

Psychotropic drugs and liver disease: A critical review of pharmacokinetics and liver toxicity

Diogo Telles-Correia, António Barbosa, Helena Cortez-Pinto, Carlos Campos, Nuno B F Rocha, Sérgio Machado

Diogo Telles-Correia, António Barbosa, Helena Cortez-Pinto, Faculty of Medicine, University of Lisbon, 1649-028 Lisbon, Portugal

Carlos Campos, Sérgio Machado, Institute of Psychiatry, Federal University of Rio de Janeiro, Rio de Janeiro 22290-140, Brazil

Nuno B F Rocha, School of Health Technologies, Polytechnic Institute of Porto, 4169-007, Porto, Portugal

Sérgio Machado, Postgraduate Program of Physical Activity Sciences, Salgado de Oliveira University, Niterói 24030-060, Brazil

Author contributions: Telles-Correia D, Barbosa A and Cortez-Pinto H contributed equally to this work; Telles-Correia D, Barbosa A, Cortez-Pinto H, Campos C, Rocha NBF and Machado S designed the study; Telles-Correia D, Barbosa A, Cortez-Pinto H and Rocha NBF wrote the paper.

Conflict-of-interest statement: The authors report no conflicts of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Dr. Diogo Telles-Correia, Faculty of Medicine, University of Lisbon, A.v. Padre Cruz, 1649-028 Lisbon, Portugal. tellesdiogo@gmail.com
Telephone: +351-21-7985100
Fax: +351-21-7985112

Received: June 2, 2016
Peer-review started: June 3, 2016
First decision: September 9, 2016

Revised: November 2, 2016

Accepted: November 16, 2016

Article in press: November 17, 2016

Published online: February 6, 2017

Abstract

The liver is the organ by which the majority of substances are metabolized, including psychotropic drugs. There are several pharmacokinetic changes in end-stage liver disease that can interfere with the metabolism of psychotropic drugs. This fact is particularly true in drugs with extensive first-pass metabolism, highly protein bound drugs and drugs depending on phase I hepatic metabolic reactions. Psychopharmacological agents are also associated with a risk of hepatotoxicity. The evidence is insufficient for definite conclusions regarding the prevalence and severity of psychiatric drug-induced liver injury. High-risk psychotropics are not advised when there is pre-existing liver disease, and after starting a psychotropic agent in a patient with hepatic impairment, frequent liver function/lesion monitoring is advised. The authors carefully review the pharmacokinetic disturbances induced by end-stage liver disease and the potential of psychopharmacological agents for liver toxicity.

Key words: Liver; Toxicity; Psychotropic drugs; Pharmacokinetics; Hepatic disease

© **The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The liver is the organ by which the majority of substances are metabolized, including psychotropic drugs. There are several pharmacokinetic changes in end-stage liver disease that can interfere with the metabolism of psychotropic drugs. The evidence is insufficient for definite conclusions regarding the

prevalence and severity of psychiatric drug-induced liver injury. High-risk psychotropics are not advised when there is pre-existing liver disease, and after starting a psychotropic agent in a patient with hepatic impairment, frequent liver function/lesion monitoring is advised.

Telles-Correia D, Barbosa A, Cortez-Pinto H, Campos C, Rocha NBF, Machado S. Psychotropic drugs and liver disease: A critical review of pharmacokinetics and liver toxicity. *World J Gastrointest Pharmacol Ther* 2017; 8(1): 26-38 Available from: URL: <http://www.wjgnet.com/2150-5349/full/v8/i1/26.htm> DOI: <http://dx.doi.org/10.4292/wjgpt.v8.i1.26>

INTRODUCTION

Among all of the organs in the human body, the liver performs the greatest number of functions. The liver's multiple activities are important and have impacts on all body systems, including the nervous system. It is also in the liver that most of the substances that we ingest are metabolized, including drugs.

Liver failure occurs when large parts of the liver become damaged beyond repair, and the liver is no longer able to function. Drug-induced liver injury (DILI) is the 4th most important cause of liver disease in Western countries^[1]. The incidence of DILI is between 1/10000 and 1/100000 patients-years^[2,3].

The drugs used in psychiatry and neurology are the second most important group of drugs implicated in hepatotoxicity, after anti-infectious drugs^[4]. The hepatic reserve is reduced in patients with cirrhosis or chronic hepatic failure, and when DILI occurs in such patients, it can be more severe^[5]. Therefore, high-risk drugs should be contraindicated in cases of pre-existing liver disease^[6].

Conversely, liver failure interferes with different stages of drug pharmacokinetics: Absorption, metabolism, distribution and elimination. Therefore, it affects drug concentrations, duration of action, and effectiveness. It is essential to be aware of these processes and consequent changes in the circulating concentrations of psychiatric drugs to prevent drug toxicity.

Psychiatric symptoms in patients with end-stage liver disease can occur due to co-existing psychological or physiologic processes (e.g., liver failure, encephalopathy, adjustment reactions to the stress of severe medical illness, etc.). All of these situations must be treated, not only with psychological interventions but also with psychotropic drugs. In these cases, patients with end-stage liver disease require special concern because they are medically vulnerable and are at increased risk for medication-induced adverse reactions.

The purpose of this paper is to review the evidence regarding fundamental pharmacokinetic alterations caused by end stage liver disease as well as the potential for liver toxicity with psychopharmacological

agents. In our review, we analyse the evidence for DILI, severe liver injury leading to death or liver transplantation, abnormalities of liver function tests in clinical trials and hepatotoxicity. Finally, we provide several recommendations and directions regarding the psychotropic drugs that require special attention and how to minimize the risks of liver toxicity.

PHARMACOKINETIC CHANGES IN END-STAGE LIVER DISEASE

Liver failure can affect some aspects of medication pharmacokinetics, ranging from absorption to distribution and elimination. We discuss the most important pharmacokinetic processes that might lead to increased drug concentrations in liver disease patients.

Distribution

In end-stage liver disease, a great part of the blood in the portal vein escapes from the liver and flows straight into the systemic circulation (by means of portosystemic shunts). This process is due to intra- and extra-hepatic shunts that can occur in these patients. Therapeutic shunts (surgical and angiographic) can also be used to alleviate portal hypertension^[7].

These shunts can affect first-pass metabolism by diminishing liver perfusion. In these cases, less drug passes through the liver before systemic distribution. Consequently, there is an elevation in drug concentrations in the blood. This effect is particularly important for drugs with extensive first-pass metabolism (Table 1). The pharmacokinetics of other psychotropic drugs, such as diazepam and paroxetine, with less affinity for liver enzymes, are not as influenced by first-pass metabolism^[8].

Although olanzapine has great first-pass metabolism, it is mostly metabolized by second-phase liver metabolic processes (preserved in liver disease), so it might not be an important factor for this particular drug^[9].

Protein binding

More than 80% of psychiatric drugs are bound to plasma proteins, such as lipoproteins, alpha₁-acid-glycoprotein and albumin. Some psychotropic drugs, such as fluoxetine, aripiprazole and diazepam, are highly protein bound. Nevertheless, there are some psychotropic drugs that minimally bind to proteins, such as venlafaxine, lithium, topiramate, gabapentin^[10], pregabalin, methylphenidate and memantine^[11-17].

The cirrhotic liver produces a smaller quantity of albumin and alpha₁-acid-glycoprotein, which is conducive to an increased concentration of free active drug in the blood^[18,19].

This increase is particularly important for highly protein-bound drugs, such as benzodiazepines (particularly diazepam, which is more than 99% protein

Table 1 Psychotropic drugs with extensive first-pass metabolism^[10-16]

Tricyclic antidepressants - first-pass metabolism greater than 50% after oral administration
SNRI antidepressants - venlafaxine
SSRI antidepressants - sertraline
NRI antidepressants - bupropion
Typical antipsychotics - chlorpromazine
Atypical antipsychotics - olanzapine (40%), quetiapine

SSRI: Selective serotonin reuptake inhibitors; SNRI: Serotonin and norepinephrine reuptake inhibitors; NRI: Norepinephrine reuptake inhibitors.

bound)^[20]. Therefore, in cirrhosis, the side effects that result from the administration of these drugs, such as sedation, can be more severe.

Metabolism

Some psychotropic drugs are water-soluble and are directly removed from the circulation in the urine and bile, which is the case with lithium, gabapentin, and topiramate^[10]. However, all of the other psychotropic drugs are lipid soluble and must be metabolized in the liver, where they undergo some chemical changes and become more soluble. Only then can they be excreted in the urine or bile.

The metabolic reactions that take place in the liver can occur in two main phases^[19]. In phase I, cytochrome P-450 enzymes (monooxygenases) are responsible for the hydrolysis, oxidation, dealkylation or reduction of the molecule. Most of the time, these reactions decrease the pharmacological activity of the substrate. However, drugs are sometimes metabolized into active metabolites, which is the case with some benzodiazepines (such as diazepam, chlordiazepoxide), tricyclic antidepressants (such as amitriptyline and imipramine) and antipsychotics (such as chlorpromazine, thioridazine, risperidone)^[10,21]. In phase II, liver enzymes are responsible for the conjugation of the drug with an endogenous molecule, such as glucuronic acid, sulphate, amino acids, acetate or glutathione. This process renders the original molecule more hydrophilic^[19], and in most of the cases, it eliminates all of the pharmacological activity.

Conjugation with glucuronic acid (glucuronidation) is normally preserved in liver disease^[21]. Therefore, it might be beneficial to select a psychiatric drug that only requires glucuronidation (and does not require a phase I reaction), which is the case with temazepam, oxazepam, and lorazepam^[8,9,19]. Olanzapine also requires almost only glucuronidation in its metabolism^[9].

Fluid status

Although it is believed that water-soluble drugs, such as lithium, are safe to use in liver disease patients, there are some aspects that must be considered.

In fact, it is not easy to maintain therapeutic serum levels of drugs such as lithium with the changes in fluid status that can occur in liver disease patients.

These changes can be due to possibly abnormal renal haemodynamics (which often occur in liver disease patients) but also to any sudden change in fluid status that can occur due to some therapeutic procedures (such as paracentesis, extreme diuresis, or diarrhoea induced in the treatment of liver encephalopathy).

