DOI: https://doi.org/10.22516/25007440.177

Structured Literature Review of Hepatic Toxicity Caused by Medicines

Alejandra Cano P.,[1] Laura Cifuentes P.,[2] Pedro Amariles, PhD.[3]

1 Pharmaceutical Chemist, Master of Science in Pharmaceutical and Food Sciences, Faculty of Pharmaceutical and Food Sciences, Pharmaceutical Promotion and Prevention Group at the University of Antioquia in Medellín, Colombia. Corresponding author alejandra.canop@udea.edu.co
2 Pharmaceutical Chemist, Pharmaceutical Promotion and Prevention Group at the University of Antioquia in Medellín, Colombia
3 Doctor of Pharmacy, Professor of the Department of Pharmacy, Faculty of Pharmaceutical and Food Sciences, Pharmaceutical Promotion and Prevention Group at the University of Antioquia in Medellín, Colombia

Received: 13-10-16
Accepted: 06-10-17

Abstract

Objectives: The aim of this study was to prepare an updated list of drugs that cause hepatotoxicity and identify drugs most likely to cause hepatotoxicity according to scientific evidence. **Method:** A search of PubMed/Medline was conducted using the MeSH terms: "Liver disease" and "Drug-induced Liver Injury". The search was filtered by case reports, reviews, clinical trials, metaanalyses and letters until December 2015. The search was limited to articles in English, Spanish and French. Articles with evidence of hepatotoxicity caused by medications and relevant references were included. Articles not related to the objectives of the search were excluded. These include articles related to hepatotoxicity due to other agents, articles about other causes of liver disease and/or articles related to predictive tests or stem cells. Some aspects of hepatotoxic drugs were appearance of hepatotoxicity, type of injury, mechanisms of hepatotoxicity, risk factors and clinical manifestations. Three categories, definite, probable and possible, were established to assess probability of hepatotoxicity and type of lesion. **Results:** Six hundred ten articles were identified, 402 articles were chosen, and 208 articles were excluded. A list was prepared with 181 drugs and 17 combined pharmaceutical forms or therapeutic regimens likely to cause hepatotoxicity. Of these, methotrexate, minocycline, vancomycin, everolimus, isoniazid, and tamoxifen were categorized as definite probabilities. **Conclusions:** More than 180 hepatotoxic drugs were identified, six were categorized as definite probabilities, and most were categorized as possibilities. The consolidation of information shows that diverse categories of drugs are likely to cause liver toxicity.

Keywords

Liver disease, drug-induced liver damage.

INTRODUCTION

Hepatotoxicity is damage caused by exposure to a drug or non-pharmacological agents. Risk factors include idiosyncrasy, age, gender, alcohol consumption, smoking, concomitant use of other drugs, previous or underlying liver disease, genetic and environmental. (1-3) Although most lipophilic drugs can cause hepatotoxicity, (4) antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs) and anticonvulsants are the pharmacological groups which are the most frequent causes. (1, 5-9). Among drugs administered intravenously, antibiotics and drugs to treat neoplasia are the groups most associated with liver toxicity. (10)

Hepatotoxicity can be classified into intrinsic reactions and idiosyncratic reactions. The former are predictable, dose-dependent, and reproducible, but there is limited information on their frequency of occurrence. Idiosyncratic reactions are either immune or metabolic and are unpredictable, not dose-dependent, and non-reproducible, but they affect only a small proportion of patients (between 1/1,000 and 1/100,000 exposed patients). (11-17)

Intrinsic hepatotoxicity is less common than idiosyncratic hepatotoxicity. (12, 18-20) Liver histology is ideal for defining patterns of liver toxicity, but in clinical practice the majority of hepatotoxic damage is classified according to biochemical tests. (21) According to the international consensus of the Council for International Organizations of Medical Sciences (CIOMS), liver damage is present when liver enzymes are over two times the upper limit of normal (ULN). On the other hand, types of injuries are classified in (12, 22, 23):

- Hepatocellular damage is defined as isolated increases of alanine aminotransferase (ALT) to over two times the ULN or an ALT/alkaline phosphatase ratio greater than five. Hy's law defines this type of injury as ALT values greater than three times the ULN. (24, 25)
- Cholestatic damage is defined as isolated increases of alkaline phosphatase to over two times the ULN or a ratio of less than two.
- Mixed damage is defined as ALT and alkaline phosphatase over two times the ULN and a ratio greater tha two, but less than five.

Hepatotoxicity is related to mitochondrial dysfunction, inhibition of cellular respiration or alteration in β oxidation of fatty acids. (26, 27) These result in apoptosis, necrosis, autophagy and, therefore, cell death. (28, 29) The main clinical-pathological manifestations of hepatotoxicity and its histological findings are

a. Acute hepatitis (characterized by parenchymal inflammation, necrosis and Kupffer cells in the sinusoids)
b. Chronic hepatitis (fibrosis)
c. Fulminant hepatitis (necrosis and inflammation)
d. Cholestatic hepatitis (inflammation and liver damage)
e. Cholestasis (biliary plugs in zone 3)
f. Vanishing bile duct syndrome (damage to the bile ducts, cholestasis and inflammation)
g. Granulomatous hepatitis (granulomas in portal tracts or parenchyma)
h. Macrovesicular steatosis (lipid droplets in the cytoplasm of the hepatocyte)
i. Microvesicular steatosis (tiny drops of lipids in the cytoplasm of the hepatocyte)
j. Steatohepatitis (steatosis, lobular inflammation, engorged hepatocytes and pericellular fibrosis) (12, 29-31).

These manifestations are accompanied by nonspecific signs and symptoms such as fever, fatigue, nausea, abdominal pain, jaundice, dark urine, pruritus, ascites, encephalopathy and increased transaminases. (16, 32, 33)

Although some 1,100 drugs, excluding substances of abuse and natural products, have been associated with hepatotoxicity, (19) identification of this adverse event is a complex process. Therefore, a meticulous investigation is required, aimed at identifying any substance and ruling out other causes of liver disease. (3, 8, 34). In addition, liver biopsy is fundamental for identifying hepatotoxicity. (35) The chronological relationship between exposure to the suspect agent and the hepatotoxic reaction is key. To establish the likelihood that a drug is associated with hepatotoxicity, clinical scales such as the Roussel Uclaf Causality Assessment Method (RUCAM) and the Maria & Victorino (M&V) clinical scale have been developed. It is considered that the RUCAM scale's content and criterion validity make it most appropriate and that it generates results compatible with medical judgment and expert opinion on hepatotoxicity. Nevertheless, due to its high cost of application, its usefulness in clinical practice is limited. (36-38)

In the absence of a specific pharmacotherapy, treatment of hepatotoxicity is based on suspension of the suspect medication, treatment of symptoms and follow-up laboratory tests. (39) However, the use of N-acetylcysteine as an antidote for acetaminophen toxicity and hepatotoxicity due to phenytoin and carbamazepine, and the use of carnitine to treat valproic acid toxicity are exceptions. (40)

An updated list of hepatotoxic drugs and associated factors could help optimize identification and prevention of this adverse event. Therefore, the objectives of this review were to prepare an updated list of drugs associated with hepatotoxicity and identify, according to scientific evidence, the drugs most likely to cause hepatotoxicity. In addition, this review will systematize and specify key information such as type of injury, probability of occurrence, pathophysiological mechanisms, clinical and pathological manifestations, variation in liver enzyme levels, intrinsic or idiosyncratic reaction, risk factors and clinical outcomes.

