, SCD1 PLIN4, ADFP genes' expression. Reduction in GSH levels
Tamoxifen	Impairment of the mtFAO, induction of *de novo* lipogenesis by upregulation of SREBP1c and its downstream genes. Stimulation of MTP expression and VLDL assembly and secretion. Reduction in GSH levels
Methotrexate	Effect on mitochondrial activity by hampering of folate entry into mitochondria, generation of ROS, disruption of the intestinal epithelial barrier
5-Fluorouracil, irinotecan, l-asparaginase	Impairment of mtFAO and enhancement of ROS accumulation in hepatocytes
Valproate	Competition with other FFAs for mtFAO, decrease in CoA levels. Induction of systemic insulin resistance and weight gain
Tetracycline	Inhibition of MTP enzyme, decrease in the PAARα, CPTI and FABP1 genes' expression, which are all involved in mtFAO. Enhancement of ROS generation by activation of ATF4
NRTIs	Inhibition of human DNA polymerase γ, decrease in mitochondrial DNA replication, induction of oxidative stress

ACLY, ATP-citrate synthase; ADFP, adipose differentiation-related protein; ATF4, transcription factor 4; CoA, coenzyme A; CPT1, carnitine palmitoyltransferase-1; CPTI, carnitine palmitoyltransferase I; FABP-1, fatty acid-binding protein 1; FASN, fatty acid synthase; FFA, free fatty acid; GSH, glutathione; MTP, microsomal triglyceride transfer protein; PLIN4, perilipin-4; SCD1, stearoyl-CoA desaturase; SREBP1, sterol regulatory element-binding protein 1; THRSP, thyroid hormone-inducible hepatic protein.

of the amiodarone-induced hepatotoxic effect was achieved with antioxidants such as N-acetyl-cysteine and vitamins C and E.[75] Further clinical trials on humans are needed to confirm these observations.

Conclusions

DIFLD remains a great challenge for researchers and clinicians because of the lack of adequate diagnostic tools and numerous underlying pathophysiologic mechanisms involved. Therefore, many cases of DIFLD are unrecognized or confirmation of diagnosis occurs in later irreversible stages of liver disease. Elucidation of various pathways by which specific drugs cause DIFLD represents a step forward in the development of appropriate therapy. It is important to emphasize that drug withdrawal or dose adjustment are so far the best therapeutic recommendation when it comes to DILI/DIFLD cases. Nevertheless, some treatments, such as UDCA for cholestasis, have shown benefit in the early stages.[98] However, the field needs more studies, especially in the use of pharmacogenetics to predict and avoid DILI, and in identifying individuals who may benefit from pharmacological interventions.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conceived of and designed the article, and critically revised the manuscript (MS, TOK, VN), obtained funding, and provided administrative, technical and material support (MS), performed literature searches and wrote the manuscript (VN, LK, KD, KB), updated the text of the manuscript (TOK, NRL, SV, GYW), performed figure generation (TOK), and performed critical revision of the manuscript for important intellectual content (MS, GYW).

References

[1] Ding WX, Yang L. Alcohol and drug-induced liver injury: Metabolism, mechanisms, pathogenesis and potential therapies. Liver Res 2019;3(3-4):129–131. doi:10.1016/j.livres.2019.11.006.
[2] Björnsson ES. Global Epidemiology of drug-induced liver injury (DILI). Curr Hepatology Rep 2019;18:274–279. doi:10.1007/s11901-019-00475-z.
[3] Weiler S, Merz M, Kullak-Ublick GA. Drug-induced liver injury: the dawn of biomarkers? F1000Prime Rep 2015;7:34. doi:10.12703/P7-34.
[4] Kuna L, Bozic I, Kizivat T, Bojanic K, Mrso M, Kralj E, *et al*. Models of drug induced liver injury (DILI) - Current issues and future perspectives. Curr Drug Metab 2018;19(10):830–838. doi:10.2174/1389200219666180523095355.
[5] Sundaram V, Björnsson ES. Drug-induced cholestasis. Hepatol Commun 2017;1(8):726–735. doi:10.1002/hep4.1088.