If the total volume of body fluid is suddenly reduced, the regular therapeutic drug level can become critically toxic. Therefore, when using these types of drugs (such as lithium) in patients with cirrhosis, a strict coordination is mandatory between the different medical specialists that assist the patient^[10,17].

DILI

DILI can be classified depending on different criteria: Underlying injury; pathophysiological mechanism; clinical evolution; and severity of the lesion. Each of these criteria are reviewed.

Underlying liver injury

DILI can be classified into three main categories according to the pattern of liver injury (*i.e.*, hepatocellular and cholestatic or mixed). Hepatocellular injury accounts for 90% of drug-induced hepatotoxicity and is associated with abnormally high serum alanine aminotransferase (ALT) titres, with a small or no increase in alkaline phosphatase (ALP) titres; an associated high serum bilirubin level, found in cases of severe hepatocellular damage, is a marker for poor prognosis^[22]. Cholestatic liver injury is associated with high serum ALP titres only slightly higher than normal ALT levels; serum bilirubin concentrations might also be high. In cases of mixed injury, both ALT and ALP levels are abnormally high.

Another type of lesion is steatosis. This reaction is generally chronic and occurs with gradual and increased fat accumulation in the liver (especially triglycerides), which can be caused by different situations, including the use of certain drugs. In drug-induced steatosis (almost always reversible), benign macrovacuolar steatosis can become steatohepatitis and cirrhosis in some cases^[23].

Steatosis can occur with exposure to some antipsychotics (*e.g.*, clozapine, olanzapine) and antiepileptics (*e.g.*, valproate)^[23-28]. Less frequently, steatosis can be microvesicular, consistent with a more serious form of fat deposition in the hepatocytes, associated with more severe and acute clinical consequences (*i.e.*, valproate or Reye's syndrome).

Pathophysiological types of DILI

Two pathophysiological types of DILI have been identified.

The more common type is idiosyncratic, dose independent and unpredictable^[29]. It is the consequence either of immune-mediated liver damage (immunoallergic idiosyncratic DILI) or of direct cellular injury (metabolic idiosyncratic DILI)^[30]. A hypersensitivity syndrome (fever,

rash, eosinophilia, auto-antibodies) and a short latency period (1-6 wk)^[30] suggest immune-mediated hepatic injury, whereas the absence of any hypersensitivity syndrome and a longer latency period (1 mo to 1 year) suggest an idiosyncratic metabolic mechanism^[31]. Intrinsic DILI, related to drug accumulation, has also been described; it is dose dependent and predictable and has generally been observed during preclinical and clinical trials, leading to early drug withdrawal.

Clinical evolution (acute/chronic)

DILI can be acute or chronic, depending on clinical presentation. Acute DILI is the most common form of DILI, accounting for 10% of all cases of acute hepatitis. Histologically, it can present as acute hepatitis, cholestatic injury, a mixed pattern or acute steatosis. Chronic DILI is defined as persistence of abnormal liver enzymes for > 6 mo, and it accounts for 10% of DILI cases, more often following acute cholestasis. It can resemble other causes of chronic liver disease, such as autoimmune hepatitis or alcoholic liver disease^[32].

Severity of DILI

Regarding its severity, DILI can be mild, severe and fatal.

According to the Drug-Induced Liver Injury Network (DILIN), in mild DILI, there is elevation of ALT and/or alkaline phosphatase, but no important increases in bilirubin and no impairment of coagulation. In severe DILI, there is elevation of ALT and/or alkaline phosphatase, bilirubin is also increased, and one or more of the following exists: Extended jaundice for more than three months; and liver or other organ failure (induced by the drug). In fatal DILI, death occurs if the patient does not undergo liver transplantation^[33].

The available data show that all psychotropic agents are associated with a risk of hepatotoxicity^[34]. Most of the cases of DILI are mild, and liver tests normalize after drug withdrawal. Nevertheless, sometimes the consequences are very severe, leading to death or liver transplantation.

The most important means of assessing the potential for a psychotropic drug to cause severe or fatal hepatic injury is to review the published case reports. Nevertheless, there is no way to determine incidence rates, and the inexistence of case reports cannot be interpreted as the medication being free of risk regarding severe or fatal DILI. Conversely, the risks with different medications cannot be compared by this methodology because they are prescribed in different rates, and they have existed for different periods of time. For example, the probability of having case reports for older drugs is much higher than for newer ones^[35].

Another problem is that, in many cases of reported DILI for a certain drug, the patient has co-medications and several medical co-morbidities.

Detection of DILI during premarketing clinical trials is a difficult challenge because of the small numbers of

patients treated and the short duration of the majority of clinical trials (6-12 wk) relative to the latency of DILI^[36,37].

Antidepressants

Antidepressant-associated DILI is generally of the hepatocellular type and less frequently of the cholestatic or mixed type^[31-34]. Concerning pathophysiology, it can be immunoallergic or metabolic. Various biological and clinical presentations are possible, ranging from isolated increases in liver enzyme levels to loss of hepatocellular function, acute liver failure, and death^[38].

Based on severity and frequency of liver injuries reported for the different antidepressants, Voican classified the agents as high risk and lower risk. High-risk agents include tricyclic antidepressants (imipramine, amitriptyline) and nefazodone (which has been withdrawn from the market in several countries, due to 55 severe cases of DILI reported, including 20 deaths), as well as venlafaxine, duloxetine, sertraline, bupropion, trazodone, and agomelatine^[22,38-42].

Drugs with apparently lower risks are citalopram, escitalopram, paroxetine and fluvoxamine^[38,43].

Gahr *et al.*^[44] confirmed the results of Voican's comprehensive review using an innovative method. They calculated and compared reporting odds ratios, based on the number of adverse drug reactions related to hepatic disorders/total number of adverse drug reaction among several antidepressants^[44].

Regarding agomelatine (AGM), there is disagreement between the pervasive idea that this antidepressant might have a great risk of liver toxicity and the availability of published data providing this evidence perhaps because of the short life of this antidepressant^[44].

However, in a recent EMA (European Medicines Agency) post-authorization opinion, AGM was reported to be associated with a high hepatotoxic risk, and some limitations on its use were suggested. Clinical trials have shown a higher prevalence of increased ALT in patients treated with AGM (1.34% on AGM 25 mg/d, 2.51 on AGM 50 mg/d), compared to placebo (0.5%). Moreover, since the marketing authorization for AGM in 2009, several cases of severe liver injury-associated with AGM have been reported^[6,30].

These cases indicate that AGM should be avoided in patients with pre-existing liver function compromise. Furthermore, it is recommended by the company responsible for this drug that regular laboratory analysis be performed in cases of prescription of AGM. If there is treatment-associated elevation of liver enzymes, AGM should be rapidly discontinued. Patients of female sex, who are older than 50 years of age, and who are poly-medicated can have increased risk of liver toxicity related to AGM, although there is still only scarce regarding these matters. More studies are expected in this field, and they could likely affect the actual recommendations regarding AGM^[6,44]. Table 2 summarizes the data on

Table 2 Antidepressants and liver toxicity

	Epidemiology	Type of lesion	Mechanism
Tricyclic antidepressants			
Imipramine	ALT transient elevation-20% ^[45] Cholestatic jaundice: 0.5%-1% ^[2] DILI: 4/100000 patient-years ^[2,46] Fatal/Trxp DILI: 1 ^[47]	Hepatocellular, cholestatic	Immuno-allergic
Amitriptiline	ALT transient elevation-10% ^[45] Abnormal LFT: 3% ^[48] Fatal/Trxp DILI: 1 ^[39]	Hepatocellular, cholestatic	Immuno-allergic
Clomipramine	Severe DILI: 2 reports ^[42,49]	Hepatocellular	Immuno-allergic
MAO inhibitors			
Moclobemide	Abnormal LFT: 3% ^[50] Fatal DILI: 1 ^[51]	Hepatocellular, cholestatic	Immuno-allergic
Serotonin-norepinephrine reuptake inhibitors			
Venlafaxine	ALT > 3ULN: 0.4% ^[52] Severe DILI: 6 ^[53-56] Fatal DILI/Trxp: 1 ^[57]	Hepatocellular, cholestatic	Immuno-allergic, metabolic
Duloxetine	ALT > 3ULN: 1.1% ^[58] ALT > 5ULN: 0.6% ^[59] DILI: 26.2/100000 patient-years ^[60,61] Severe DILI-7 ^[5] Fatal/Trxp DILI: 13 ^[60]	Hepatocellular, cholestatic, mixed	Immuno-allergic, metabolic
Serotonin-reuptake inhibitors			
Sertraline	ALT > 3ULN: 0.5%-1.3% ^[46] DILI: 1.28/100000 patient-years ^[46] Severe DILI: 4 ^[62-65] Fatal/Trxp DILI: 2 ^[66,67]	Hepatocellular, cholestatic, mixed	Immuno-allergic, metabolic
Paroxetine	ALT > 3ULN: 1% ^[46] Severe DILI: 4 ^[68-71]	Hepatocellular, cholestatic, chronic hepatitis	Metabolic
Fluoxetine	ALT > 3ULN: 0.5% ^[46] Severe DILI: 6 ^[72-77]	Hepatocellular, cholestatic, chronic hepatitis	Metabolic
Fluvoxamine	Unknown ^[38] DILI: 3 ^[78-80]	Hepatocellular	Metabolic
Citalopram, escitalopram	No difference in LFT <i>vs</i> placebo ^[81,82]	?	?
Other antidepressants			
Nefazodone	DILI: 28.96/10000 patient-years ^[38] Severe DILI-35 ^[83] Fatal-20 ^[83]	Hepatocellular, cholestatic, mixed	Metabolic
Trazodone	ALT > 3 unknown ^[38] Severe DILI-7 ^[84] Fatal/Trxp DILI-2 ^[57,85]	Hepatocellular, cholestatic	Immuno-allergic
Bupropion	ALT > 3ULN: 0.1%-1% ^[86] Severe DILI: 3 ^[86-88] Fatal/Trxp DILI: 2 ^[89,90]	?	?
Agomelatine	ALT > 3ULN: 1.4% (25 mg/d) ALT > 3ULN: 2.5% (50 mg/d) ^[6,91] Severe DILI: 6 reports ^[92,93] Fatal/Trxp DILI: 1 ^[94]	Hepatocellular	
Mirtazapine	ALT > 3ULN: 2% ^[95] Severe DILI 2: reports ^[96]		

DILI: Drug-induced liver injury; ALT: Alanine aminotransferase; LFT: Liver function tests; ULN: Upper normal limit.

hepatotoxicity of the main antidepressant drugs.