METHOD

Bibliographical Search

A PubMed/Medline search was performed using the MeSH terms "liver disease" (drug effects, injuries, pathology) and "drug-induced liver injury". The search was filtered by articles with keywords in the title or summary published until December 2015 in English, Spanish and French and for which access was available to the full text. Articles were classified as case reports, reviews, systematic reviews, clinical trials, clinical trials controlled trials, randomized clinical trials, meta-analyzes and letters to the editor. Articles with evidence of hepatotoxicity only due to medications and those considered relevant to the subject were included. Articles unrelated to the objectives of the search were excluded as were articles related to hepatotoxicity due to other substances such as natural products, dietary supple-

ments, substances of abuse and industrial substances, those concerning other causes of liver disease and those related to predictive tests for hepatotoxicity or stem cells.

Information Analysis

Two independent reviewers determined eligibility of articles and extracted information from them while discrepancies between them were resolved by a third reviewer. The title, author, year of publication, type of study, related pharmacological group and compliance with inclusion criteria for each of the references found was recorded in a database in Excel 2010 for Windows®. In addition, the pharmacological group, ATC code (Anatomical, Therapeutic, Chemical classification), probability of occurrence of hepatotoxicity, type of injury, and probability of occurrence of that type of lesion were tabulated for each of the hepatotoxic drugs found. Mechanisms of hepatotoxicity, risk factors, clinical manifestations, management, outcome, measurements of liver enzymes and medication dosages were also recorded. Means and standard deviations were calculated for numerical data such as liver enzyme values (aspartate aminotransferase [AST], ALT, FA and total bilirubin [TB]) and dosages of drugs administered.

Assessment of Appearance of Hepatotoxicity and Type of Injury

Assessment of the appearance of hepatotoxicity and the type of injury was based on probability of occurrence. (41) Three categories were established according to the evidence found:

a. *Definite*: evidence in meta-analysis, systematic reviews or clinical trials (randomized or not)
b. *Probable*: analytical studies or description in three or more reports of clinical cases
c. *Possible*: less than 3 reported cases or recommendations from expert groups. (41)

In cases of drugs for which several references and different types of study were available, articles with the highest level of evidence were used.

RESULTS

The search identified 610 articles of which 402 met the inclusion criteria and were selected while 208 did not meet the inclusion criteria and were excluded. Forty-six other articles considered relevant for the review were included (Figure 1). A list of 181 drugs and 17 combined pharmaceutical forms or therapeutic regimens likely to cause hepatotoxicity was prepared. Six of these drugs (methotrexate, minocycline, vancomycin, everolimus, isoniazid, and tamoxifen) and one therapeutic regimen (isoniazid, rifampicin plus pyrazinamide) were classified as *definite*, 56 drugs and five combined pharmaceutical forms or therapeutic regimens were classified as *probable*, and 119 drugs and 11 combined dosage forms were classified as *possible*.

The type of lesion caused by each drug was identified, and hepatocellular damage was found to be more common than cholestatic or mixed damage. Information found for each drug with *definite* probability that was tabulated included type of hepatotoxicity, type of lesion, appearance, mechanism of hepatotoxicity, risk factors, clinical manifestations and outcomes (Table 1). The drugs found were classified according to their pharmacological group and their ATC code to unify them. Drugs found to have probable probability are found in Table 2 and the drugs with probable probability are found in Table 3. Figures for liver enzymes and dosages found are in Table 4.

Among antidiabetic agents, the *probable* probability of causing hepatotoxicity of acarbose (42) and troglitazone (43,44) (withdrawn from the market) has been determined. Case reports indicate that it causes hepatocellular, cholestatic and mixed type lesions accompanied by jaundice, rashes, fevers, and other symptoms. The antiarrhythmic agents associated with *probable* hepatotoxicity were propafenone and amiodarone. (45) There were more reported cases for amiodarone, and they were associated with elevated liver enzymes in 15% -55% of the patients. (46) Patients improved upon suspension of medication, but there are reports of death associated with amiodarone. (47) Antihypertensives such as enalapril increased liver enzyme levels and produced jaundice and structural changes in the liver confirmed by biopsies which led to transplantation and death. (48) For methyldopa (probable), there were nine reported cases of idiosyncratic liver toxicity. (17) They had a pattern of hepatocellular injury, especially in women, manifested by jaundice, anorexia and nausea. In addition, liver biopsies identified necrosis and inflammatory infiltrates. (49, 50) Hepatocellular lesions accompanied by elevated liver enzymes, jaundice, fever and asthenia were found to be associated with atorvastatin and ezetimibe. (51, 52)

Propylthiouracil caused the death of one patient, affected women and girls, generated symptoms such as jaundice, pruritus and weight loss; necrosis, fibrosis, inflammatory infiltrate and ductopenia and was found in liver biopsies. Suspension of the drug improved the evolution of some patients. (53) Four cases of increased liver enzyme values, weakness and jaundice were identified in patients taking methylprednisolone. Symptoms improved upon suspension of the medication. (54)

Among the antibiotics, idiosyncratic reactions were identified in association with vancomycin (55) and mino-

