Structured Literature Review of Hepatic Toxicity Caused by Medicines

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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. 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)
Hepatocellular damage is defined as isolated increases of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) 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) 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 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 than 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-analyses 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:

- **Definite**: evidence in meta-analysis, systematic reviews or clinical trials (randomized or not)
- **Probable**: analytical studies or description in three or more reports of clinical cases
- **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-
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.

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), fluoxacinilin (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)
<table>
<thead>
<tr>
<th>Pharmacological group</th>
<th>Drug (number of articles) [ATC code]</th>
<th>Evidence of hepatotoxicity (types of study design)</th>
<th>Hepatotoxicity Type</th>
<th>Type of injury (probability of onset)</th>
<th>Hepatotoxicity mechanism</th>
<th>Risk factors</th>
<th>Clinical manifestations</th>
<th>Management and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>Vancomycin (1) [J01XA01]</td>
<td>Definite (systematic review and metaanalysis)</td>
<td>Idiosyncratic</td>
<td>Hepatocellular (Definite)</td>
<td>Direct toxicity or adverse immune reactions</td>
<td>No information</td>
<td>Elevated aminotransferases</td>
<td>No information</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Minocycline (5) [J01AA08]</td>
<td>Definite (systematic review, report of 2 clinical cases and review of expert groups)</td>
<td>Idiosyncratic</td>
<td>Hepatocellular (Definite)</td>
<td>Lipid peroxidation-necrosis</td>
<td>Women between 16 and 57 years with acne</td>
<td>Autoimmune hepatitis. Elevation of aminotransferases, positive antinuclear antibodies, jaundice, anorexia, fever, arthritis, fatigue, abdominal pain, nausea, rash, eosinophilia, portal inflammation, pruritis. Swollen and collapsed hepatocytes. Steatitis</td>
<td>Liver transplantation, death. Suspension of drug and favorable evolution</td>
</tr>
<tr>
<td>Antituberculosis agents</td>
<td>Isoniazid (3) [J04AC01]</td>
<td>Definite (prospective and retrospective study and expert group reviews)</td>
<td>Idiosyncratic</td>
<td>Hepatocellular (probable)</td>
<td>Lipid peroxidation-necrosis</td>
<td>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</td>
<td>Acute hepatitis. Elevation of aminotransferases, jaundice, abdominal pain, fatigue, anorexia, vomiting, dark urine. Hepatocellular necrosis</td>
<td>Suspension of drug. Liver transplantation, death.</td>
</tr>
<tr>
<td>Antituberculosis agents</td>
<td>Isoniazid + rifampicin + pyrazinamide (4) [J04AM05]</td>
<td>Definite (systematic review and reviews of expert groups)</td>
<td>Idiosyncratic</td>
<td>Hepatocellular (possible)</td>
<td>Lipid peroxidation-necrosis. Genetic polymorphism, formation of hepatotoxic metabolites</td>
<td>Advanced age and female sex, coinfection with HIV. Genetic polymorphism</td>
<td>Elevated liver enzymes, jaundice, abdominal pain, nausea, vomiting, asthenia, steatosis and necrosis. Hepatic encephalopathy, granulomatous inflammation</td>
<td>Change or suspension of medication and favorable evolution. Liver transplant</td>
</tr>
<tr>
<td>Estrogen antagonist</td>
<td>Tamoxifen (5) [L02BA01]</td>
<td>Definite (randomized controlled clinical study and reporting of 6 clinical cases)</td>
<td>No information</td>
<td>Hepatocellular (Definite)</td>
<td>Decreased β oxidation of fatty acids, steatohepatitis</td>
<td>Women of 50 to 70 years with mastectomies, diabetes, consumption of alcohol &lt;20 g/day, hysterectomy, overweight, hypercholesterolemia, hypertension, osteoporosis</td>
<td>Steatohepatitis, fibrosis, hepatocellular necrosis, micronodular cirrhosis, hepatomegaly. Elevation of ALT. Nausea, vomiting, malaise, inflammatory infiltrate. Pain in the upper right quadrant and hepatic peliosis.</td>
<td>Favorable evolution. Death.</td>
</tr>
<tr>
<td>Antineoplastic</td>
<td>Everolimus (1) [L01XE10]</td>
<td>Definite (systematic review and metaanalysis)</td>
<td>No information</td>
<td>No information</td>
<td>No information</td>
<td>Patients with neoplasms and organ transplants</td>
<td>ALT elevation, fatigue</td>
<td>Adjustment of treatment or suspension of medication</td>
</tr>
</tbody>
</table>

ALT: Alanine aminotransferase; ATC: Anatomical, Therapeutic, Chemical; DM2: diabetes mellitus type 2; HIV: human immunodeficiency virus.
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, obesity, DM2 and insulin resistance. (72) Causative agents include diclofenac, lumiracoxib and nimesulide. Acetaminophen is widely recognized 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 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.