Antipsychotics

Cytochrome P450 (in the liver) is responsible for the metabolism of most antipsychotics (excluding sulpiride, amisulpride, and paliperidone)^[97,98]. Antipsychotics can induce liver injury by means of three main mechanisms: Hepatocellular, cholestatic and steatosis.

Typical antipsychotics: The risk of hepatotoxicity with chlorpromazine is well established^[34].

The main mechanism by which chlorpromazine and other phenothiazines induce cholestatic disease remains unclear. The existence of eosinophilia and rash during its early onset (frequently 1 mo) and that there is not a dose relationship for its toxicity reveal that the mechanism could be some type of hypersensitivity. Nevertheless, some authors have indicated that its toxicity might be related to an idiosyncratic metabolic reaction that depends on individual sensitivity^[2]. The bile duct can be the most affected, and as a consequence, a severe ductopenic syndrome can occur^[2].

Table 3 Antipsychotics and liver toxicity

	Epidemiology	Type of lesion	Mechanism
Typical			
Chlorpromazine	Jaundice: 0.16%-0.3% ^[99] Severe DILI: > 350 ^[100,101,115-124]	Cholestatic	Immuno-allergic
Haloperidol	Fatal Injury: 8 ^[102-109] ALT > 3ULN: 2% ^[110] Severe DILI: 1 ^[111]	Cholestatic	Immuno-allergic
Atypical			
Clozapine	ALT > 3ULN: 15% ^[125] Severe DILI: 16 ^[126-140] Fatal Injury: 2 ^[141,142]	Hepatocellular Cholestatic Chronic esteatosis	Immuno-allergic Chronic estatois
Olanzapine	ALT > 3ULN: 6% ^[143] Severe DILI: 7 ^[139,144-149]	Hepatocellular Cholestatic Chronic esteatosis	Immuno-allergic, Chronic estatois
Risperidone	ALT > 3ULN: 3% ^[150] Severe DILI: 13 ^[150-162]	Hepatocellular Cholestatic Chronic esteatosis	Immuno-allergic Chronic estatois
Quetiapine	ALT > 3ULN: 0% ^[143] Severe DILI: 3 ^[151,163,164] Fatal injury: 2 ^[165,166]	?	?
Ziprasidone	Not reported Severe DILI: 1 ^[167]	?	?
Aripiprazole	Not reported		
Amisulpride	Not reported		

DILI: Drug-induced liver injury; ALT: Alanine aminotransferase; ULN: Upper normal limit.

A study that reviewed prescriptions in the United Kingdom between 1985 and 1991 showed a total incidence of chlorpromazine jaundice of 0.16% (more elevated in patients who were older than 70 years old, 0.3%)^[99].

Severe DILI was reported in more than 350 cases^[100,101], and fatal injury in 8 cases^[102-109].

Haloperidol, while structurally similar to the phenothiazines, rarely causes severe liver compromise. When it occurs, the mechanisms of liver toxicity are similar to those of phenothiazines (cholestatic lesions)^[2]. A frequency of elevated liver enzymes of 2%^[110] was reported, but only 1 case of severe DILI was reported^[111].

Atypical antipsychotics: Atypical antipsychotics rarely induce severe liver toxicity. Nevertheless, asymptomatic increases in the levels of liver enzymes and bilirubin are not uncommon when using these psychotropic drugs. In most cases, the laboratory changes appear after 6 wk of treatment, and they tend to disappear and not worsen^[35].

The type of hepatic lesion associated with antipsychotics can follow a primary hepatocellular pattern; therefore, the main change in laboratory tests seems to be an elevation in aminotransferases^[35]. Nonalcoholic fatty liver disease can also be associated with treatment with atypical antipsychotics *via* metabolic syndrome, which they can induce^[112].

Hence, many authors have advocated that it is important to assess liver function tests before initiating treatment with atypical antipsychotics, and subsequently, routine control of aminotransferases must

be performed. Checking every year (and 6/6 mo in the case of clozapine) has been recommended^[113]. In patients with heavy use of alcohol or other substances, more frequent control might be necessary. In this latter group of patients, it is also recommended to be more careful with slight changes in laboratory tests. If signs of liver compromise (*e.g.*, jaundice, pruritus, nausea, anorexia, *etc.*) are present, laboratory tests should be assessed at once.

The antipsychotic should be stopped if there is an asymptomatic increase in aminotransferases higher than 3 times the maximum level of normal (aminotransferases are sensitive marker of liver injury)^[114].

It is necessary to pay special attention to patients with pre-existing hepatic disease or patients treated with other drugs that can be aggressive to the liver. Because the majority of atypical antipsychotics are relatively new, there still are no long-term hepatic follow-ups with some of these drugs. Therefore, new evidence might appear in longer controlled studies regarding the frequency of and risk factors for liver damage^[108].

In his comprehensive review, Marwick stated that LFT abnormalities in adults receiving regular antipsychotics are "common, early, mild, and often transient"^[35]. Severe or fatal DILI is very rare. Chlorpromazine is the antipsychotic most associated with severe liver toxicity and therefore should not be used in patients with pre-existing liver dysfunction^[35]. Among the atypical antipsychotics clozapine, is the antipsychotic most associated with LFT abnormalities, and aripiprazole, ziprasidone and amisulpride might be associated with

Table 4 Mood stabilizers and benzodiazepines and liver toxicity

	Epidemiology	Type of lesion	Mechanism
Antiepileptics			
Carbamazepine	Transient ALT, AST, GGT elevations: 61% patients 1%-22% ^[3] DILI: 1% ^[170]	Hepatocellular, cholestatic	++Hypersensitivity -- Metabolic
Valproate	Transient ALT, AST elevations: 10%-15% patients ^[170] Hyperrubirubinemia-44% ^[170] DILI: 3%-44% ^[173]	Hepatocellular	Metabolic (Toxic metabolites through w-oxidation)
Lamotrigine	Fatal DILI: 0.02% (0.2% children < 2a) ^[1] Transient ALT, AST elevations < 1% Rare hepatotoxicity ^[170] (4 severe DILI) ^[174]	Hepatocellular	Statisis Metabolic
Topiramate	Transient ALT, AST elevations < 1% ^[1] Rare hepatotoxicity (2 severe DILI) ^[174]	Hepatocellular	Metabolic
Gabapentine; pregabalin	Rare hepatotoxicity ^[1]	?	?
Benzodiazepines			
Chlordiazepoxide, diazepam, flurazepam	Rare hepatotoxicity ^[171,172]	Cholestatic	Hypersensitivity
Lithium	Very rare hepatotoxicity ^[1]	?	?

DILI: Drug-induced liver injury; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase.

Table 5 Pharmacokinetic changes caused by end-stage liver disease: Psychotropic drugs that require special attention

Avoid drugs with extensive first-pass metabolism	Avoid Tricyclic Antidepressants (first-pass metabolism 50%), venlafaxine, sertraline, bupropion, chlorpromazine, quetiapine
Avoid highly protein bound drugs	Avoid most psychotropic drugs (specially fluoxetine, aripiprazole and benzodiazepines). Except: Venlafaxine, lithium, topiramate, a gabapentin, a pregabalin, memantine
Avoid drugs depending on phase I hepatic metabolic reactions	Preferable: Lithium, gabapentin, topiramate, amisulpride (depending mainly on renal excretion) and some benzodiazepines (oxazepam, temazepam, lorazepam) that depend on phase II reaction or glucuronidation, which is preserved in cirrhosis

fewer LFT abnormalities. Table 3 summarizes the data about the hepatotoxicity of the main antipsychotics.

Mood stabilizers and benzodiazepines

The overall incidence of the hepatotoxicity of antiepileptics has been estimated at 1/26000 to 1/36000. The most used antiepileptic drugs in psychiatry are valproate, carbamazepine, topiramate, lamotrigine and gabapentin. Of these drugs, Valproate is associated with the greatest risk of potential liver toxicity. Gabapentin and pregabalin are the safest^[129].

Valproate hepatotoxicity is generally idiosyncratic. The period of treatment before the onset of the injury can range from 3 d to 2 years. The absence of hypersensitivity symptoms, the morphology of the DILI and the slow onset suggest that the idiosyncrasy is metabolic. It is more common in infants and children^[129].

Transient elevations of aminotransferases can be present in 10%-15% of patients and hyperbilirubinemia in up to 44%. Therapy can be continued as long the elevations in aminotransferases are less than 3 times the ULN. Sometimes, normalization of liver tests occurs likely because of adaptation^[168]. Regarding carbamazepine, hepatic adverse events are frequent but are most represented by transient asymptomatic elevations in liver tests (ALT, AST, GGT).

Severe liver damage caused by carbamazepine is infrequent, but it has a very typical presentation. One to eight weeks after beginning treatment with this drug, a hypersensitivity syndrome occurs, with fever, rash, facial oedema, lymph node enlargement, and leucocytosis (with eosinophilia)^[1,169].

Less frequently, carbamazepine-induced DILI can occur without immuno-allergic characteristics. In these cases, the resulting clinical syndrome has a late onset (up to 6 mo after initiating treatment)^[1,169].

Hypersensitivity is noted in up to 10% of patients. Hepatic adverse events have been reported to constitute 10% of all hypersensitivity reactions, for a total incidence of DILI due to carbamazepine hypersensitivity reactions of 1%^[170].

Elevations in occur in less than 1% of patients on lamotrigine. Hepatotoxicity is rare and idiosyncratic, and it typically exhibits a hepatocellular pattern of injury^[170]. The same outcome occurs with topiramate^[1].

Benzodiazepine-induced liver damage is rare, with few cases reported in the literature, generally with a cholestatic pattern^[171,172].

Long-term treatment with lithium can, in some cases, induce some LFT abnormalities. These changes are generally temporary and asymptomatic, reverting even if treatment continues. In cases of lithium over-

dose, these LFT changes can be marked, although the damage is much more severe in other organs, such as the kidney^[1]. Table 4 summarizes the data about the hepatotoxicity of the main mood stabilizers and benzodiazepines.