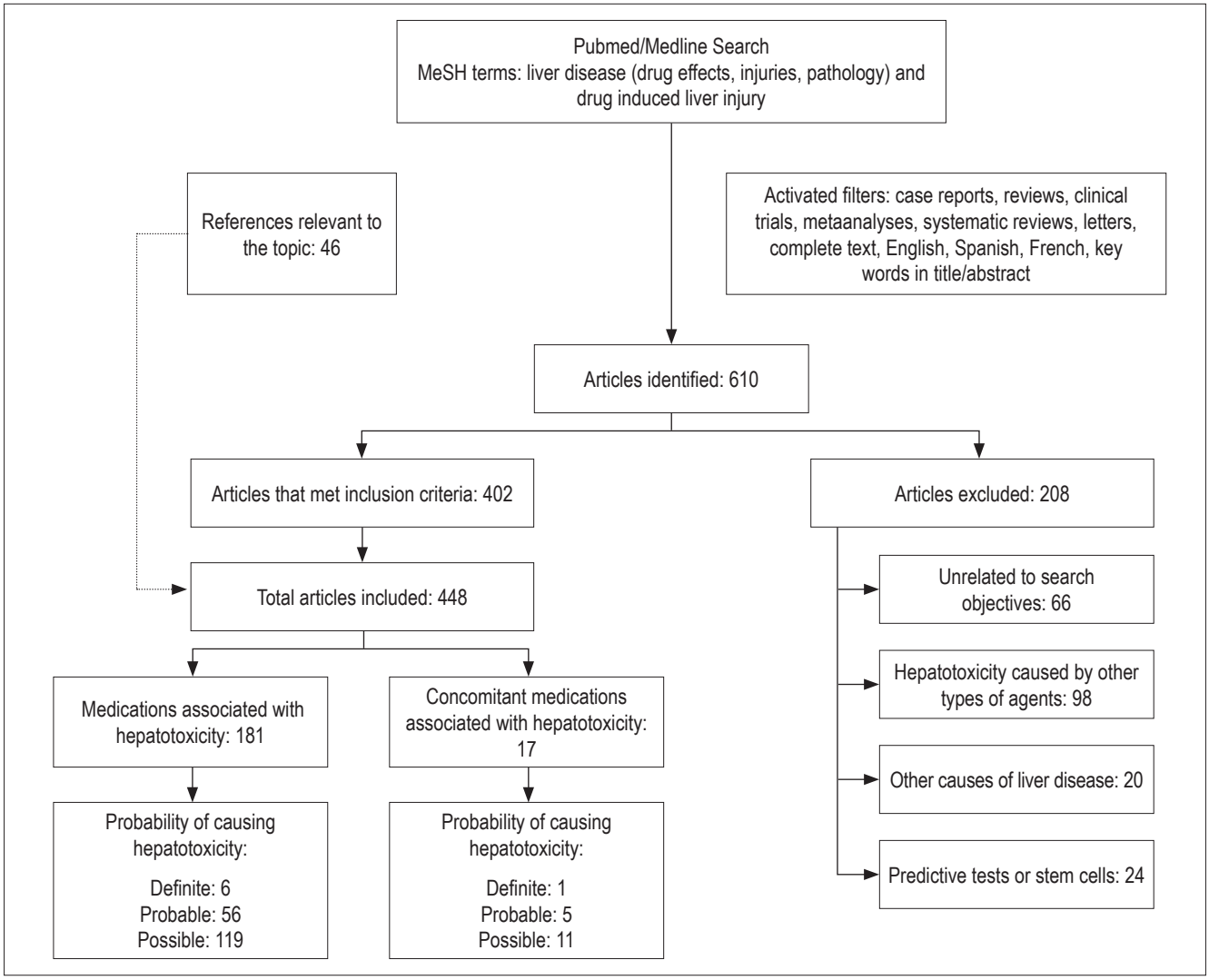

Figure 1. General results of the structured review: drugs that cause liver toxicity.

cycline. (17, 33, 55, 56) Minocycline affected women between 16 and 57 years of age who had been diagnosed with autoimmune hepatitis. Rifampicin caused hepatocellular lesions and especially affected women. (57, 58) The following antibiotics were classified as *probable* causes of hepatotoxicity: nitrofurantoin (12% frequency of cases, idiosyncratic), (59, 60), flucoxacillin (11 cases, idiosyncratic), (61) telithromycin (hepatocellular lesions with elevated transaminases and fever), (62) ciprofloxacin and trovafloxacin (withdrawal from the market). In general, the outcomes varied from favorable evolutions to liver transplantation and death of the patient.

Liver damage associated with the antifungal agents itraconazole, fluconazole and ketoconazole improved with suspension of the medications. (63-66) Antiretroviral agents, especially reverse transcriptase inhibitors, nucleoside analogues and protease inhibitors, can cause dose-dependent hepatotoxicity. (67) Cases reported with efavirenz and nevirapine had elevated transaminases and an incidence between 1% and 14%. (9) Coinfection with hepatitis B or C virus can increase the level of hepatotoxicity associated with antiretroviral treatments. (68, 69)

Chemotherapy has increased life expectancy, but it can cause liver damage ranging from steatosis and steatohepatitis to cirrhosis. (70, 71) The probability of hepatotoxicity for tamoxifen, everolimus and methotrexate is *definite*. Medications such as flutamide, etoposide, imatinib, ipilimumab, oxaliplatin, temozolomide, thioguanine, glatiramer, azathioprine, and infliximab were classified as *probable* causes of hepatotoxicity.

Table 1. Drugs with a probability of causing *definite* hepatotoxicity

Pharmacological group	Drug (number of articles) [ATC code]	Evidence of hepatotoxicity (types of study design)	Hepatotoxicity Type	Type of injury (probability of onset)	Hepatotoxicity mechanism	Risk factors	Clinical manifestations	Management and outcome
Antibiotics	Vancomycin (1) [J01XA01]	Definite (systematic review and metaanalysis)	Idiosyncratic (allergic)	Hepatocellular (Definite)	Direct toxicity or adverse immune reactions	No information	Elevated aminotransferases	No information
Antibiotics	Minocycline (5) [J01AA08]	Definite (systematic review, report of 2 clinical cases and review of expert groups)	Idiosyncratic	Hepatocellular (Definite)	Lipid peroxidation-necrosis	Women between 16 and 57 years with acne	Autoimmune hepatitis. Elevation of aminotransferases, positive antinuclear antibodies, jaundice, anorexia, fever, arthralgia, fatigue, abdominal pain, nausea, rash, eosinophilia, periportal inflammation, pruritus. Swollen and collapsed hepatocytes. Steatosis	Liver transplantation, death. Suspension of drug and favorable evolution
Antituberculosis agents	Isoniazid (3) [J04AC01]	Definite (prospective and retrospective study and expert group reviews)	Idiosyncratic	Hepatocellular (probable)	Lipid peroxidation-necrosis	Women with an average age of 60 years and men with an average age of 54. Patients with average age of 49 years 70% of whom are women	Acute hepatitis. Elevation of aminotransferases, nausea, jaundice, abdominal pain, fatigue, anorexia, vomiting, dark urine. Hepatocellular necrosis	Suspension of drug Liver transplantation, death.
Antituberculosis agents	Isoniazid + rifampicin + pyrazinamide (4) [J04AM05]	Definite (systematic review and reviews of expert groups)	Idiosyncratic	Hepatocellular (possible)	Lipid peroxidation-necrosis. Genetic polymorphism, formation of hepatotoxic metabolites	Advanced age and female sex, coinfection with HIV. Genetic polymorphism	Elevated liver enzymes, jaundice, abdominal pain, nausea, vomiting, asthenia, steatosis and necrosis. Hepatic encephalopathy, granulomatous inflammation	Change or suspension of medication and favorable evolution. Liver transplant
Estrogen antagonist	Tamoxifen (5) [L02BA01]	Definite (randomized controlled clinical study and reporting of 6 clinical cases)	No information	Hepatocellular (Definite)	Decreased β oxidation of fatty acids, steatohepatitis	Women of 50 to 70 years with mastectomies, diabetes, consumption of alcohol <20 g/day, hysterectomy, overweight, hypercholesterolemia, hypertension, osteoporosis	Steatohepatitis, fibrosis, hepatocellular necrosis, micronodular cirrhosis, hepatomegaly. Elevation of ALT. Nausea, vomiting, malaise, inflammatory infiltrate. Pain in the upper right quadrant and hepatic peliosis.	Favorable evolution. Death.
Antineoplastic	Everolimus (1) [L01XE10]	Definite (systematic review and metaanalysis)	No information	No information	No information	Patients with neoplasms and organ transplants	ALT elevation, fatigue	Adjustment of treatment or suspension of medication
Antineoplastic/ immunomodulatory	Methotrexate (7) [L04AX03]	Definite (metaanalysis, prospective study, analytical study	No information	Hepatocellular (possible)	Lipid peroxidation-necrosis. Mitochondrial depletion	Children with previous liver disease. Alcoholism. Adult or advanced age. Accumulated doses. Obesity and DM2. Steroids. Previous exposure to hepatotoxins	Elevated liver enzymes. Fibrosis. Inflammatory infiltrates. Steatohepatitis. Necrosis. Cirrhosis	Change of pharmacotherapy. Suspension of drug and favorable evolution, death

ALT: Alanine aminotransferase; ATC: Anatomical, Therapeutic, Chemical; DM2: diabetes mellitus type 2; HIV: human immunodeficiency virus.