[6] Kolarić TO, Ninčević V, Smolić R, Smolić M, Wu GY. Mechanisms of hepatic cholestatic drug injury. J Clin Transl Hepatol 2019;7(1):86–92. doi:10.14218/JCTH.2018.00042.
[7] Ghabril M, Chalasani N, Björnsson E. Drug-induced liver injury: a clinical update. Curr Opin Gastroenterol 2010;26(3):222–226. doi:10.1097/MOG.0b013e3283383c7c.
[8] Yip WW, Burt AD. Alcoholic liver disease. Semin Diagn Pathol 2006;23(3-4):149–160. doi:10.1053/j.semdp.2006.11.002.
[9] Padda MS, Sanchez M, Akhtar AJ, Boyer JL. Drug-induced cholestasis. Hepatology 2011;53(4):1377–1387. doi:10.1002/hep.24229.
[10] Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, *et al*. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020;73(1):202–209. doi:10.1016/j.jhep.2020.03.039.
[11] Eslam M, Sanyal AJ, George J. MAFLD: A consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020;158(7):1999–2014.e1. doi:10.1053/j.gastro.2019.11.312.
[12] Younossi ZM. Long-term outcomes of nonalcoholic fatty liver disease: From nonalcoholic steatohepatitis to nonalcoholic steatofibrosis. Clin Gastroenterol Hepatol 2017;15(8):1144–1147. doi:10.1016/j.cgh.2017.05.029.
[13] Dongiovanni P, Stender S, Pietrelli A, Mancina RM, Cespiati A, Petta S, *et al*. Causal relationship of hepatic fat with liver damage and insulin re-

sistance in nonalcoholic fatty liver. J Intern Med 2018;283(4):356–370. doi:10.1111/joim.12719.
[14] Nasr P, Fredrikson M, Ekstedt M, Kechagias S. The amount of liver fat predicts mortality and development of type 2 diabetes in non-alcoholic fatty liver disease. Liver Int 2020;40(5):1069–1078. doi:10.1111/liv.14414.
[15] Lin S, Huang J, Wang M, Kumar R, Liu Y, Liu S, *et al*. Comparison of MAFLD and NAFLD diagnostic criteria in real world. Liver Int 2020;40(9):2082–2089. doi:10.1111/liv.14548.
[16] Abou Assi R, Abdulbaqi IM, Siok Yee C. The evaluation of drug delivery nanocarrier development and pharmacological briefing for metabolic-associated fatty liver disease (MAFLD): An update. Pharmaceuticals (Basel) 2021;14(3):215. doi:10.3390/ph14030215.
[17] Allard J, Le Guillou D, Begriche K, Fromenty B. Drug-induced liver injury in obesity and nonalcoholic fatty liver disease. Adv Pharmacol 2019;85:75–107. doi:10.1016/bs.apha.2019.01.003.
[18] Massart J, Begriche K, Moreau C, Fromenty B. Role of nonalcoholic fatty liver disease as risk factor for drug-induced hepatotoxicity. J Clin Transl Res 2017(Suppl 1):212–232. doi:10.18053/jctres.03.2017S1.006.
[19] Massart J, Begriche K, Buron N, Porceddu M, Borgne-Sanchez A, Fromenty B. Drug-induced inhibition of mitochondrial fatty acid oxidation and steatosis. Curr Pathobiol Rep 2013;1:147–157. doi:10.1007/s40139-013-0022-y.
[20] Meunier L, Larrey D. Chemotherapy-associated steatohepatitis. Ann Hepatol 2020;19(6):597–601. doi:10.1016/j.aohep.2019.11.012.
[21] Zheng KI, Fan JG, Shi JP, Wong VW, Eslam M, George J, *et al*. From NAFLD to MAFLD: a "redefining" moment for fatty liver disease. Chin Med J (Engl) 2020;133(19):2271–2273. doi:10.1097/CM9.0000000000000981.
[22] Ferron PJ, Gicquel T, Mégarbane B, Clément B, Fromenty B. Treatments in Covid-19 patients with pre-existing metabolic dysfunction-associated fatty liver disease: A potential threat for drug-induced liver injury? Biochimie 2020;179:266–274. doi:10.1016/j.biochi.2020.08.018.