CONCLUSION AND GENERAL RECOMMENDATIONS

The available data on psychotropic drug-induced hepatic toxicity are mostly from reported cases and, to a lesser extent, from the results of clinical trials and other studies, especially for the most recent drugs. It is therefore difficult to draw conclusions about the prevalence and severity of DILI.

Regarding pharmacokinetic changes in end-stage liver disease, there are some psychotropic drugs that require special attention, as shown in Table 5.

It is likely that all psychopharmacological agents are associated with a risk of hepatotoxicity. However, the evidence is insufficient for rigorous conclusions to be drawn about the prevalence and severity of psychiatric DILI^[175].

Hepatic reserve is reduced in patients with cirrhosis or chronic hepatic failure, and when DILI occurs in such patients, it can be more severe^[5,176]. Therefore, high-risk drugs should be contraindicated in cases of pre-existing liver disease^[6] (based on comprehensive reviews).

Before starting a psychotropic agent, baseline laboratory testing (e.g., LFT, ALT) is recommended^[113,177]. If liver disease is present, it is preferable to use psychotropic drugs with minimal liver metabolism (e.g., topiramate, sulpiride and amisulpride)^[35]. High-risk psychotropic agents (referred to in comprehensive reviews, see above) are not advised when there is pre-existing liver disease. After starting a psychotropic agent in a patient with hepatic impairment, frequent liver function/lesion monitoring is advised^[113].

If a patient has normal laboratory tests (e.g., LFT, ALT) before initiating treatment, there is no clear unanimity regarding the frequency of analysis re-assessment. Laboratory tests with ALT > 3ULN or ALP > 2ULN are considered sensitive markers for liver damage, and in these cases, the psychotropic agent should be stopped^[35,114].

After starting a psychotropic agent, patients should be counselled to report signs and symptoms of liver dysfunction that could be associated with the use of their drug, including weight loss/decreased appetite, gastrointestinal problems or changes, dark (*i.e.*, tea-coloured) urine, yellowing of eyes (*i.e.*, jaundice), weakness, or unexplained/increasing fatigue. Other signs and symptoms include pruritus, clay-coloured stools, muscle pain, and increased confusion. Some of these conditions are already associated with chronic hepatitis infection, so it is important to emphasize observations of new-onset signs and symptoms. Patients and/or their caretakers should be encouraged

to report these observations to their clinicians should they occur at any time after starting a psychotropic agent. Prompt discontinuation of the suspected agent at symptom onset might decrease the likelihood of worsening progression, which can lead to permanent liver damage^[83].

REFERENCES

- 1 **Schuster D**, Lagner C, Langer T. Why drugs fail--a study on side effects in new chemical entities. *Curr Pharm Des* 2005; **11**: 3545-3559 [PMID: 16248807 DOI: 10.2174/138161205774414510]
- 2 **Selim K**, Kaplowitz N. Hepatotoxicity of psychotropic drugs. *Hepatology* 1999; **29**: 1347-1351 [PMID: 10216114 DOI: 10.1002/hep.510290535]
- 3 **DeSanty KP**, Amabile CM. Antidepressant-induced liver injury. *Ann Pharmacother* 2007; **41**: 1201-1211 [PMID: 17609231 DOI: 10.1345/aph.1K114]
- 4 **Biour M**, Salem CB, Chazouillères O, Grangé J-D, Serfati L, Poupon R. Hépatotoxicité des médicaments 14e mise à jour du fichier bibliographique des atteintes hépatiques et des médicaments responsables. *Gastroentérologie Clinique et Biologique* 2004; **28**: 720-59
- 5 **Vuppalanchi R**, Hayashi PH, Chalasani N, Fontana RJ, Bonkovsky H, Saxena R, Kleiner D, Hoofnagle JH. Duloxetine hepatotoxicity: a case-series from the drug-induced liver injury network. *Aliment Pharmacol Ther* 2010; **32**: 1174-1183 [PMID: 20815829 DOI: 10.1111/j.1365-2036.2010.04449.x]
- 6 **Gahr M**, Freudenmann RW, Conemann BJ, Hiemke C, Schönfeldt-Lecuona C. Agomelatine and hepatotoxicity: implications of cumulated data derived from spontaneous reports of adverse drug reactions. *Pharmacopsychiatry* 2013; **46**: 214-220 [PMID: 23966266 DOI: 10.1055/s-0033-1353156]
- 7 **Powell DW**. Approach to the patients with liver diseases. In: Goldman L, Bennett JC, editors. *Cecil Textbook of Medicine*. 21 ed. Philadelphia: Saunders, 2000: 767-768
- 8 **Howden CW**, Birnie GG, Brodie MJ. Drug metabolism in liver disease. *Pharmacol Ther* 1989; **40**: 439-474 [PMID: 2646653 DOI: 10.1016/0163-7258(89)90088-0]
- 9 **Withers N**. The Liver-Impaired Patient. In: Leigh H, Streltzer J, editors. *Handbook of Consultation Liaison Psychiatry*. New York: Springer, 2008: 248-269
- 10 **Stevens J**, Fava M, Rosenbaum J, Alpert J. Psychopharmacology in the medical setting. In: Stern T, Fricchione G, Cassem N, Jellinek M, Rosenbaum J, editors. *Handbook of General Hospital Psychiatry*. 6 ed. Philadelphia: Saunders Elsevier, 2010
- 11 **DeVane CL**, Savett M, Jusko WJ. Desipramine and 2-hydroxy-desipramine pharmacokinetics in normal volunteers. *Eur J Clin Pharmacol* 1981; **19**: 61-64 [PMID: 7461025 DOI: 10.1007/BF00558386]
- 12 **Schroeder DH**. Metabolism and kinetics of bupropion. *J Clin Psychiatry* 1983; **44**: 79-81 [PMID: 6406469]
- 13 **Wetzel H**, Szegedi A, Hain C, Wiesner J, Schlegel S, Benkert O. Seroquel (ICI 204 636), a putative "atypical" antipsychotic, in schizophrenia with positive symptomatology: results of an open clinical trial and changes of neuroendocrinological and EEG parameters. *Psychopharmacology (Berl)* 1995; **119**: 231-238 [PMID: 7659771 DOI: 10.1007/BF02246165]
- 14 **Klamerus KJ**, Maloney K, Rudolph RL, Sisenwine SF, Jusko WJ, Chiang ST. Introduction of a composite parameter to the pharmacokinetics of venlafaxine and its active O-desmethyl metabolite. *J Clin Pharmacol* 1992; **32**: 716-724 [PMID: 1487561 DOI: 10.1002/j.1552-4604.1992.tb03875.x]
- 15 **Troy SM**, Parker VP, Hicks DR, Pollack GM, Chiang ST. Pharmacokinetics and effect of food on the bioavailability of orally administered venlafaxine. *J Clin Pharmacol* 1997; **37**: 954-961 [PMID: 9505987 DOI: 10.1002/j.1552-4604.1997.tb04270.x]
- 16 **Mandrioli R**, Mercolini L, Raggi MA. Evaluation of the