Table 2. Drugs likely to cause *probable* hepatotoxicity

Medicines				
Acarbose	Acetaminophen	Allopurinol	Azathioprine	Valproic acid
Amiodarone	Benzarone	Sodium Aurothiomalate	Buprenorphine	Ciprofloxacin
Atorvastatin	Doxapram Hydrochloride	Bentazepam	Etoposide	Clomethiazole
Enalapril	Efavirenz	Carbamazepine	Flutamide	Dextropropoxyphene
Ezetimibe	Fluconazole	Cyproterone acetate	Glatiramer	Flucloxacillin
Flupirtine	Itraconazole	Dantrolene	Imatinib	Lamotrigine
Methyldopa	Ketoconazole	Diclofenac	Infliximab	Nitrofurantoin
Papaverine	Methylprednisolone	Halothane	Ipilimumab	Ornidazole
Perhexiline	Nevirapine	Isoflurane	Oxaliplatin	Telithromycin
Propafenone	Propylthiouracil	Lumiracoxib	Temozolomide	Tolcapone
Troglitazone	Rifampicin	Nimesulide	Thioguanine	Trovafloxacin
Vitamin A (retinol)				

Table 3. Medications likely to cause *possible* hepatotoxicity

Drugs					
Lipoic acid	Alfuzosin	Amodiaquine	Amoxicillin	Nicotinic acid	Acetylsalicylic acid
Actinomicina D	Carmustina	Clozapine	Amphotericin B	Tienilic acid	Alendronate sodium
Busulfan	Cyclofenil	Enflurane	Atomoxetine	Ajmaline	Aurothioglucose
Donepezil	Cyclophosphamide	Felbamate	Brivudine	Bosentan	Bromfenac sodium
Esomeprazole	Citarabine	Phenytoin	Cefdinir	Candesartan	Etretinate
Glibenclamide	Dacarbazine	Phenobarbital	Clindamycin	Clopidogrel	Glucosamine
Gliclazide	Disulfiram	Imipramine	Dapsone	Dabigatran	Ibuprofen
Glimepiride	Leflunomide	Mefloquine	Daptomycin	Dalteparin	Indomethacin
Loratadine	Mitoxantrone	Methylphenidate	Didanosine	Diltiazem	Mebendazole
Mesalamine	Naftidrofuryl	Methoxyflurane	Doxycycline	Dipyrone	Methimazole
Mesalazine	Pazopanib	Mirtazapine	Erythromycin	Phenprocoumon	Metronidazole
Metformin	Pravastatin	Nefazodone	Spiramycin	Fosinopril	Nafamostat
Nilutamide	Raloxifene	Nomifensine	Spironolactone	Ferrous fumarate	Octreotide
Indicine N-oxide	Simvastatin	Propofol	Fosfomycin	Hydralazine	Oxaprozin
Orlistat	Sirolimus	Quetiapine	Levofloxacin	Irbesartan	Piroxicam
Oxymetholone	Thalidomide	Risperidone	Nafcillin	Labetalol	Rofecoxib
Pioglitazone	Tamsulosin	Sertraline	Oxacillin	Lisinopril	Sitaxentan
Ranitidine	Tocilizumab	Sevoflurane	Quinine	Nicardipine	Terbinafine
Rosiglitazone	Trabectedin	Thiopental	Sulfadimethoxine	Quinidine	
Sulfasalazine	Undecanoate de testosterone	Zolmitriptan	Zidovudine	Ticlopidine	

NSAIDs were identified as an important group that can cause liver damage, mainly idiosyncratic, in cases of abuse or overdose. (1, 72, 73, 74) Risk factors identified included age, female gender, chronic alcohol consumption, concomitant drugs, underlying diseases, obesity, DM2 and insulin resistance. (72) Causative agents include diclofenac, lumiracoxib and nimesulide. Acetaminophen is widely recognized as an intrinsic hepatotoxic substance due to a metabolite that causes hepatic necrosis,. Fourteen case reports characterized by hepatocellular lesions were identified. When managed with N-acetylcysteine and prednisone patients improved. (75, 76)

Halothane was the general anesthetic most likely to cause liver toxicity. Genetic predisposition, repeated doses, obe-

Table 4. Liver enzyme values and dosages associated with hepatotoxic drugs

Drug	AST (U/L)		ALT (U/L)		AP (U/L)		TB (mg/dL)		Dosage		
	Avg.	SD	Avg.	SD	Avg.	SD	Avg.	SD	Avg.	SD	Unit
Acetaminophen	10432.00	9533.8	2780.33	2471.0	247.78	122.5	6.78	4.6	4.38	1.3	g/day
Diclofenac	259.80	238.5	491.86	424.5	294.67	129.0	10.6	0	135.7	37.8	mg/day
Buprenorphine	1023.6	1016.2	2301	2455.2	216.75	74.9	86.67	93.6	10	4	mg/day
Isoflurane	7342.0	12129.7	5963.5	6265.7	176	110.0	9.55	5.5	-	-	-
Amiodarone	359.9	523.4	716.00	867.4	208.67	128.2	3.0	2.3	528.57	226.8	mg/day
Propafenone	106	109.1	111.67	96.0	791.33	418.4	6.79	2.9	375	106.1	mg/day
Nitrofurantoin	652.5	717.7	690.5	291.5	214.1	112.0	9.6	9.9	144.4	110.2	mg/day
Ornidazole	1027.4	543.9	1315.4	1018.5	509.6	353.2	23.3	17.6	1000.0	0.0	mg/day
Telithromycin	1209	1663.1	1008.25	862.0	281	215.8	115.2	103.0	800	0	mg/day
Minocycline	833.83	689.1	1090	830.7	132.20	77.5	6.82	9.7	140.88	108.5	mg/day
Ciprofloxacin	360	260.6	520	210.7	308.67	288.8	3.77	1.8	833.33	288.7	mg/day
Carbamazepine	276.40	376.7	92	0	275.3	110.1	4.7	5.8	433.3	331.7	mg/day
Lamotrigine	1824	2716.7	2578.3	4061.4	147	33.9	13.07	2.3	75	0	mg/day
Valproic Acid	3196	4911.6	1361.3	1169.5	238.7	44.2	7.0	6.4	1050	320.2	mg/day
Itraconazole	189	181.1	177.7	79.0	1276	143.0	11	6.6	233.3	152.8	mg/day
Allopurinol	373.7	225.5	839.7	861.3	225.67	28.9	3.45	2.8	260.0	89.4	mg/day
Enalapril	849	461.9	689.25	537.8	542.75	180.4	10.525	6.3	15	5.8	mg/day
Etoposide	1540	177.8	1476.7	745.7	212	59.0	170	84.1	155.7	82.5	mg/day
Temozolomide	387.75	363.3	719.75	722.9	364.25	160.3	8.4	6.5	180	24.5	mg/day
Tolcapone	2947.5	1563.0	1551.3	1296.3	176.33	112.0	11.4	13.0	166.7	57.7	mg/day
Propylthiouracil	639.17	557.3	784.80	506.2	520.6	520.7	19.1	11.5	316.7	103.3	mg/day
Rifampicin	-	-	450.67	82.2	231	146.4	103.33	12.5	300	259.8	mg/day
Atorvastatin	638.3	503.7	480.7	443.7	495.7	88.9	60.6	13.5	40	34.6	mg/day
Infliximab	893.20	1042.6	720.6	638.3	250.5	46.0	11.267	9.2	4.33	1.0	g/day