[23] Grieco A, Forgione A, Miele L, Vero V, Greco AV, Gasbarrini A, *et al*. Fatty liver and drugs. Eur Rev Med Pharmacol Sci 2005;9(5):261–263.
[24] Rabinowich L, Shibolet O. Drug induced steatohepatitis: An uncommon culprit of a common disease. Biomed Res Int 2015;2015:168905. doi:10.1155/2015/168905.
[25] Farrell GC. Drugs and steatohepatitis. Semin Liver Dis 2002;22(2):185–194. doi:10.1055/s-2002-30106.
[26] Özkan A, Stolley D, Cressman ENK, McMillin M, DeMorrow S, Yankeelov TE, *et al*. The influence of chronic liver diseases on hepatic vasculature: A liver-on-a-chip review. Micromachines (Basel) 2020;11(5):487. doi:10.3390/mi11050487.
[27] Satapathy SK, Kuwajima V, Nadelson J, Atiq O, Sanyal AJ. Drug-induced fatty liver disease: An overview of pathogenesis and management. Ann Hepatol 2015;14(6):789–806. doi:10.5604/16652681.1171749.
[28] Kotiloglu G, Aki ZS, Ozyilkan O, Kutlay L. Tamoxifen-induced cirrhotic process. Breast J 2001;7(6):442–443. doi:10.1046/j.1524-4741.2001.07613.x.
[29] Buggey J, Kappus M, Lagoo AS, Brady CW. Amiodarone-induced liver injury and cirrhosis. ACG Case Rep J 2015;2(2):116–118. doi:10.14309/crj.2015.23.
[30] Tsuda T, Tada H, Tanaka Y, Nishida N, Yoshida T, Sawada T, *et al*. Amiodarone-induced reversible and irreversible hepatotoxicity: two case reports. J Med Case Rep 2018;12(1):95. doi:10.1186/s13256-018-1629-8.
[31] Daneshvar F. Amiodarone-induced cirrhosis: A well known underrecognized complication. J Am Coll Cardiol 2020;75(11_Supplement_1):2307.
[32] Lewis JH, Ranard RC, Caruso A, Jackson LK, Mullick F, Ishak KG, *et al*. Amiodarone hepatotoxicity: prevalence and clinicopathologic correlations among 104 patients. Hepatology 1989;9(5):679–685. doi:10.1002/hep.1840090504.
[33] Huang CH, Lai YY, Kuo YJ, Yang SC, Chang YJ, Chang KK, *et al*. Amiodarone and risk of liver cirrhosis: a nationwide, population-based study. Ther Clin Risk Manag 2019;15:103–112. doi:10.2147/TCRM.S174868.
[34] Schumacher JD, Guo GL. Mechanistic review of drug-induced steatohepatitis. Toxicol Appl Pharmacol 2015;289(1):40–47. doi:10.1016/j.taap.2015.08.022.
[35] Björnsson ES. Epidemiology, predisposing factors, and outcomes of drug-induced liver injury. Clin Liver Dis 2020;24(1):1–10. doi:10.1016/j.cld.2019.08.002.
[36] Kleiner DE, Chalasani NP, Lee WM, Fontana RJ, Bonkovsky HL, Watkins PB, *et al*. Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations. Hepatology 2014;59(2):661–670. doi:10.1002/hep.26709.
[37] Zimmerman HJ. Hepatotoxicity: The adverse effects of drugs and other chemical on the liver. 2nd ed. Lippincot, Williams & Wilkins: Philadelphia, 1999.
[38] Macsween RMN, Burt AD, Portmann BC, Ishak KG, Scheurer PJ, Anthony PP, *et al*. Pathology of the liver, 4th edition. Diagn Cytopathol 2003;29:43. doi:10.1002/dc.10338.
[39] Ramachandran R, Kakar S. Histological patterns in drug-induced liver disease. J Clin Pathol 2009;62(6):481–492. doi:10.1136/jcp.2008.058248.
[40] Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, *et al*. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN prospective study. Gastroenterology 2015;148(7):1340–1352.e7. doi:10.1053/j.gastro.2015.03.006.
[41] Lettéron P, Sutton A, Mansouri A, Fromenty B, Pessayre D. Inhibition of microsomal triglyceride transfer protein: another mechanism for drug-induced steatosis in mice. Hepatology 2003;38(1):133–140. doi:10.1053/jhep.2003.50309.