- pharmacokinetics, safety and clinical efficacy of sertraline used to treat social anxiety. *Expert Opin Drug Metab Toxicol* 2013; **9**: 1495-1505 [PMID: 23834458 DOI: 10.1517/17425255.2013.816675]
- 17 **Crone CC**, Gabriel GM, DiMartini A. An overview of psychiatric issues in liver disease for the consultation-liaison psychiatrist. *Psychosomatics* 2006; **47**: 188-205 [PMID: 16684936 DOI: 10.1176/appi.psy.47.3.188]
- 18 **Blaschke TF**. Protein binding and kinetics of drugs in liver diseases. *Clin Pharmacokinet* 1977; **2**: 32-44 [PMID: 322909 DOI: 10.2165/00003088-197702010-00003]
- 19 **Adedoyin A**, Branch RA. Pharmacokinetics. In: Zakim D, Boyer TD, editors. *Hepatology: A Textbook of Liver Disease*. 3 ed. Philadelphia: Saunders Elsevier, 1996
- 20 **Doweiko H**. *Concepts of Chemical Dependency*. 8 ed. Belmont: Brooks/Cole, 2009
- 21 **Beers MH**, Berkow R. *The Merck Manual of Diagnosis and Therapy*. 17 ed. West Point, PA: Merck and Co, Inc, 1999
- 22 **Aithal GP**, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, Hunt CM, Wilke RA, Avigan M, Kaplowitz N, Bjornsson E, Daly AK. Case definition and phenotype standardization in drug-induced liver injury. *Clin Pharmacol Ther* 2011; **89**: 806-815 [PMID: 21544079 DOI: 10.1038/clpt.2011.58]
- 23 **Zhang X**, Ouyang J, Thung S. Histopathologic Manifestations of Drug-induced Hepatotoxicity. In: Pysopoulos N, editor. *Clinics Review Articles: Drug Hepatotoxicity*. Philadelphia: Elsevier, 2013: 547-559
- 24 **Donato MT**, Gómez-Lechón MJ. Drug-induced liver steatosis and phospholipidosis: cell-based assays for early screening of drug candidates. *Curr Drug Metab* 2012; **13**: 1160-1173 [PMID: 22746303 DOI: 10.2174/138920012802850001]
- 25 **Zhang WV**, Ramzan I, Murray M. Impaired microsomal oxidation of the atypical antipsychotic agent clozapine in hepatic steatosis. *J Pharmacol Exp Ther* 2007; **322**: 770-777 [PMID: 17522342 DOI: 10.1124/jpet.107.124024]
- 26 **Soliman HM**, Wagih HM, Algaidi SA, Hafiz AH. Histological evaluation of the role of atypical antipsychotic drugs in inducing non-alcoholic fatty liver disease in adult male albino rats (light and electron microscopic study). *Folia Biol (Praha)* 2013; **59**: 173-180 [PMID: 24280139]
- 27 **Kleiner DE**, Chalasani NP, Lee WM, Fontana RJ, Bonkovsky HL, Watkins PB, Hayashi PH, Davern TJ, Navarro V, Reddy R, Talwalkar JA, Stolz A, Gu J, Barnhart H, Hoofnagle JH. Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations. *Hepatology* 2014; **59**: 661-670 [PMID: 24037963 DOI: 10.1002/hep.26709]
- 28 **Amacher DE**, Chalasani N. Drug-induced hepatic steatosis. *Semin Liver Dis* 2014; **34**: 205-214 [PMID: 24879984 DOI: 10.1055/s-0034-1375960]
- 29 **Lammert C**, Einarsson S, Saha C, Niklasson A, Bjornsson E, Chalasani N. Relationship between daily dose of oral medications and idiosyncratic drug-induced liver injury: search for signals. *Hepatology* 2008; **47**: 2003-2009 [PMID: 18454504 DOI: 10.1002/hep.22272]
- 30 **Kaplowitz N**. Idiosyncratic drug hepatotoxicity. *Nat Rev Drug Discov* 2005; **4**: 489-499 [PMID: 15931258 DOI: 10.1038/nrd1750]
- 31 **Andrade RJ**, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, García-Ruiz E, García-Muñoz B, González-Grande R, Pizarro A, Durán JA, Jiménez M, Rodrigo L, Romero-Gomez M, Navarro JM, Planas R, Costa J, Borrás A, Soler A, Salmerón J, Martín-Vivaldi R. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology* 2005; **129**: 512-21
- 32 **Mark D**, Harbord M. *Emergencies in Gastroenterology and Hepatology*. Oxford: Oxford University Press, 2013
- 33 **Fontana RJ**, Seeff LB, Andrade RJ, Björnsson E, Day CP, Serrano J, Hoofnagle JH. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. *Hepatology* 2010; **52**: 730-742 [PMID: 20564754 DOI: 10.1002/hep.23696]
- 34 **Aronson JK**. *Meyler's Side Effects of Psychiatric Drugs*. Oxford: Elsevier, 2009
- 35 **Marwick KF**, Taylor M, Walker SW. Antipsychotics and abnormal liver function tests: systematic review. *Clin Neuropharmacol* 2012; **35**: 244-253 [PMID: 22986798 DOI: 10.1097/WNF.0b013e-31826818b6]
- 36 **Koran LM**, Gelenberg AJ, Kornstein SG, Howland RH, Friedman RA, DeBattista C, Klein D, Kocsis JH, Schatzberg AF, Thase ME, Rush AJ, Hirschfeld RM, LaVange LM, Keller MB. Sertraline versus imipramine to prevent relapse in chronic depression. *J Affect Disord* 2001; **65**: 27-36 [PMID: 11426506 DOI: 10.1016/S0165-0327(00)00272-X]
- 37 **Van Amerongen AP**, Ferrey G, Tournoux A. A randomised, double-blind comparison of milnacipran and imipramine in the treatment of depression. *J Affect Disord* 2002; **72**: 21-31 [PMID: 12204314 DOI: 10.1016/S0165-0327(01)00422-0]
- 38 **Voican CS**, Corruble E, Naveau S, Perlemuter G. Antidepressant-induced liver injury: a review for clinicians. *Am J Psychiatry* 2014; **171**: 404-415 [PMID: 24362450 DOI: 10.1176/appi.ajp.2-013.13050709]
- 39 **Randeva HS**, Bangar V, Sailesh S, Hillhouse EW. Fatal cholestatic jaundice associated with amitriptyline. *Int J Clin Pract* 2000; **54**: 405-406 [PMID: 11092117]
- 40 **Conway CR**, McGuire JM, Baram VY. Nefazodone-induced liver failure. *J Clin Psychopharmacol* 2004; **24**: 353-354 [PMID: 15118496]
- 41 **Medicines and Healthcare products Regulatory Agency**. Agomelatine (Valdoxan): risk of liver toxicity. Drug Safety Update, 2014; 8(4). Available from: URL: <https://www.gov.uk/drug-safety-update/agomelatine-valdoxan-risk-of-liver-toxicity>
- 42 **Atmaca M**. Acute Severe Hepatotoxicity Associated with Clomipramine. *Klin Psikofarmakol B* 2011; **21**: 154-5 [DOI: 10.5455/bcp.20110706030609]
- 43 **Boyer WF**, Blumhardt CL. The safety profile of paroxetine. *J Clin Psychiatry* 1992; **53** Suppl: 61-66 [PMID: 1531828]
- 44 **Gahr M**, Zeiss R, Lang D, Connemann BJ, Schönfeldt-Lecuona C. Hepatotoxicity associated with agomelatine and other antidepressants: Disproportionality analysis using pooled pharmacovigilance data from the Uppsala Monitoring Centre. *J Clin Pharmacol* 2015; **55**: 768-773 [PMID: 25650773 DOI: 10.1002/jcph.475]
- 45 **Kaplowitz N**. Drug-Induced Liver Injury: Introduction and Overview. In: Kaplowitz N, DeLeve L, editors. *Drug-Induced Liver Disease*. 3rd ed. San Diego, USA: Elsevier, 2013
- 46 **Carvajal García-Pando A**, García del Pozo J, Sánchez AS, Velasco MA, Rueda de Castro AM, Lucena MI. Hepatotoxicity associated with the new antidepressants. *J Clin Psychiatry* 2002; **63**: 135-137 [PMID: 11874214 DOI: 10.4088/JCP.v63n0208]
- 47 **Powell WJ**, Koch-Weser J, Williams RA. Lethal hepatic necrosis after therapy with imipramine and desipramine. *JAMA* 1968; **206**: 642-645 [PMID: 4234079 DOI: 10.1001/jama.206.3.642]
- 48 **Holmberg MB**. A study of blood count and serum transaminase in prolonged treatment with amitriptyline. *J New Drugs* 1962; **2**: 361-365 [PMID: 13961401 DOI: 10.1177/009127006200200606]
- 49 **Alderman CP**, Atchison MM, McNeece JI. Concurrent agranulocytosis and hepatitis secondary to clomipramine therapy. *Br J Psychiatry* 1993; **162**: 688-689 [PMID: 8149124 DOI: 10.1192/bjp.162.5.688]
- 50 **Zimmerman HJ**, Ishak KG. The hepatic injury of monoamine oxidase inhibitors. *J Clin Psychopharmacol* 1987; **7**: 211-213 [PMID: 3624504]
- 51 **Timmings P**, Lamont D. Intrahepatic cholestasis associated with moclobemide leading to death. *Lancet* 1996; **347**: 762-763 [PMID: 8602021 DOI: 10.1016/S0140-6736(96)90114-2]
- 52 **Rudolph RL**, Derivan AT. The safety and tolerability of venlafaxine hydrochloride: analysis of the clinical trials database. *J Clin Psychopharmacol* 1996; **16**: 54S-59S; discussion 59S-61S [PMID: 8784648 DOI: 10.1097/00004714-199606002-00011]
- 53 **Sencan I**, Sahin I, Ozcetin A. Low-dose venlafaxine-associated liver toxicity in chronic hepatitis. *Ann Pharmacother* 2004; **38**: 352-353 [PMID: 14742779 DOI: 10.1345/aph.1D205]
- 54 **Horsmans Y**, De Clercq M, Sempoux C. Venlafaxine-associated