ALT: Alanine aminotransferase; AST: aspartate aminotransferase; TB: Total bilirubin; SD: standard deviation; AP: alkaline phosphatase; avg.: average

sity and advanced age were some risk factors. Women are more likely to suffer liver damage including hepatocellular lesions, increased liver enzymes, necrosis, fever, jaundice and fatigue. (77-79)

Among the anticonvulsants, valproic acid had the largest number of cases of hepatotoxicity (hepatocellular type) which manifested with elevated transaminases, abdominal pain, jaundice and anorexia. In addition, microvesicular and macrovesicular steatosis, necrosis and inflammatory infiltrate were identified in liver biopsies. This medication can cause liver damage in people under 30 years of age. (80, 81) Carbamazepine cases identified were mainly of the mixed type with the formation of granulomas. (82, 83) Lamotrigine generated cases of idiosyncratic hepatotoxicity that required liver transplantation. (84, 85)

We found 17 combined pharmaceutical forms or therapeutic regimens (drugs used simultaneously) capable of causing idiosyncratic hepatocellular damage. Among them is the combination isoniazid, rifampicin and pyrazinamide (definite probability). Hepatotoxicity manifested with elevated liver enzymes, abdominal pain, jaundice, asthenia, nausea, vomiting and necrosis and has been confirmed by liver biopsies. (86-88) In the case of the combined pharmaceutical forms of antibiotics, such as trimethoprim/sulfamethoxazole and amoxicillin/clavulanic acid, cases of hepatotoxicity were identified as idiosyncratic and classified as probable. (57) Hepatotoxicity occurred mainly in men and caused jaundice and pruritus. In some cases caused by amoxicillin/clavulanic acid, the outcome was liver transplantation or death. (89) The antiretroviral regimen of ritonavir, indinavir, darunavir and fosamprenavir was associated with hepatocellular damage and necrosis. (68, 90) Case reports of antineoplastic agents 6-thioguanine, daunomycin, and cytosine arabinose used as part of the therapeutic regimen for myeloid leukemia in children have shown hepatomegaly, cirrhosis, and veno-occlusive disease. (91)

DISCUSSION

Antibiotics, antineoplastic agents and antituberculosis drugs were the groups of drugs identified as most likely to cause hepatotoxicity. This is in accordance with the results of previous reviews. (5, 23, 33, 57) Sufficient evidence was found for the capacities of two antibiotics, vancomycin and minocycline, to cause idiosyncratic hepatotoxicity and a type of hepatocellular lesion. (17, 33, 55, 56, 92) They were assessed as *definite*. Among the other antibiotics, tetracycline was identified as being able to generate steatohepatitis, (93) but the search did not yield enough information for its inclusion.

Case reports allowed identification of tamoxifen, everolimus and methotrexate as agents that can cause liver damage, with a *definite* probability. In the case of methotrexate, a previously published study reported increased liver enzymes, but did not identify associated methotrexate concentrations or the probability of causing hepatotoxicity. (94) With the information found it was not possible to establish types of hepatotoxicity for these three drugs, but damage tends to be hepatocellular with elevated transaminases and outcomes that range from favorable to death.

In this review, no reports of specific cases of isoniazid hepatotoxicity were found, but some authors claim that this medication causes liver damage. (95) Thus, it is important to note that the concomitant use of isoniazid, rifampicin and pyrazinamide was identified as the cause of idiosyncratic hepatotoxicity and hepatocellular damage followed by suspension of the regimen. (86, 87)

In this review, the likelihood for acetaminophen to cause liver toxicity was assessed as *probable* because only opinions of expert groups and case reports were identified. The absence of evidence from metaanalyses, systematic reviews and clinical trials did not allow it to be classified as a *definite* probability.

In the case of amiodarone, there are doubts about the type of hepatotoxicity it generates. Although information was found that supports idiosyncratic reactions, (32, 96-98) intrinsic reactions secondary to drug deposition in liver tissue have also been reported. (23)

There are medications that have been withdrawn from the world market or from certain countries because they are associated with the probability of causing hepatotoxicity. (99) Some of those identified in this review are dextropropoxyphene, ketoconazole (still marketed in Colombia), nefazodone, propofol and sitaxentan.

Elevated liver enzymes were present in many of the case reports which suggests that it could be a marker for suspicion of drug hepatotoxicity. In this framework, ALT, AST, AP and TB were reported for some medications in some case reports. In addition, the available data for dosages administered doses could support the hypothesis of onset of hepatotixicty at therapeutic doses.

A limitation of this review is that it used only one database: PubMed/Medline. This may decrease the number of drugs identified as likely to cause liver toxicity and could influence assessment of the probabilities found for medications tabulated. To reduce the risk of information biases, a procedure proposed by Amariles et al. that is based on the probability of the occurrence of hepatotoxicity was used. (41) Three categories were established, definite, probable and possible, according to the types of published studies (level of evidence) for each drug. To decrease the confusion bias between and among drugs that were used at the same time, a difference is made between combined pharmaceutical forms (several drugs in a single pharmaceutical form) and therapeutic regimens.

CONCLUSIONS

We identified more than 180 drugs associated with hepatotoxicity. Of these, six have *definite* probabilities while most of the rest have *possible* probabilities. It is noteworthy that more than 50% of the drugs found are associated with idiosyncratic hepatotoxicity and that female sex is the main risk factor. The age range of people affected is broad. In addition, the elevation of liver enzymes, jaundice and fever the symptoms that occur most often. They can lead to hepatocellular lesions followed by liver necrosis. In most cases, adequate patient evolution occurs after identifying and suspending the causative agent. The consolidation of information on hepatotoxicity shows that several groups of drugs have greater evidence of being substances that cause liver toxicity. Nevertheless, precise understanding of the mechanisms that explain the development and onset of hepatotoxicity is scarce.

Source of Financial Support

The Promotion and Pharmaceutical Prevention group received funding from the 2014-2015 sustainability call of the Committee for the Development of Research (CODI) of the University of Antioquia in Medellín, Colombia.

Conflict of Interests

The authors declare that they have no conflicts of interest.