[42] Lauressergues E, Staels B, Valeille K, Majd Z, Hum DW, Duriez P, *et al*. Antipsychotic drug action on SREBPs-related lipogenesis and cholesterogenesis in primary rat hepatocytes. Naunyn Schmiedebergs Arch Pharmacol 2010;381(5):427–439. doi:10.1007/s00210-010-0499-4.
[43] Chaggar PS, Shaw SM, Williams SG. Effect of antipsychotic medications on glucose and lipid levels. J Clin Pharmacol 2011;51(5):631–638. doi:10.1177/0091270010368678.
[44] Miele L, Liguori A, Marrone G, Biolato M, Araneo C, Vaccaro FG, *et al*. Fatty liver and drugs: the two sides of the same coin. Eur Rev Med Pharmacol Sci 2017;21(1 Suppl):86–94.
[45] Fromenty B, Pessayre D. Inhibition of mitochondrial beta-oxidation as a mechanism of hepatotoxicity. Pharmacol Ther 1995;67(1):101–154. doi:10.1016/0163-7258(95)00012-6.
[46] Dowman JK, Tomlinson JW, Newsome PN. Pathogenesis of non-alcoholic fatty liver disease. QJM 2010;103(2):71–83. doi:10.1093/qjmed/hcp158.
[47] Pessayre D, Berson A, Fromenty B, Mansouri A. Mitochondria in steatohepatitis. Semin Liver Dis 2001;21(1):57–69. doi:10.1055/s-2001-12929.
[48] Begriche K, Massart J, Robin MA, Borgne-Sanchez A, Fromenty B. Drug-induced toxicity on mitochondria and lipid metabolism: mechanistic diversity and deleterious consequences for the liver. J Hepatol 2011;54(4):773–794. doi:10.1016/j.jhep.2010.11.006.
[49] Suzuki A, Brunt EM, Kleiner DE, Miquel R, Smyrk TC, Andrade RJ, *et al*. The use of liver biopsy evaluation in discrimination of idiopathic autoimmune hepatitis versus drug-induced liver injury. Hepatology 2011;54(3):931–939. doi:10.1002/hep.24481.
[50] Crawford JM. Histologic findings in alcoholic liver disease. Clin Liver Dis 2012;16(4):699–716. doi:10.1016/j.cld.2012.08.004.
[51] Fromenty B, Berson A, Pessayre D. Microvesicular steatosis and steatohepatitis: role of mitochondrial dysfunction and lipid peroxidation. J Hepatol 1997;26(Suppl 1):13–22. doi:10.1016/s0168-8278(97)82328-8.
[52] Pavlik L, Regev A, Ardayfio PA, Chalasani NP. Drug-induced steatosis and steatohepatitis: The search for novel serum biomarkers among potential biomarkers for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Drug Saf 2019;42(6):701–711. doi:10.1007/s40264-018-00790-2.
[53] Lee J, Homma T, Kurahashi T, Kang ES, Fujii J. Oxidative stress triggers lipid droplet accumulation in primary cultured hepatocytes by activating fatty acid synthesis. Biochem Biophys Res Commun 2015;464(1):229–235. doi:10.1016/j.bbrc.2015.06.121.
[54] Miele L, Valenza V, La Torre G, Montalto M, Cammarota G, Ricci R, *et al*. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. Hepatology 2009;49(6):1877–1887. doi:10.1002/hep.22848.
[55] Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, *et al*. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 2007;56(7):1761–1772. doi:10.2337/db06-1491.
[56] Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. Hepatology 2010;52(5):1836–1846. doi:10.1002/hep.24001.
[57] Dongiovanni P, Valenti L. Genetics of nonalcoholic fatty liver disease. Metabolism 2016;65(8):1026–1037. doi:10.1016/j.metabol.2015.08.018.
[58] Morse BL, Kim RB. Is personalized medicine a dream or a reality? Crit Rev Clin Lab Sci 2015;52(1):1–11. doi:10.3109/10408363.2014.950407.
[59] Bozina N. Farmakogenomika u personaliziranoj medicini: priručnik: poslijediplomski tečaj stalnog usavršavanja I. kategorije Medicinska Naklada: Zagreb, 2019:280str.