- hepatitis. *Ann Intern Med* 1999; **130**: 944 [PMID: 10375350 DOI: 10.7326/0003-4819-130-11-199906010-00014]
- 55 **Cardona X**, Avila A, Castellanos P. Venlafaxine-associated hepatitis. *Ann Intern Med* 2000; **132**: 417 [PMID: 10691596 DOI: 10.7326/0003-4819-132-5-200003070-00016]
- 56 **Yildirim B**, Tuncer C, Ergun M, Unal S. Venlafaxine-induced hepatotoxicity in a patient with ulcerative colitis. *Ann Hepatol* 2009; **8**: 271-272 [PMID: 19841512]
- 57 **Detry O**, Delwaide J, De Roover A, Hans MF, Delbouille MH, Monard J, Honoré P. Fulminant hepatic failure induced by venlafaxine and trazodone therapy: a case report. *Transplant Proc* 2009; **41**: 3435-3436 [PMID: 19857765 DOI: 10.1016/j.transproceed.2009.09.022]
- 58 **Xue F**, Strombom I, Turnbull B, Zhu S, Seeger JD. Duloxetine for depression and the incidence of hepatic events in adults. *J Clin Psychopharmacol* 2011; **31**: 517-522 [PMID: 21694615 DOI: 10.1097/JCP.0b013e31822347d9]
- 59 **Choy EH**, Mease PJ, Kajdasz DK, Wohlreich MM, Crits-Christoph P, Walker DJ, Chappell AS. Safety and tolerability of duloxetine in the treatment of patients with fibromyalgia: pooled analysis of data from five clinical trials. *Clin Rheumatol* 2009; **28**: 1035-1044 [PMID: 19533210 DOI: 10.1007/s10067-009-1203-2]
- 60 **McIntyre RS**, Panjwani ZD, Nguyen HT, Woldeyohannes HO, Alsuwaidan M, Soczynska JK, Lourenco MT, Konarski JZ, Kennedy SH. The hepatic safety profile of duloxetine: a review. *Expert Opin Drug Metab Toxicol* 2008; **4**: 281-285 [PMID: 18363543 DOI: 10.1517/17425255.4.3.281]
- 61 **Wernicke J**, Acharya N, Strombom I, Gahimer JL, D'Souza DN, DiPietro N, Utrecht JP. Hepatic effects of duloxetine-II: spontaneous reports and epidemiology of hepatic events. *Curr Drug Saf* 2008; **3**: 143-153 [PMID: 18690992 DOI: 10.2174/157488608784529198]
- 62 **Hautekeete ML**, Colle I, van Vlierberghe H, Elewaut A. Symptomatic liver injury probably related to sertraline. *Gastroenterol Clin Biol* 1998; **22**: 364-365 [PMID: 9762229]
- 63 **Persky S**, Reinus JF. Sertraline hepatotoxicity: a case report and review of the literature on selective serotonin reuptake inhibitor hepatotoxicity. *Dig Dis Sci* 2003; **48**: 939-944 [PMID: 12772794]
- 64 **Tabak F**, Gunduz F, Tahan V, Tabak O, Ozaras R. Sertraline hepatotoxicity: report of a case and review of the literature. *Dig Dis Sci* 2009; **54**: 1589-1591 [PMID: 18958618 DOI: 10.1007/s10620-008-0524-3]
- 65 **Menon RR**, Howard R. Sertraline and liver toxicity in the elderly (letter). *Int J Geriatr Psychiatr* 1994; **9**: 332-4 [DOI: 10.1002/gps.930090411]
- 66 **Verrico MM**, Nace DA, Towers AL. Fulminant chemical hepatitis possibly associated with donepezil and sertraline therapy. *J Am Geriatr Soc* 2000; **48**: 1659-1663 [PMID: 11129758 DOI: 10.1111/j.1532-5415.2000.tb03879.x]
- 67 **Fartoux-Heymann L**, Hézode C, Zafrani ES, Dhumeaux D, Mallat A. Acute fatal hepatitis related to sertraline. *J Hepatol* 2001; **35**: 683-684 [PMID: 11690719 DOI: 10.1016/S0168-8278(01)00159-3]
- 68 **Cadranel JF**, Di Martino V, Cazier A, Pras V, Bachmeyer C, Olympio P, Gonzenbach A, Mofredj A, Coutarel P, Devergie B, Biour M. Atrium and paroxetine-related severe hepatitis. *J Clin Gastroenterol* 1999; **28**: 52-55 [PMID: 9916669 DOI: 10.1097/0004836-199901000-00014]
- 69 **Odeh M**, Misseleveh I, Boss JH, Oliven A. Severe hepatotoxicity with jaundice associated with paroxetine. *Am J Gastroenterol* 2001; **96**: 2494-2496 [PMID: 11513198 DOI: 10.1111/j.1572-0241.2001.04060.x]
- 70 **Colakoglu O**, Tankurt E, Unsal B, Ugur F, Kupelioglu A, Buyrac Z, Akpinar Z. Toxic hepatitis associated with paroxetine. *Int J Clin Pract* 2005; **59**: 861-862 [PMID: 15963219 DOI: 10.1111/j.1368-5031.2005.00572.x]
- 71 **Pompili M**, Tittoto P, Mascianà R, Gasbarrini G, Rapaccini GL. Acute hepatitis associated with use of paroxetine. *Intern Emerg Med* 2008; **3**: 275-277 [PMID: 18265937 DOI: 10.1007/s11739-008-0111-9]
- 72 **Cosme A**, Barrio J, Lobo C, Gil I, Castiella A, Arenas JI. Acute cholestasis by fluoxetine. *Am J Gastroenterol* 1996; **91**: 2449-2450 [PMID: 8931446]
- 73 **Friedenberg FK**, Rothstein KD. Hepatitis secondary to fluoxetine treatment. *Am J Psychiatry* 1996; **153**: 580 [PMID: 8599417 DOI: 10.1176/ajp.153.4.580a]
- 74 **Johnston DE**, Wheeler DE. Chronic hepatitis related to use of fluoxetine. *Am J Gastroenterol* 1997; **92**: 1225-1226 [PMID: 9219808]
- 75 **Cai Q**, Benson MA, Talbot TJ, Devadas G, Swanson HJ, Olson JL, Kirchner JP. Acute hepatitis due to fluoxetine therapy. *Mayo Clin Proc* 1999; **74**: 692-694 [PMID: 10405699 DOI: 10.4065/74.7.692]
- 76 **Shuster J**. Fluoxetine and hepatitis. *Nursing* 2000; **30**: 78 [PMID: 11249443]
- 77 **Capellà D**, Bruguera M, Figueras A, Laporte J. Fluoxetine-induced hepatitis: why is postmarketing surveillance needed? *Eur J Clin Pharmacol* 1999; **55**: 545-546 [PMID: 10501826 DOI: 10.1007/s002280050671]
- 78 **Solomons K**, Gooch S, Wong A. Toxicity with selective serotonin reuptake inhibitors. *Am J Psychiatry* 2005; **162**: 1225 [PMID: 15930079 DOI: 10.1176/appi.ajp.162.6.1225]
- 79 **Bamrah JS**, Benbow SM, McKenna J. Fluvoxamine and liver enzymes. *Br J Psychiatry* 1990; **156**: 286-287 [PMID: 2107955 DOI: 10.1192/bjp.156.2.286b]
- 80 **Green BH**. Fluvoxamine and hepatic function. *Br J Psychiatry* 1988; **153**: 130-131 [PMID: 2906264 DOI: 10.1192/bjp.153.1.130]
- 81 **Gleason OC**, Yates WR, Isbell MD, Philipsen MA. An open-label trial of citalopram for major depression in patients with hepatitis C. *J Clin Psychiatry* 2002; **63**: 194-198 [PMID: 11926717]
- 82 **Schaefer M**, Sarkar R, Knop V, Effenberg S, Friebe A, Heinze L, Spengler U, Schlaepfer T, Reimer J, Buggisch P, Ockenga J, Link R, Rentrop M, Weidenbach H, Fromm G, Lieb K, Baumert TF, Heinz A, Discher T, Neumann K, Zeuzem S, Berg T. Escitalopram for the prevention of peginterferon- α 2a-associated depression in hepatitis C virus-infected patients without previous psychiatric disease: a randomized trial. *Ann Intern Med* 2012; **157**: 94-103 [PMID: 22801672 DOI: 10.7326/0003-4819-157-2-201207170-00006]
- 83 **Park SH**, Ishino R. Liver injury associated with antidepressants. *Curr Drug Saf* 2013; **8**: 207-223 [PMID: 23914755 DOI: 10.2174/1574886311308030011]
- 84 **Retzman KS**, McClintock C. Hepatotoxicity after short-term trazodone therapy. *Ann Pharmacother* 2001; **35**: 1559-1561 [PMID: 11793619]
- 85 **Hull M**, Jones R, Bendall M. Fatal hepatic necrosis associated with trazodone and neuroleptic drugs. *BMJ* 1994; **309**: 378 [PMID: 7915924 DOI: 10.1136/bmj.309.6951.378]
- 86 **Hu KQ**, Tiyyagura L, Kanel G, Redeker AG. Acute hepatitis induced by bupropion. *Dig Dis Sci* 2000; **45**: 1872-1873 [PMID: 11052334]
- 87 **Alonso Rodríguez L**, Barcina Pajares R, Fuentes Vigil J, Gutiérrez González A, Rodríguez Pérez L. Acute toxic hepatitis secondary to a single dose of bupropion. *Gastroenterol Hepatol* 2010; **33**: 547-549 [PMID: 20435378 DOI: 10.1016/j.gastrohep.2010.02.009]
- 88 **Alvaro D**, Onetti-Muda A, Moscatelli R, Atili AF. Acute cholestatic hepatitis induced by bupropion prescribed as pharmacological support to stop smoking. A case report. *Dig Liver Dis* 2001; **33**: 703-706 [PMID: 11785718 DOI: 10.1016/S1590-8658(01)80049-9]
- 89 **Khoo AL**, Tham LS, Lee KH, Lim GK. Acute liver failure with concurrent bupropion and carbimazole therapy. *Ann Pharmacother* 2003; **37**: 220-223 [PMID: 12549952 DOI: 10.1345/aph.1C159]
- 90 **Humayun F**, Shehab TM, Tworek JA, Fontana RJ. A fatal case of bupropion (Zyban) hepatotoxicity with autoimmune features: Case report. *J Med Case Rep* 2007; **1**: 88 [PMID: 17877816 DOI: 10.1186/1752-1947-1-88]
- 91 **Howland RH**. A benefit-risk assessment of agomelatine in the treatment of major depression. *Drug Saf* 2011; **34**: 709-731 [PMID: 21830835 DOI: 10.2165/11593960-000000000-00000]
- 92 **Montastruc F**, Scotto S, Vaz IR, Guerra LN, Escudero A, Sáinz M, Falomir T, Bagheri H, Herdeiro MT, Venegoni M, Montastruc JL, Carvajal A. Hepatotoxicity related to agomelatine and other new antidepressants: a case/noncase approach with information from the Portuguese, French, Spanish, and Italian pharmacovigilance systems. *J Clin Psychopharmacol* 2014; **34**: 327-330 [PMID: 24511446]