REFERENCES

1. Ibáñez L, Pérez E, Vidal X, et al. Prospective surveillance of acute serious liver disease unrelated to infectious, obstructive, or metabolic diseases: epidemiological and clinical

features, and exposure to drugs. J Hepatol. 2002;37(5):592-600. https://doi.org/10.1016/S0168-8278(02)00231-3
2. Fernández-Castañer A, García-Cortés M, Lucena M, et al. An analysis of the causes, characteristics, and consequences of reexposure to a drug or compound responsible for a hepatotoxicity event. Rev Esp Enferm Dig. 2008;100(5):278-84.
3. Lee W. Drug-Induced Hepatotoxicity. N Engl J Med. 2003;349(5):474-85. https://doi.org/10.1056/NEJMra021844
4. Chen M, Borlak J, Tong W. High lipophilicity and high daily dose of oral medications are associated with significant risk for drug-induced liver injury. Hepatology. 2013;58(1):388-96. https://doi.org/10.1002/hep.26208
5. Tejada F. Hepatotoxicidad por fármacos. Rev clínica Med Fam. 2010;3(3):177-91.
6. Sgro C, Clinard F, Ouazir K, et al. Incidence of drug-induced hepatic injuries: A French population-based study. Hepatology. 2002;36(2):451-5. https://doi.org/10.1053/jhep.2002.34857
7. Martí L, Olmo J, Tosca J, et al. Clinical evaluation of drug-induced hepatitis. Rev Esp Enfermedades Dig. 2005;97(4):258-65. https://doi.org/10.4321/S1130-01082005000400006
8. Hernández N, Bessone F, Sánchez A, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol. 2014;13(2):231-9.
9. Liss G, Lewis J. Drug-induced liver injury: what was new in 2008? Expert Opin Drug Metab Toxicol. 2009;5(8):843-60. https://doi.org/10.1517/17425250903018904
10. Ghabril M, Fontana R, Rockey D, et al. Drug induced liver injury caused by intramuscular administered medications: the drug induced liver injury network (DILIN) experience. J Clin Gastroenterol. 2013;47(6):553-8. https://doi.org/10.1097/MCG.0b013e318276bf00
11. Larrey D. Epidemiology and individual susceptibility to adverse drug reactions affecting the liver. Semin Liver Dis. 2002;22(2):145-55. https://doi.org/10.1055/s-2002-30101 https://doi.org/10.1055/s-2002-30105
12. Ramachandran R, Kakar S. Histological patterns in drug-induced liver disease. J Clin Pathol. 2009;62(6):481-92. https://doi.org/10.1136/jcp.2008.058248
13. Fisher K, Vuppalanchi R, Saxena R. Drug-induced liver injury. Arch Pathol Lab Med. 2015;139(7):876-87. https://doi.org/10.5858/arpa.2014-0214-RA
14. Castell J, Miñana M. Hepatitis inducida por tóxicos. Mecanismos de toxicidad y patrones de lesión. GH Contin. 2003;2(5):190-6.
15. Lee WM. Drug induced hepatotoxicity. N Engl J Med. 1995;333(17):1118-27. https:// doi.org/ 10.1056/NEJM199510263331706
16. Kaplowitz N. Drug-induced liver injury. Clin Infect Dis. 2004;38(Suppl 2):44-8. https://doi.org/10.1086/381446
17. Adams D, Ju C, Ramaiah S, et al. Mechanisms of immune-mediated liver injury. Toxicol Sci. 2010;115(2):307-21. https://doi.org/10.1093/toxsci/kfq009
18. Grattagliano I, Bonfrate L, Diogo C, et al. Biochemical mechanisms in drug-induced liver injury: Certainties and doubts. World J Gastroenterol. 2009;15(39):4865-76. https://doi.org/10.3748/wjg.15.4865
19. García-Cortés M, Andrade R, Lucena M, et al. Hepatotoxicidad secundaria a fármacos de uso común. Gastroenterol Hepatol. 2005;28(8):461-72. https://doi.org/10.1157/13079002
20. Tarantino G, Di Minno M, Capone D. Drug-induced liver injury: Is it somehow foreseeable? World J Gastroenterol. 2009;15(23):2817-33. https://doi.org/10.3748/wjg.15.2817
21. Bakke O, Manochia M, De Abajo F, et al. Drug safety discontinuations in the United Kingdom, the United States, and Spain from 1974 through 1993: a regulatory perspective. Clin Pharmacol Ther. 1995;58(1):108-17. https://doi.org/10.1016/0009-9236(95)90078-0
22. Bénichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol. 1990;11(2):272-6. https://doi.org/10.1016/0168-8278(90)90124-A
23. Kaplowitz N. Drug Induced - Hepatotoxicity. Ann Intern Med. 1986;104(6):826-39. https://doi.org/10.7326/0003-4819-104-6-826
24. Reuben A. Hy's Law. Hepatology. 2004;39(2):574-8. https://doi.org/10.1002/hep.20081
25. Björnsson E. Drug-induced liver injury: Hy's rule revisited. Clin Pharmacol Ther. 2006;79(6):521-8. https://doi.org/10.1016/j.clpt.2006.02.012
26. Pessayre D, Fromenty B, Berson A, et al. Central role of mitochondria in drug-induced liver injury. Drug Metab Rev. 2012;44(1):34-87. https://doi.org/10.3109/03602532.2011.604086
27. Pessayre D, Mansouri A, Berson A, et al. Mitochondrial involvement in drug-induced liver injury. Handb Exp Pharmacol. 2010;(196):311-65. https://doi.org/10.1007/978-3-642-00663-0_11
28. Kass G, Price S. Role of mitochondria in drug-induced cholestatic injury. Clin Liver Dis. 2008;12(1):27-51. https://doi.org/10.1016/j.cld.2007.11.005
29. 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):335-53. https://doi.org/10.1111/j.1472-8206.2008.00608.x
30. Amacher D. A toxicologist's guide to biomarkers of hepatic response. Hum Exp Toxicol. 2002;21(5):253-62. https://doi.org/10.1191/0960327102ht247oa
31. Brunt E. Nonalcoholic steatohepatiiis (NASH): further expansion of this clinical entity? Liver. 1999;19(4):263-4. https://doi.org/10.1111/j.1478-3231.1999.tb00047.x
32. Gunawan B, Kaplowitz N. Clinical perspectives on xenobiotic-induced hepatotoxicity. Drug Metab Rev. 2004;36(2):301-12. https://doi.org/10.1081/DMR-120034148
33. Hayashi P, Fontana R. Clinical features, diagnosis, and natural history of drug-induced liver injury. Semin Liver Dis. 2014;34(2):134-44. https://doi.org/10.1055/s-0034-1375955
34. Hewitt M, Enoch S, Madden J, et al. Hepatotoxicity: a scheme for generating chemical categories for read-across,