[60] Suthandiram S, Gan GG, Zain SM, Bee PC, Lian LH, Chang KM, *et al*. Effect of polymorphisms within methotrexate pathway genes on methotrexate toxicity and plasma levels in adults with hematological malignancies. Pharmacogenomics 2014;15(11):1479–1494. doi:10.2217/pgs.14.97.
[61] Lunenburg CATC, van der Wouden CH, Nijenhuis M, Crommentuijn-van Rhenen MH, de Boer-Veger NJ, Buunk AM, *et al*. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction of DPYD and fluoropyrimidines. Eur J Hum Genet 2020;28(4):508–517. doi:10.1038/s41431-019-0540-0.
[62] Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, *et al*. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 2008;40(12):1461–1465. doi:10.1038/ng.257.
[63] Yuan X, Waterworth D, Perry JR, Lim N, Song K, Chambers JC, *et al*. Population-based genome-wide association studies reveal six loci influencing plasma levels of liver enzymes. Am J Hum Genet 2008;83(4):520–528. doi:10.1016/j.ajhg.2008.09.012.
[64] Valenti L, Pelusi S. Redefining fatty liver disease classification in 2020. Liver Int 2020;40(5):1016–1017. doi:10.1111/liv.14430.
[65] Romeo S, Sentinelli F, Cambuli VM, Incani M, Congiu T, Matta V, *et al*. The 148M allele of the PNPLA3 gene is associated with indices of liver damage early in life. J Hepatol 2010;53(2):335–338. doi:10.1016/j.jhep.2010.02.034.
[66] Sookoian S, Pirola CJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. Hepatology 2011;53(6):1883–1894. doi:10.1002/hep.24283.
[67] Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, *et al*. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 2004;40(6):1387–1395. doi:10.1002/hep.20466.
[68] Makkonen J, Pietiläinen KH, Rissanen A, Kaprio J, Yki-Järvinen H. Genetic factors contribute to variation in serum alanine aminotransferase activity independent of obesity and alcohol: a study in monozygotic and dizygotic twins. J Hepatol 2009;50(5):1035–1042. doi:10.1016/j.jhep.2008.12.025.
[69] Morgan MY, Reshef R, Shah RR, Oates NS, Smith RL, Sherlock S. Impaired oxidation of debrisoquine in patients with perhexiline liver injury. Gut 1984;25(10):1057–1064. doi:10.1136/gut.25.10.1057.
[70] Marino JS, Stechschulte LA, Stec DE, Nestor-Kalinoski A, Coleman S, Hinds TD Jr. Glucocorticoid receptor β induces hepatic steatosis by augmenting inflammation and inhibition of the peroxisome proliferator-activated recep-

tor (PPAR) α. J Biol Chem 2016;291(50):25776–25788. doi:10.1074/jbc.M116.752311.
[71] Grieco A, Vecchio FM, Natale L, Gasbarrini G. Acute fatty liver after malaria prophylaxis with mefloquine. Lancet 1999;353(9149):295–296. doi:10.1016/S0140-6736(05)74932-1.
[72] Bruno S, Maisonneuve P, Castellana P, Rotmensz N, Rossi S, Maggioni M, *et al*. Incidence and risk factors for non-alcoholic steatohepatitis: prospective study of 5408 women enrolled in Italian tamoxifen chemoprevention trial. BMJ 2005;330(7497):932. doi:10.1136/bmj.38391.663287.E0.
[73] Ninčević V, Omanović Kolarić T, Roguljić H, Kizivat T, Smolić M, Bilić Ćurčić I. Renal benefits of SGLT 2 inhibitors and GLP-1 receptor agonists: Evidence supporting a paradigm shift in the medical management of type 2 diabetes. Int J Mol Sci 2019;20(23):5831. doi:10.3390/ijms20235831.
[74] Amacher DE, Chalasani N. Drug-induced hepatic steatosis. Semin Liver Dis 2014;34(2):205–214. doi:10.1055/s-0034-1375960.