### Table 2. Drugs likely to cause probable hepatotoxicity

<table>
<thead>
<tr>
<th>Medicines</th>
<th>Acarbose</th>
<th>Acetaminophen</th>
<th>Allopurinol</th>
<th>Azathioprine</th>
<th>Valproic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Benzarone</td>
<td>Sodium Aurothiomalate</td>
<td>Buprenorphine</td>
<td>Ciprofloxacin</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Doxapram Hydrochloride</td>
<td>Bentazepam</td>
<td>Etoposide</td>
<td>Clomethiazole</td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>Efavirenz</td>
<td>Carbamazepine</td>
<td>Flutamide</td>
<td>Dextropropoxyphene</td>
<td></td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Fluconazole</td>
<td>Cyproterone acetate</td>
<td>Glatiramer</td>
<td>Flucloxacillin</td>
<td></td>
</tr>
<tr>
<td>Flupirtine</td>
<td>Itraconazole</td>
<td>Dantrolene</td>
<td>Imatinib</td>
<td>Lamotrigine</td>
<td></td>
</tr>
<tr>
<td>Methylene</td>
<td>Ketoconazole</td>
<td>Diclofenac</td>
<td>Infliximab</td>
<td>Nitrofurantoin</td>
<td></td>
</tr>
<tr>
<td>Papaverine</td>
<td>Methylprednisolone</td>
<td>Halothane</td>
<td>Iplimumab</td>
<td>Ornidazole</td>
<td></td>
</tr>
<tr>
<td>Perhexiline</td>
<td>Nevirapine</td>
<td>Isoflurane</td>
<td>Oxaliplatin</td>
<td>Telithromycin</td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td>Propylthiouracil</td>
<td>Lumiracoxib</td>
<td>Temozolomide</td>
<td>Tocapone</td>
<td></td>
</tr>
<tr>
<td>Troglitazone</td>
<td>Rifampicin</td>
<td>Nimesulide</td>
<td>Thioguanine</td>
<td>Trovafloxacin</td>
<td></td>
</tr>
</tbody>
</table>

Vitamin A (retinol)

### Table 3. Medications likely to cause possible hepatotoxicity

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Lipoic acid</th>
<th>Alfuzosin</th>
<th>Amodiaquine</th>
<th>Amoxicillin</th>
<th>Nicotinic acid</th>
<th>Acetylsalicylic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinomycin D</td>
<td>Carmustina</td>
<td>Clozapine</td>
<td>Amphotericin B</td>
<td>Cefdinir</td>
<td>Ticlofenac</td>
<td>Alendronate sodium</td>
</tr>
<tr>
<td>Busulfan</td>
<td>Cyclofenil</td>
<td>Enflurane</td>
<td>Atomoxetine</td>
<td>Dapsone</td>
<td>Dabigatran</td>
<td>Aurothioglucose</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Cyclophosphamide</td>
<td>Felbamate</td>
<td>Brivudine</td>
<td>Candesartan</td>
<td>Etretinate</td>
<td></td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>Citarabine</td>
<td>Phenytin</td>
<td>Clindamycin</td>
<td>Clopidogrel</td>
<td>Glucosamine</td>
<td></td>
</tr>
<tr>
<td>Gilbenclamide</td>
<td>Dacarbazine</td>
<td>Phenobarbital</td>
<td>Daptomycin</td>
<td>Dalteparin</td>
<td>Indomethacin</td>
<td></td>
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<tr>
<td>Gliclizide</td>
<td>Disulfiram</td>
<td>Imiprime</td>
<td>Didanosine</td>
<td>Dalteparin</td>
<td>Indomethacin</td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Lefunomide</td>
<td>Melfloquine</td>
<td>Dapoxycycline</td>
<td>Diltiazem</td>
<td>Mebendazole</td>
<td></td>
</tr>
<tr>
<td>Loratadine</td>
<td>Mitoxantrone</td>
<td>Methylphenidate</td>
<td>Dapoxycycline</td>
<td>Diltiazem</td>
<td>Metimazol</td>
<td></td>
</tr>
<tr>
<td>Mesalamine</td>
<td>Nafidodfreyl</td>
<td>Methoxyflurane</td>
<td>Spironavacinc</td>
<td>Fosinopril</td>
<td>Nafamostat</td>
<td></td>
</tr>
<tr>
<td>Mesalazine</td>
<td>Pazopanib</td>
<td>Mirtazapine</td>
<td>Entherapycin</td>
<td>Phenprocoumon</td>
<td>Metronidazole</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>Pravastatin</td>
<td>Nefazodone</td>
<td>Piracyclindine</td>
<td>Phenprocoumon</td>
<td>Metronidazole</td>
<td></td>
</tr>
<tr>
<td>Nilotamide</td>
<td>Raloxifene</td>
<td>Nomifensine</td>
<td>Spironolactone</td>
<td>Ferrous fumarate</td>
<td>Octreotide</td>
<td></td>
</tr>
<tr>
<td>Indicine N-oxide</td>
<td>Simvastatin</td>
<td>Propofol</td>
<td>Fosomycin</td>
<td>Hydralazine</td>
<td>Oxaprinz</td>
<td></td>
</tr>
<tr>
<td>Olristat</td>
<td>Sirolimus</td>
<td>Quetiapine</td>
<td>Levofloxacin</td>
<td>Irbesartan</td>
<td>Piroxicam</td>
<td></td>
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<tr>
<td>Oxymetholone</td>
<td>Thalidomide</td>
<td>Risperidone</td>
<td>Nafillin</td>
<td>Labetalol</td>
<td>Rofecoxib</td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Tamsulosin</td>
<td>Sertraline</td>
<td>Oxacillin</td>
<td>Lisinopril</td>
<td>Sitaxentan</td>
<td></td>
</tr>
<tr>
<td>Ralnidozine</td>
<td>Ticlidumab</td>
<td>Sevoflurane</td>
<td>Quinine</td>
<td>Nicardpine</td>
<td>Terbinafine</td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Trabectedin</td>
<td>Thiopental</td>
<td>Sulafidimethoxine</td>
<td>Quinidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Undecanate de testosterone</td>
<td>Zolmitriptan</td>
<td>Zidovudine</td>
<td>Ticlopidine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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, microversiclar 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, asthma, 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 arabinoside used as part of the therapeutic regimen for myeloid leukemia in children have shown hepatomagly, cirrhosis, and veno-occlusive disease. (91)