structural alerts and insights into mechanism(s) of action. Crit Rev Toxicol. 2013;43(7):537-58. https://doi.org/10.3109/10408444.2013.811215
35. Kleiner D. The pathology of drug-induced liver injury. Semin Liver Dis. 2009;29(4):364-72. https://doi.org/10.1055/s-0029-1240005
36. Regev A, Seeff L, Merz M, et al. Causality assessment for suspected DILI during clinical phases of drug development. Drug Saf. 2014;37(S1):S47-56. https://doi.org/10.1007/s40264-014-0185-4
37. Lucena M, Camargo R, Andrade R, et al. Comparison of two clinical scales for causality assessment in hepatotoxicity. Hepatology. 2001;33(1):123-30. https://doi.org/10.1053/jhep.2001.20645
38. Lucena M, Andrade R, Rodrigo L, et al. Trovafloxacin-Induced Acute Hepatitis. Clin Infect Dis. 2000;30(2):400-1. https://doi.org/10.1086/313680
39. Andrade R, López-Ortega S. Hepatitis tóxicas. Rev Española Enfermedades Dig. 2006;98(9):701. DOI: 10.4321/S1130-01082006000900009.
40. Björnsson E. Hepatotoxicity associated with antiepileptic drugs. Acta Neurol Scand. 2008;118(5):281-90. https://doi.org/10.4321/S1130-01082006000900009
41. Amariles P, Giraldo N, Faus M. Interacciones medicamentosas: Aproximación para establecer y evaluar su relevancia clínica. Med Clin (Barc). 2007;129(1):27-35. https://doi.org/10.1157/13106681
42. Fujimoto Y, Ohhira M, Miyokawa N, et al. Acarbose-induced hepatic injury. Lancet. 1998;351(9099):340. https://doi.org/10.1016/S0140-6736(05)78337-9
43. Schiano TD, Bellary S V, Cassidy MJ, et al. Subfulminant liver failure and severe hepatotoxicity caused by loratadine use. Ann Intern Med. 1996;125(9):738-40. https://doi.org/10.7326/0003-4819-125-9-199611010-00006
44. Li H, Heller D, Leevy C, et al. Troglitazone-induced fulminant hepatitis. Report of a case withautopsy findings. J Diabetes Complications. 2000;14(3):175-7. https://doi.org/10.1016/S1056-8727(00)00076-3
45. Cocozzella D, Curciarello J, Corallini O, et al. Propafenone hepatotoxicity: report of two new cases. Dig Liver Dis. 2003;48(2):354-7.
46. Flaharty K, Chase S, Yaghsezian H, et al. Hepatotoxicity associated with amiodarone therapy. Pharmacotherapy. 1989;9(1):39-44. https://doi.org/10.1002/j.1875-9114.1989.tb04102.x
47. Shepherd N, Dawson A, Crocker P, et al. Granular cells as a marker of early amiodarone hepatotoxicity: a pathological and analytical study. J Clin Pathol. 1987;40(4):418-23. https://doi.org/10.1136/jcp.40.4.418
48. Jeserich M, Ihling C, Allgaier H, et al. Acute liver failure due to enalapril. Herz. 2000;25(7):689-93. https://doi.org/10.1007/PL00001983
49. Thomas E, Rosenthal W, Zapiach L, et al. Spectrum of methyldopa liver injury. Am J Gastroenterol. 1977;68(2):125-33.
50. Puppala A, Steinheber F. Fulminant hepatic failure associated with methyldopa. Am J Gastroenterol. 1977;68(6):578-81.
51. Pelli N, Setti M, Ceppa P, et al. Autoimmune hepatitis revealed by atorvastatin. Eur J Gastroenterol Hepatol. 2003;15(8):921-4. https://doi.org/10.1097/00042737-200308000-00014
52. Stolk M, Becx M, Kuypers K, et al. Severe hepatic side effects of ezetimibe. Clin Gastroenterol Hepatol. 2006;4(7):908-11. https://doi.org/10.1016/j.cgh.2006.04.014
53. Jonas M, Eidson M. Propylthiouracil hepatotoxicity: two pediatric cases and review of literature. J Pediatr Gastroenterol Nutr. 1988;7(5):776-8. https://doi.org/10.1097/00005176-198809000-00027
54. Melamud B, Lurie Y, Goldin E, et al. Methylprednisolone-induced liver injury: a diagnostic challenge. IMAJ. 2014;16(3):180-1.
55. Chen Y, Yang X, Zeckel M, et al. Risk of hepatic events in patients treated with vancomycin in clinical studies: a systematic review and meta-analysis. Drug saf. 2011;34(1):73-82. https://doi.org/10.2165/11539560-000000000-00000
56. Lawrenson R, Seaman H, Sundström A, et al. Liver damage associated with minocycline use in acne: a systematic review of the published literature and pharmacovigilance data. Drug Saf. 2000;23(4):333-49. https://doi.org/10.2165/00002018-200023040-00006
57. Navarro V, Senior J. Drug-related hepatotoxicity. N Engl J Med. 2006;354(7):731-9. https://doi.org/10.1056/NEJMra052270
58. Prince M, Burt A, Jones D. Hepatitis and liver dysfunction with rifampicin therapy for pruritus in primary biliary cirrhosis. Gut. 2002;50(3):436-9. https://doi.org/10.1136/gut.50.3.436
59. Hydes T, Wright M, Jaynes E, et al. Nitrofurantoin immune-mediated drug-induced liver injury: a serious complication of a commonly prescribed medication. BMJ Case Rep. 2014;2014. https://doi.org/10.1136/bcr-2013-203136
60. Edoute Y, Karmon Y, Roguin A, et al. Fatal liver necrosis associated with the use of nitrofurantoin. Isr Med Assoc J. 2001;3(5):382-3.
61. Koek G, Striker B, Blok A, et al. Flucloxacillin-associated hepatic iniurv. Liver. 1994;14(5):225-9. https://doi.org/10.1111/j.1600-0676.1994.tb00079.x
62. Clay K, Hanson J, Pope S, et al. Telithromycin: a possible cause of severe liver damage? Ann Intern Med. 2006;144(6):I42.
63. Adriaenssens B, Roskams T, Steger P, et al. Hepatotoxicity related to itraconazole: report of three cases. Acta Clin Belg. 2001;56(6):364-9. https://doi.org/10.1179/acb.2001.055
64. Jacobson M, Hanks D, Ferrell L. Fatal acute hepatic necrosis due to fluconazole. Am J Med. 1994;96(2):188-90. https://doi.org/10.1016/0002-9343(94)90141-4
65. Chien R, Yang L, Lin P, et al. Hepatic injury during ketoconazole therapy in patients with onychomycosis: a controlled cohort study. Hepatology. 1997;25(1):103-7. https://doi.org/10.1002/hep.510250119
66. Van Parys G, Evenepoel C, Van Damme B, et al. Ketoconazole-induced hepatitis: a case with a definite