[75] Akbay E, Erdem B, Ünlü A, Durukan AB, Onur MA. Effects of N-acetyl cysteine, vitamin E and vitamin C on liver glutathione levels following amiodarone treatment in rats. Kardiochir Torakochirurgia Pol 2019;16(2):88–92. doi:10.5114/kitp.2019.86361.
[76] Kim G, Choi HK, Lee H, Moon KS, Oh JH, Lee J, *et al*. Increased hepatic acylcarnitines after oral administration of amiodarone in rats. J Appl Toxicol 2020;40(7):1004–1013. doi:10.1002/jat.3960.
[77] Fromenty B, Fisch C, Labbe G, Degott C, Deschamps D, Berson A, *et al*. Amiodarone inhibits the mitochondrial beta-oxidation of fatty acids and produces microvesicular steatosis of the liver in mice. J Pharmacol Exp Ther 1990;255(3):1371–1376.
[78] Anthérieu S, Rogue A, Fromenty B, Guillouzo A, Robin MA. Induction of vesicular steatosis by amiodarone and tetracycline is associated with up-regulation of lipogenic genes in HepaRG cells. Hepatology 2011;53(6):1895–1905. doi:10.1002/hep.24290.
[79] Cole LK, Jacobs RL, Vance DE. Tamoxifen induces triacylglycerol accumulation in the mouse liver by activation of fatty acid synthesis. Hepatology 2010;52(4):1258–1265. doi:10.1002/hep.23813.
[80] Zhao F, Xie P, Jiang J, Zhang L, An W, Zhan Y. The effect and mechanism of tamoxifen-induced hepatocyte steatosis in vitro. Int J Mol Sci 2014;15(3):4019–4030. doi:10.3390/ijms15034019.
[81] Suddek GM. Protective role of thymoquinone against liver damage induced by tamoxifen in female rats. Can J Physiol Pharmacol 2014;92(8):640–644. doi:10.1139/cjpp-2014-0148.
[82] Kremer JM, Galivan J, Streckfuss A, Kamen B. Methotrexate metabolism analysis in blood and liver of rheumatoid arthritis patients. Association with hepatic folate deficiency and formation of polyglutamates. Arthritis Rheum 1986;29(7):832–835. doi:10.1002/art.1780290703.
[83] Tabassum H, Parvez S, Pasha ST, Banerjee BD, Raisuddin S. Protective effect of lipoic acid against methotrexate-induced oxidative stress in liver mitochondria. Food Chem Toxicol 2010;48(7):1973–1979. doi:10.1016/j.fct.2010.04.047.
[84] Bath RK, Brar NK, Forouhar FA, Wu GY. A review of methotrexate-associated hepatotoxicity. J Dig Dis 2014;15(10):517–524. doi:10.1111/1751-2980.12184.
[85] Labbe G, Pessayre D, Fromenty B. Drug-induced liver injury through mitochondrial dysfunction: mechanisms and detection during preclinical safety studies. Fundam Clin Pharmacol 2008;22(4):335–353. doi:10.1111/j.1472-8206.2008.00608.x.
[86] Patel V, Sanyal AJ. Drug-induced steatohepatitis. Clin Liver Dis 2013;17(4):533–546. doi:10.1016/j.cld.2013.07.012.
[87] Luef G, Rauchenzauner M, Waldmann M, Sturm W, Sandhofer A, Seppi K, *et al*. Non-alcoholic fatty liver disease (NAFLD), insulin resistance and lipid profile in antiepileptic drug treatment. Epilepsy Res 2009;86(1):42–47. doi:10.1016/j.eplepsyres.2009.04.004.
[88] Szalowska E, van der Burg B, Man HY, Hendriksen PJ, Peijnenburg AA. Model steatogenic compounds (amiodarone, valproic acid, and tetracycline) alter lipid metabolism by different mechanisms in mouse liver slices. PLoS One 2014;9(1):e86795. doi:10.1371/journal.pone.0086795.
[89] Brüning A, Brem GJ, Vogel M, Mylonas I. Tetracyclines cause cell stress-dependent ATF4 activation and mTOR inhibition. Exp Cell Res 2014;320(2):281–289. doi:10.1016/j.yexcr.2013.11.012.