- 24561328 DOI: 10.1097/JCP.0000000000000094]
- 93 **Medicines and Healthcare products Regulatory Agency**, Commission on Human Medicines. Agomelatine (Valdoxan/Thymanax): risk of dose-related hepatotoxicity and liver failure - updated warnings and monitoring guidance. Drug Safety Update [Internet]. 2012; 6. Available from: URL: <https://www.sussexpartnership.nhs.uk/sites/default/files/documents/drug-safety-update-1012.pdf>
 - 94 **Gruz F**, Raffa S, Santucci C, Papale RM, Videla MG, Fernández MG, Yantorno S, Descalzi VI. Agomelatine: fulminant liver failure in a patient with fatty liver. *Gastroenterol Hepatol* 2014; **37**: 92-94 [PMID: 23849766 DOI: 10.1016/j.gastrohep.2013.04.008]
 - 95 **Montgomery SA**. Safety of mirtazapine: a review. *Int Clin Psychopharmacol* 1995; **10** Suppl 4: 37-45 [PMID: 8930008 DOI: 10.1097/00004850-199512004-00006]
 - 96 **Hui CK**, Yuen MF, Wong WM, Lam SK, Lai CL. Mirtazapine-induced hepatotoxicity. *J Clin Gastroenterol* 2002; **35**: 270-271 [PMID: 12192206 DOI: 10.1097/01.MCG.0000024793.18323.0B]
 - 97 **Bressolle F**, Bres J, Blanchin MD, Gomeni R. Sulpiride pharmacokinetics in humans after intramuscular administration at three dose levels. *J Pharm Sci* 1984; **73**: 1128-1136 [PMID: 6491918 DOI: 10.1002/jps.2600730826]
 - 98 **Urichuk L**, Prior TI, Dursun S, Baker G. Metabolism of atypical antipsychotics: involvement of cytochrome p450 enzymes and relevance for drug-drug interactions. *Curr Drug Metab* 2008; **9**: 410-418 [PMID: 18537577 DOI: 10.2174/138920008784746373]
 - 99 **Derby LE**, Gutthann SP, Jick H, Dean AD. Liver disorders in patients receiving chlorpromazine or isoniazid. *Pharmacotherapy* 1993; **13**: 353-358 [PMID: 8361861 DOI: 10.1002/j.1875-9114.1993.tb02742.x]
 - 100 **Ahmed A**. Hepatitis and phenothiazines. *J Indian Med Assoc* 1972; **58**: 300 [PMID: 4635961]
 - 101 **Bach N**, Thung SN, Schaffner F, Tobias H. Exaggerated cholestasis and hepatic fibrosis following simultaneous administration of chlorpromazine and sodium valproate. *Dig Dis Sci* 1989; **34**: 1303-1307 [PMID: 2502367 DOI: 10.1007/BF01537284]
 - 102 **Walker CO**, Combes B. Biliary cirrhosis induced by chlorpromazine. *Gastroenterology* 1966; **51**: 631-640 [PMID: 5926937]
 - 103 **Gruber LN**, Chapman WW, Pratt-thomas HR. Fatal toxic reaction to chlorpromazine (Thorazine). Case report and brief review of literature. *J S C Med Assoc* 1963; **59**: 203-204 [PMID: 13950880]
 - 104 **Rodin AE**, Robertson DM. Fatal toxic hepatitis following chlorpromazine therapy; report of a case with autopsy findings. *AMA Arch Pathol* 1958; **66**: 170-175 [PMID: 13558828]
 - 105 **Murphy JD**, Ofner F. A case of chlorpromazine jaundice. *Med J Aust* 1956; **43**: 504-505 [PMID: 13308597]
 - 106 **Boardman RH**. Fatal case of toxic hepatitis implicating chlorpromazine. *Br Med J* 1954; **2**: 579 [PMID: 13182288 DOI: 10.1136/bmj.2.4887.579]
 - 107 **Cammack KV**, Hoffman JW, Dodds M. Thorazine jaundice. *J Mich State Med Soc* 1958; **57**: 582-586 passim [PMID: 13539583]
 - 108 **Isaacs B**, Macarthur JG, Taylor RM. Jaundice in relation to chlorpromazine therapy. *Br Med J* 1955; **2**: 1122-1124 [PMID: 13260678 DOI: 10.1136/bmj.2.4948.1122]
 - 109 **Elliott RN**, Schrut AH, Marra JJ. Fatal acute aseptic necrosis of the liver associated with chlorpromazine. *Am J Psychiatry* 1956; **112**: 940 [PMID: 13313806 DOI: 10.1176/ajp.112.11.940]
 - 110 **Gaertner I**, Altendorf K, Batra A, Gaertner HJ. Relevance of liver enzyme elevations with four different neuroleptics: a retrospective review of 7,263 treatment courses. *J Clin Psychopharmacol* 2001; **21**: 215-222 [PMID: 11270919 DOI: 10.1097/00004714-200104000-00014]
 - 111 **Fuller CM**, Yassinger S, Donlon P, Imperato TJ, Ruebner B. Haloperidol-induced liver disease. *West J Med* 1977; **127**: 515-518 [PMID: 595591]
 - 112 **DE Hert M**, Schreurs V, Vancampfort D, VAN Winkel R. Metabolic syndrome in people with schizophrenia: a review. *World Psychiatry* 2009; **8**: 15-22 [PMID: 19293950 DOI: 10.1002/j.2051-5545.2009.tb00199.x]
 - 113 **Taylor D**, Patron C, Shitij K. Maudsley Prescribing Guidelines. 10 ed. London, England: Informa Healthcare, 2009
 - 114 **Verma S**, Kaplowitz N. Diagnosis, management and prevention of drug-induced liver injury. *Gut* 2009; **58**: 1555-1564 [PMID: 19834119 DOI: 10.1136/gut.2008.163675]
 - 115 **Ben-Yehuda A**, Bloom A, Lijovetzky G, Flusser D, Tur-Kaspa R. Chlorpromazine-induced liver and bone marrow granulomas associated with agranulocytosis. *Isr J Med Sci* 1990; **26**: 449-451 [PMID: 2401609]
 - 116 **Bolton BH**. Prolonged chlorpromazine jaundice. *Am J Gastroenterol* 1967; **48**: 497-503 [PMID: 5583132]
 - 117 **Cheongvee EM**, Hurst L, Smith RH. Agranulocytosis and jaundice associated with chlorpromazine. *Br J Clin Pract* 1967; **21**: 95-96 [PMID: 6037940]
 - 118 **Chlumská A**, Curík R, Boudová L, Mukensnabl P, Klvana P. Chlorpromazine-induced cholestatic liver disease with ductopenia. *Cesk Patol* 2001; **37**: 118-122 [PMID: 11669021]
 - 119 **Johnson EI**, Lanford RE, Solomon K. Chlorpromazine, eosinophilia, and hepatotoxicity. *Va Med* 1979; **106**: 683-684 [PMID: 484004]
 - 120 **Levine RA**, Briggs GW, Lowell DM. Chronic chlorpromazine cholangiolitic hepatitis. Report of a case with immunofluorescent studies. *Gastroenterology* 1966; **50**: 665-670 [PMID: 5327471 DOI: 10.1016/S0016-5085(66)80126-9]
 - 121 **Moradpour D**, Altorfer J, Flury R, Greminger P, Meyenberger C, Jost R, Schmid M. Chlorpromazine-induced vanishing bile duct syndrome leading to biliary cirrhosis. *Hepatology* 1994; **20**: 1437-1441 [PMID: 7982642 DOI: 10.1002/hep.1840200610]
 - 122 **Russell RI**, Allan JG, Patrick R. Active chronic hepatitis after chlorpromazine ingestion. *Br Med J* 1973; **1**: 655-656 [PMID: 4692711 DOI: 10.1136/bmj.1.5854.655]
 - 123 **Sidi Y**, Douer D, Pinkhas J. Simultaneous appearance of agranulocytosis and cholestatic jaundice following chlorpromazine treatment. *Med Interne* 1989; **27**: 69-71 [PMID: 2749161]
 - 124 **Swett C**. Adverse reactions to chlorpromazine in medical patients: a report from the Boston Collaborative Drug Surveillance Program, Boston University Medical Center. *Curr Ther Res Clin Exp* 1975; **18**: 199-206 [PMID: 809235]
 - 125 **Gaertner HJ**, Fischer E, Hoss J. Side effects of clozapine. *Psychopharmacology* (Berl) 1989; **99** Suppl: S97-100 [PMID: 2813671 DOI: 10.1007/BF00442570]
 - 126 **Barrons E**, Johnson E, Nynkowski P. Restarting clozapine: a case report. *Psychiatr Serv* 1996; **47**: 92 [PMID: 8925356 DOI: 10.1176/ps.47.1.92]
 - 127 **Bauer M**. Concurrent agranulocytosis and acute hepatitis resulting from combination of classic neuroleptics and subsequent successful clozapine treatment. *Pharmacopsychiatry* 1995; **28**: 29-31 [PMID: 7746843 DOI: 10.1055/s-2007-979585]
 - 128 **Eggert AE**, Crismon ML, Dorson PG, Taylor RL. Clozapine rechallenge after marked liver enzyme elevation. *J Clin Psychopharmacol* 1994; **14**: 425-426 [PMID: 7884025 DOI: 10.1097/00004714-199412000-00010]
 - 129 **Erdogan A**, Kocabasoglu N, Yalug I, Ozbay G, Senturk H. Management of marked liver enzyme increase during clozapine treatment: a case report and review of the literature. *Int J Psychiatry Med* 2004; **34**: 83-89 [PMID: 15242144 DOI: 10.2190/44WA-WXF7-3UHA-FDV1]
 - 130 **Fong SY**, Au Yeung KL, Tosh JM, Wing YK. Clozapine-induced toxic hepatitis with skin rash. *J Psychopharmacol* 2005; **19**: 107 [PMID: 15671137 DOI: 10.1177/0269881105047287]
 - 131 **Keane S**, Lane A, Larkin T, Clarke M. Management of clozapine-related hepatotoxicity. *J Clin Psychopharmacol* 2009; **29**: 606-607 [PMID: 19910731 DOI: 10.1097/JCP.0b013e3181c163ef]
 - 132 **Kellner M**, Wiedemann K, Krieg JC, Berg PA. Toxic hepatitis by clozapine treatment. *Am J Psychiatry* 1993; **150**: 985-986 [PMID: 8494085 DOI: 10.1176/ajp.150.6.985b]
 - 133 **Markowitz JS**, Grinberg R, Jackson C. Marked liver enzyme elevations with clozapine. *J Clin Psychopharmacol* 1997; **17**: 70-71 [PMID: 9004073 DOI: 10.1097/00004714-199702000-00025]
 - 134 **Thatcher GW**, Cates M, Bair B. Clozapine-induced toxic hepatitis. *Am J Psychiatry* 1995; **152**: 296-297 [PMID: 7840371 DOI: 10.1176/ajp.152.2.296b]
 - 135 **Thompson J**, Chengappa KN, Good CB, Baker RW, Kiewe RP,