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>AST (U/L)</th>
<th>ALT (U/L)</th>
<th>AP (U/L)</th>
<th>TB (mg/dL)</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avg.</td>
<td>SD</td>
<td>Avg.</td>
<td>SD</td>
<td>Avg.</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>10432.00</td>
<td>9533.8</td>
<td>2780.33</td>
<td>2471.0</td>
<td>247.78</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>259.80</td>
<td>238.5</td>
<td>491.86</td>
<td>424.5</td>
<td>294.67</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>1023.6</td>
<td>1016.2</td>
<td>2301.0</td>
<td>2455.2</td>
<td>216.75</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>7342.0</td>
<td>12129.7</td>
<td>5963.5</td>
<td>6265.7</td>
<td>176</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>359.9</td>
<td>523.4</td>
<td>716.00</td>
<td>867.4</td>
<td>208.67</td>
</tr>
<tr>
<td>Propafenone</td>
<td>106</td>
<td>109.1</td>
<td>111.67</td>
<td>96.0</td>
<td>791.33</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>652.5</td>
<td>717.7</td>
<td>690.5</td>
<td>291.5</td>
<td>214.1</td>
</tr>
<tr>
<td>Ornidazole</td>
<td>1027.4</td>
<td>543.9</td>
<td>1315.4</td>
<td>1018.5</td>
<td>509.6</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>1209</td>
<td>1663.1</td>
<td>1008.25</td>
<td>862.0</td>
<td>281</td>
</tr>
<tr>
<td>Minocycline</td>
<td>833.83</td>
<td>689.1</td>
<td>1090</td>
<td>830.7</td>
<td>132.20</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>360</td>
<td>260.6</td>
<td>520</td>
<td>210.7</td>
<td>308.67</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>276.40</td>
<td>376.7</td>
<td>92</td>
<td>0</td>
<td>275.3</td>
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<td>Lamotrigine</td>
<td>1824</td>
<td>2716.7</td>
<td>2578.3</td>
<td>4061.4</td>
<td>147</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>3196</td>
<td>4911.6</td>
<td>1163.1</td>
<td>1169.5</td>
<td>238.7</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>189</td>
<td>181.1</td>
<td>177.7</td>
<td>79.0</td>
<td>1276</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>373.7</td>
<td>225.5</td>
<td>839.7</td>
<td>861.3</td>
<td>225.67</td>
</tr>
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<td>Enalapril</td>
<td>849</td>
<td>461.9</td>
<td>689.25</td>
<td>537.8</td>
<td>542.75</td>
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<tr>
<td>Etoposide</td>
<td>1540</td>
<td>177.8</td>
<td>1476.7</td>
<td>745.7</td>
<td>212</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>387.75</td>
<td>363.3</td>
<td>719.75</td>
<td>722.9</td>
<td>364.25</td>
</tr>
<tr>
<td>Tolcapone</td>
<td>2947.5</td>
<td>1563.0</td>
<td>1551.3</td>
<td>1296.3</td>
<td>176.33</td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td>639.17</td>
<td>557.3</td>
<td>784.80</td>
<td>506.2</td>
<td>520.6</td>
</tr>
<tr>
<td>Rifampicin</td>
<td></td>
<td></td>
<td>450.67</td>
<td>82.2</td>
<td>231</td>
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<tr>
<td>Atorvastatin</td>
<td>638.3</td>
<td>503.7</td>
<td>480.7</td>
<td>443.7</td>
<td>495.7</td>
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<tr>
<td>Infliximab</td>
<td>893.20</td>
<td>1042.6</td>
<td>720.6</td>
<td>638.3</td>
<td>250.5</td>
</tr>
</tbody>
</table>

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

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Conflict of Interests

The authors declare that they have no conflicts of interest.

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