[90] Banerjee A, Abdelmegeed MA, Jang S, Song BJ. Zidovudine (AZT) and hepatic lipid accumulation: implication of inflammation, oxidative and endoplasmic reticulum stress mediators. PLoS One 2013;8(10):e76850. doi:10.1371/journal.pone.0076850.
[91] Gardner K, Hall PA, Chinnery PF, Payne BA. HIV treatment and associated mitochondrial pathology: review of 25 years of in vitro, animal, and human studies. Toxicol Pathol 2014;42(5):811–822. doi:10.1177/0192623313503519.
[92] Yu YC, Mao YM, Chen CW, Chen JJ, Chen J, Cong WM, *et al*. CSH guidelines for the diagnosis and treatment of drug-induced liver injury. Hepatol Int 2017;11(3):221–241. doi:10.1007/s12072-017-9793-2.
[93] Ford R, Schwartz L, Dancey J, Dodd LE, Eisenhauer EA, Gwyther S, *et al*. Lessons learned from independent central review. Eur J Cancer 2009;45(2):268–274. doi:10.1016/j.ejca.2008.10.031.
[94] Wree A, Dechêne A, Herzer K, Hilgard P, Syn WK, Gerken G, *et al*. Steroid and ursodesoxycholic Acid combination therapy in severe drug-induced liver injury. Digestion 2011;84(1):54–59. doi:10.1159/000322298.
[95] Cicognani C, Malavolti M, Morselli-Labate AM, Sama C, Barbara L. Flutamide-induced toxic hepatitis. Potential utility of ursodeoxycholic acid administration in toxic hepatitis. Dig Dis Sci 1996;41(11):2219–2221. doi:10.1007/BF02071403.
[96] Piotrowicz A, Polkey M, Wilkinson M. Ursodeoxycholic acid for the treatment of flucloxacillin-associated cholestasis. J Hepatol 1995;22(1):119–120. doi:10.1016/0168-8278(95)80272-x.
[97] Kallinowski B, Theilmann L, Zimmermann R, Gams E, Kommerell B, Stiehl A. Effective treatment of cyclosporine-induced cholestasis in heart-transplanted patients treated with ursodeoxycholic acid. Transplantation 1991;51(5):1128–1129. doi:10.1097/00007890-199105000-00041.
[98] Velayudham LS, Farrell GC. Drug-induced cholestasis. Expert Opin Drug Saf 2003;2(3):287–304. doi:10.1517/14740338.2.3.287.
[99] Poupon RE, Poupon R, Balkau B. Ursodiol for the long-term treatment of primary biliary cirrhosis. The UDCA-PBC Study Group. N Engl J Med 1994;330(19):1342–1347. doi:10.1056/NEJM199405123301903.
[100] Poupon RE, Lindor KD, Cauch-Dudek K, Dickson ER, Poupon R, Heathcote EJ. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. Gastroenterology 1997;113(3):884–890. doi:10.1016/s0016-5085(97)70183-5.
[101] Bataller R, Bragulat E, Nogué S, Görbig MN, Bruguera M, Rodés J. Prolonged cholestasis after acute paraquat poisoning through skin absorption. Am J Gastroenterol 2000;95(5):1340–1343. doi:10.1111/j.1572-0241.2000.02021.x.
[102] Katsinelos P, Vasiliadis T, Xiarchos P, Patakiouta F, Christodoulou K, Pilpilidis I, *et al*. Ursodeoxycholic acid (UDCA) for the treatment of amoxycillin-clavulanate potassium (Augmentin)-induced intra-hepatic cholestasis: report of two cases. Eur J Gastroenterol Hepatol 2000;12(3):365–368. doi:10.1097/00042737-200012030-00017.
[103] Wengrower D. Possible ticlopidine-induced cholestatic jaundice. Am Fam Physician 2000;62(6):1258–1264.
[104] Hunt CM, Washington K. Tetracycline-induced bile duct paucity and prolonged cholestasis. Gastroenterology 1994;107(6):1844–1847. doi:10.1016/0016-5085(94)90830-3.
[105] Uraz S, Tahan V, Aygun C, Eren F, Unluguzel G, Yuksel M, *et al*. Role of ursodeoxycholic acid in prevention of methotrexate-induced liver toxicity. Dig Dis Sci 2008;53(4):1071–1077. doi:10.1007/s10620-007-9949-3.