- Bezner J, Schooler NR. Hepatitis, hyperglycemia, pleural effusion, eosinophilia, hematuria and proteinuria occurring early in clozapine treatment. *Int Clin Psychopharmacol* 1998; **13**: 95-98 [PMID: 9669191 DOI: 10.1097/00004850-199803000-00007]
- 136 **Wirshing WC**, Ames D, Bisheff S, Pierre JM, Mendoza A, Sun A. Hepatic encephalopathy associated with combined clozapine and divalproex sodium treatment. *J Clin Psychopharmacol* 1997; **17**: 120-121 [PMID: 10950478 DOI: 10.1097/00004714-199704000-0013]
- 137 **Worrall R**, Wilson A, Cullen M. Dystonia and drug-induced hepatitis in a patient treated with clozapine. *Am J Psychiatry* 1995; **152**: 647-648 [PMID: 7694924 DOI: 10.1176/ajp.152.4.647b]
- 138 **Panagiotis B**. Grand mal seizures with liver toxicity in a case of clozapine treatment. *J Neuropsychiatry Clin Neurosci* 1999; **11**: 117-118 [PMID: 9990571 DOI: 10.1176/jnp.11.1.117a]
- 139 **Raz A**, Bergman R, Eilam O, Yungerman T, Hayek T. A case report of olanzapine-induced hypersensitivity syndrome. *Am J Med Sci* 2001; **321**: 156-158 [PMID: 11217818 DOI: 10.1097/00000441-200102000-00008]
- 140 **Contoreggi C**, Cheskin LJ, Lange WR. Acute hepatitis after clozapine administration: a case report and review. *Am J Addict* 1996; **5**: 5Y11 [DOI: 10.3109/10550499608995650]
- 141 **Chang A**, Krygier DS, Chatur N, Yoshida EM. Clozapine-induced fatal fulminant hepatic failure: a case report. *Can J Gastroenterol* 2009; **23**: 376-378 [PMID: 19440569 DOI: 10.1007/978-3-540-85705-1_38]
- 142 **Macfarlane B**, Davies S, Mannan K, Sarsam R, Pariente D, Dooley J. Fatal acute fulminant liver failure due to clozapine: a case report and review of clozapine-induced hepatotoxicity. *Gastroenterology* 1997; **112**: 1707-1709 [PMID: 9136851 DOI: 10.1016/S0016-5085(97)70054-4]
- 143 **Atasoy N**, Erdogan A, Yalug I, Ozturk U, Konuk N, Atik L, Ustundag Y. A review of liver function tests during treatment with atypical antipsychotic drugs: a chart review study. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; **31**: 1255-1260 [PMID: 17600607 DOI: 10.1016/j.pnpbp.2007.05.005]
- 144 **Hung CC**, Wei IH, Huang CC. Late-onset cholestatic hepatitis induced by olanzapine in a patient with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2009; **33**: 1574-1575 [PMID: 19766687 DOI: 10.1016/j.pnpbp.2009.09.011]
- 145 **Jadallah KA**, Limauro DL, Colatrella AM. Acute hepatocellular-cholestatic liver injury after olanzapine therapy. *Ann Intern Med* 2003; **138**: 357-358 [PMID: 12585842 DOI: 10.7326/0003-4819-138-4-200302180-00023]
- 146 **Lui SY**, Tso S, Lam M, Cheung EF. Possible olanzapine-induced hepatotoxicity in a young Chinese patient. *Hong Kong Med J* 2009; **15**: 394-396 [PMID: 19801701]
- 147 **Ozcanli T**, Erdogan A, Ozdemir S, Onen B, Ozmen M, Doksat K, Sonsuz A. Severe liver enzyme elevations after three years of olanzapine treatment: a case report and review of olanzapine associated hepatotoxicity. *Prog Neuropsychopharmacol Biol Psychiatry* 2006; **30**: 1163-1166 [PMID: 16632162 DOI: 10.1016/j.pnpbp.2006.03.014]
- 148 **Tchernichovsky E**, Sirota P. Hepatotoxicity, leucopenia and neutropenia associated with olanzapine therapy. *Int J Psychiatry Clin Pract* 2004; **8**: 173-177 [PMID: 24941207 DOI: 10.1080/13651500410005577]
- 149 **Waage C**, Carlsson H, Nielsen EW. Olanzapine-induced pancreatitis: a case report. *JOP* 2004; **5**: 388-391 [PMID: 15365209]
- 150 **Pae CU**, Lim HK, Kim TS, Kim JJ, Lee CU, Lee SJ, Lee C, Paik IH. Naturalistic observation on the hepatic enzyme changes in patients treated with either risperidone or olanzapine alone. *Int Clin Psychopharmacol* 2005; **20**: 173-176 [PMID: 15812269 DOI: 10.1097/00004850-200505000-00009]
- 151 **Wright TM**, Vandenberg AM. Risperidone- and quetiapine-induced cholestasis. *Ann Pharmacother* 2007; **41**: 1518-1523
- 152 **Benazzi F**. Risperidone-induced hepatotoxicity. *Pharmacopsychiatry* 1998; **31**: 241 [PMID: 9930641 DOI: 10.1055/s-2007-979337]
- 153 **Cordeiro Q**, Elkis H. Pancreatitis and cholestatic hepatitis induced by risperidone. *J Clin Psychopharmacol* 2001; **21**: 529-530 [PMID: 11593080 DOI: 10.1097/00004714-200110000-00012]
- 154 **Esposito D**, Brocvielle H, Becquemont L, Hardy P, Chouinard G, Corruble E. Risperidone-induced immunoallergic hepatitis. *Am J Psychiatry* 2005; **162**: 1984 [PMID: 16199856 DOI: 10.1176/appi.ajp.162.10.1984]
- 155 **Fuller MA**, Simon MR, Freedman L. Risperidone-associated hepatotoxicity. *J Clin Psychopharmacol* 1996; **16**: 84-85 [PMID: 8834428 DOI: 10.1097/00004714-199602000-00018]
- 156 **Krebs S**, Dormann H, Muth-Selbach U, Hahn EG, Brune K, Schneider HT. Risperidone-induced cholestatic hepatitis. *Eur J Gastroenterol Hepatol* 2001; **13**: 67-69 [PMID: 11204814 DOI: 10.1097/00042737-200101000-00013]
- 157 **Paulzen M**, Orfanos S, Gründer G. Remission of drug-induced hepatitis after switching from risperidone to paliperidone. *Am J Psychiatry* 2010; **167**: 351-352 [PMID: 20194492 DOI: 10.1176/appi.ajp.2009.09081243]
- 158 **Llinares Tello F**, Hernández Prats C, Bosacoma Ros N, Pérez Martínez E, Climent Grana E, Navarro Polo JN, Ordovás Baines JP. Acute cholestatic hepatitis probably associated with risperidone. *Int J Psychiatry Med* 2005; **35**: 199-205 [PMID: 16240976 DOI: 10.2190/5XRB-D2XX-X8AH-32KB]
- 159 **Whitworth AB**, Liensberger D, Fleischhacker WW. Transient increase of liver enzymes induced by risperidone: two case reports. *J Clin Psychopharmacol* 1999; **19**: 475-476 [PMID: 10505592 DOI: 10.1097/00004714-199910000-00015]
- 160 **Phillips EJ**, Liu BA, Knowles SR. Rapid onset of risperidone-induced hepatotoxicity. *Ann Pharmacother* 1998; **32**: 843 [PMID: 9681106 DOI: 10.1345/aph.18022]
- 161 **López-Torres E**, Süveges A, Peñas-Lledó EM, Doña A, Dorado P, LLerena A, Berecz R. Liver enzyme abnormalities during antipsychotic treatment: a case report of risperidone-associated hepatotoxicity. *Drug Metabol Drug Interact* 2014; **29**: 123-126 [PMID: 24598833 DOI: 10.1515/dmdi-2013-0064]
- 162 **Oyewole D**, Skerritt U, Montgomery S. Jaundice associated with the use of risperidone in a case of presenile dementia. *Int J Geriatr Psychiatry* 1996; **11**: 177
- 163 **Shpaner A**, Li W, Ankoma-Sey V, Botero RC. Drug-induced liver injury: hepatotoxicity of quetiapine revisited. *Eur J Gastroenterol Hepatol* 2008; **20**: 1106-1109 [PMID: 19047843 DOI: 10.1097/MEG.0b013e3282f8e3a0]
- 164 **Al Mutairi F**, Dwivedi G, Al Ameen T. Fulminant hepatic failure in association with quetiapine: a case report. *J Med Case Rep* 2012; **6**: 418 [PMID: 23234465 DOI: 10.1186/1752-1947-6-418]
- 165 **El Hajj I**, Sharara AI, Rockey DC. Subfulminant liver failure associated with quetiapine. *Eur J Gastroenterol Hepatol* 2004; **16**: 1415-1418 [PMID: 15618854 DOI: 10.1097/00042737-200412000-00029]
- 166 **Naharci MI**, Karadurmus N, Demir O, Bozoglu E, Ak M, Doruk H. Fatal hepatotoxicity in an elderly patient receiving low-dose quetiapine. *Am J Psychiatry* 2011; **168**: 212-213 [PMID: 21297052 DOI: 10.1176/appi.ajp.2010.10091292]
- 167 **Tsai CF**, Tsai SJ, Hwang JP. Ziprasidone-induced hypersensitivity syndrome in an aged schizophrenia patient. *Int J Geriatr Psychiatry* 2005; **20**: 797-799 [PMID: 16035110 DOI: 10.1002/gps.1346]
- 168 **Shorvon SD**. Handbook of Epilepsy Treatment. 3 ed. Hoboken, USA: Wiley-Blackwell, 2010
- 169 **Dostert P**, Benedetti S. Mécanismes biochimiques de l'hépatotoxicité des psychotropes. *L'Encéphale* 1984; **10**: 199-209
- 170 **Au JS**, Pockros PJ. Drug-induced liver injury from antiepileptic drugs. *Clin Liver Dis* 2013; **17**: 687-697, x [PMID: 24099025 DOI: 10.1016/j.cld.2013.07.011]
- 171 **Andrade RJ**, Lucena MI, Alcantara R, Fraile JM. Bentazepam-associated chronic liver disease. *Lancet* 1994; **343**: 860 [PMID: 7908109 DOI: 10.1016/S0140-6736(94)92065-6]
- 172 **Fang MH**, Ginsberg AL, Dobbins WO. Cholestatic jaundice associated with flurazepam hydrochloride. *Ann Intern Med* 1978; **89**: 363-364 [PMID: 28685 DOI: 10.7326/0003-4819-89-3-363]
- 173 **Howrie DL**, Zitelli BJ, J PM. Anticonvulsant-induced hepatotoxicity. *Hosp Formul* 1983; **18**: 564-570
- 174 **Ahmed SN**, Siddiqi ZA. Antiepileptic drugs and liver disease. *Seizure* 2006; **15**: 156-164 [PMID: 16442314 DOI: 10.1016/j.seizure.2005.12.009]

- 175 **Gartlehner G**, Gaynes BN, Hansen RA, Thieda P, DeVaughn-Geiss A, Krebs EE, Moore CG, Morgan L, Lohr KN. Comparative benefits and harms of second-generation antidepressants: background paper for the American College of Physicians. *Ann Intern Med* 2008; **149**: 734-750 [PMID: 19017592 DOI: 10.7326/0003-4819-155-11-201112060-00009]
- 176 **Andrade RJ**, Lucena MI, Fernández MC, Vega JL, Camargo R. Hepatotoxicity in patients with cirrhosis, an often unrecognized problem: lessons from a fatal case related to amoxicillin/clavulanic acid. *Dig Dis Sci* 2001; **46**: 1416-1419 [PMID: 11478492]
- 177 **Golebiewski K**. Antipsychotic Monitoring. *Graylands Hosp Drug Bull* 2006; **14**: 4

P- Reviewer: Milovanovic JR **S- Editor:** Song XX

L- Editor: A **E- Editor:** Wu HL





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