cause-effect relationship. Liver. 1987;7(1):27-30. https://doi.org/10.1111/j.1600-0676.1987.tb00311.x
67. Akhtar M, Mathieson K, Arey B, et al. Hepatic histopathology and clinical characteristics associated with antiretroviral therapy in HIV patients without viral hepatitis. Eur J Gastroenterol Hepatol. 2008;20(12):1194-204. https://doi.org/10.1097/MEG.0b013e328305b9e0
68. Macías J, Neukam K, Mallolas J, et al. Liver toxicity of initial antiretroviral drug regimens including two nucleoside analogs plus one non-nucleoside analog or one ritonavir-boosted protease inhibitor in HIV/HCV-coinfected patients. HIV Clin Trials. 2012;13(2):61-9. https://doi.org/10.1310/hct1302-61
69. Clarke S, Harrington P, Condon C, et al. Late onset hepatitis and prolonged deterioration in hepatic function assciated with nevirapine therapy. Int J STD AIDS. 2000;11(5):336-7. https://doi.org/10.1177/095646240001100511 https://doi.org/10.1258/0956462001915831
70. McWhirter D, Kitteringham N, Jones R, et al. Chemotherapy induced hepatotoxicity in metastatic colorectal cancer: a review of mechanisms and outcomes. Crit Rev Oncol Hematol. 2013;88(2):404-15. https://doi.org/10.1016/j.critrevonc.2013.05.011
71. Choti M. Chemotherapy-associated hepatotoxicity: do we need to be concerned? Ann Surg Oncol. 2009;16(9):2391-4. https://doi.org/10.1245/s10434-009-0512-7
72. Agúndez J, Lucena M, Martínez C, et al. Assessment of nonsteroidal anti-inflammatory drug-induced hepatotoxicity. Expert Opin Drug Metab Toxicol. 2011;7(7):817-28. https://doi.org/10.1517/17425255.2011.574613
73. Boelsterli U, Zimmerman H, Kretz-Rommel A. Idiosyncratic liver toxicity of nonsteroidal antiinflammatory drugs: molecular mechanisms and pathology. Crit Rev Toxicol. 1995;25(3):207-35. https://doi.org/10.3109/10408449509089888
74. Prescott L. Hepatotoxicity of mild analgesics. Br J Clin Pharmacol. 1980;10(Suppl 2):373S-9S. https://doi.org/10.1111/j.1365-2125.1980.tb01825.x
75. Black M. Acetaminophen hepatotoxicity. Ann Rev Med. 1984;35:577-93. https:// doi.org/ 10.1146/ annurev.me.35.020184.003045
76. Quartuccio L, Maset M, Soardo G, et al. Acetaminophen-induced liver injury in a woman with febrile flare of systemic lupus erythematosus. J Clin Rheumatol. 2014;20(6):349-51.
77. Miller D, Dwyer J, Klatskin G. Halothane hepatitis: benign resolution of a severe lesion. Ann Intern Med. 1978;89(2):212-5. https://doi.org/10.7326/0003-4819-89-2-212
78. Munro H, Snider S, Magee J. Halothane-associated hepatitis in a 6-year-old boy: evidence for native liver regeneration following failed treatment with auxiliary liver transplantion. Anesthesiology. 1998;89(2):524-7. https://doi.org/10.1097/00000542-199808000-00033
79. Camilleri M, Victorino R, Hodgson H. Halothane aggravation of chronic liver disease. Acta Med Port. 1984;5(6):194-6.
80. Colleti R, Trainer T, Krawisz B. Reversible valproate fulminant hepatic failure. J Pediatr Gastroenterol Nutr. 1986;5(6):990-4. https://doi.org/10.1097/00005176-198611000-00032
81. Bicknese A, May W, Hickey W, et al. Early childhood hepatocerebral degeneration misdiagnosed as valproate hepatotoxicity. Ann Neurol. 1992;32(6):767-75. https://doi.org/10.1002/ana.410320610
82. Levy M, Goodman M, Van Dyne B, et al. Granulomatous hepatitis secondary to carbamazepine. Ann Intern Med. 1981;95(1):64-5. https://doi.org/10.7326/0003-4819-95-1-64
83. Horowitz S, Patwardhan R, Marcus E. Hepatotoxic reactions associated with carbamazepine therapy. Epilepsia. 1988;29(2):149-54.
84. Bhayana H, Appasami S, Thapa B, et al. Lamotrigine-induced vanishing bile duct syndrome in a child. J Pediatr Gastroenterol Nutr. 2012;55(6):e147-8. https://doi.org/10.1097/MPG.0b013e31823c2500
85. Mecarelli O, Pulitano P, Mingoia M, et al. Acute hepatitis associated with lamotrigine and managed with the molecular adsorbents recirculating system (MARS). Epilepsia. 2005;46(10):1687-9. https://doi.org/10.1111/j.1528-1167.2005.00269.x
86. Tostmann A, Boeree M, Aarnoutse R, et al. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. J Gastroenterol Hepatol. 2008;23(2):192-202. https://doi.org/10.1111/j.1440-1746.2007.05207.x
87. Cramer J, Lohse A, Burchard G, et al. Low N-acetyltransferase 2 activity in isoniazid-associated acute hepatitis requiring liver transplantation. Transpl Int. 2010;23(2):231-3. https://doi.org/10.1111/j.1432-2277.2009.00921.x
88. Yew W, Leung C. Antituberculosis drugs and hepatotoxicity. Respirology. 2006;11(6):699-707. https://doi.org/10.1111/j.1440-1843.2006.00941.x
89. Lucena M, Andrade J, Fernández M, et al. Determinants of the clinical expression of amoxicillin- clavulanate hepatotoxicity: a prospective series from Spain. Hepatology. 2006;44(4):850-6. https://doi.org/10.1002/hep.21324
90. Ortu F, Weimer L, Floridia M, et al. Raltegravir, tenofovir and emtricitabine in an HIV-infected patient with HCV chronic hepatitis, NNRTI intolerance and protease inhibitors-induced severe liver toxicity. Eur J Med Res. 2010;15(2):81-3.
91. D'Cruz C, Wimmer R, Harcke T, et al. Veno-occlusive disease of the liver in children following chemotherapy for acute myelocytic leukemia. Cancer. 1983;52(10):1803-7. https://doi.org/10.1002/1097-0142(19831115)52:10<1803::AID-CNCR2820521007>3.0.CO;2-D
92. Kaplowitz N. Idiosyncratic drug hepatotoxicity. Nat Rev Drug Discov. 2005;4(6):489-99. https://doi.org/10.1038/nrd1750
93. Schumacher J, Guo G. Mechanistic review of drug-induced steatohepatitis. Toxicol Appl Pharmacol. 2015;289(1):40-7. https://doi.org/10.1016/j.taap.2015.08.022
94. Fathi N, Mitros F, Hoffman J, et al. Longitudinal measurement of methotrexate liver concentrations does not correlate with liver damage, clinical efficacy, or toxicity during a 3.5 year double blind study in rheumatoid arthritis. J Rheumatol. 2002;29(10):2092-8.

95. Hayashi P, Fontana R, Chalasani N, et al. Under-reporting and poor adherence to monitoring guidelines for severe cases of isoniazid hepatotoxicity. Clin Gastroenterol Hepatol. 2015;13(9):1676-82. https://doi.org/10.1016/j.cgh.2015.02.024
96. Rigas B, Rosenfeld L, Barwick K, et al. Amiodarone hepatotoxicity. A clinicopathologic study of five patients. Ann Intern Med. 1986;104(3):348-51. https://doi.org/10.7326/0003-4819-104-3-348
97. Jain D, Bowlus C, James A, et al. Granular cells as a marker of early amiodarone hepatotoxicity. J Clin Gastroenterol. 2000;31(3):241-3. https://doi.org/10.1097/00004836-200010000-00012
98. Lupon-Rosés J, Simó-Canonge R, Lu-Cortez L, et al. Probable early acute hepatitis with parenteral amiodarone. Clin Cardiol. 1986;9(5):223-5. https://doi.org/10.1002/clc.4960090512
99. Onakpoya I, Heneghan C, Aronson J. Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. BMC Med. 2016;14(10):1-11. Ann Intern Med. 1986;104:348-51. https://doi.org/10.1186/s12916-016-0553-2