**Name of Journal: *World Journal of Gastrointestinal Pharmacology and Therapeutics***

**ESPS Manuscript NO: 30070**

**Manuscript Type: Review**

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

Telles-Correia D *et al*. Psychotropic drugs and liver disease

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

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**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:**

**Published online:**

**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 metabolization 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

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**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 metabolization 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 M. Psychotropic drugs and liver disease: A critical review of pharmacokinetics and liver toxicity. *World J Gastrointest Pharmacol Ther* 2016; In press

**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](http://www.webmd.com/digestive-disorders/digestive-diseases-liver-failure) occurs when large parts of the [liver](http://www.webmd.com/digestive-disorders/picture-of-the-liver) become damaged beyond repair, and the [liver](http://www.webmd.com/hepatitis/rmq-know-your-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 1/10.000 and 1/100.000 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 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 metabolization[9].

***Fluid status***

Although it is believed that water-soluble drugs, such as lithium, are safe to use in liver disease patients, there 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].

Elevation of liver enzymes 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 hepatotoxicity of the main antidepressant drugs.

***Antipsychotics***

Cytochrome P450 (in the liver) is responsible for the metabolization 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].

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 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 days 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 months 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 overdose, 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].

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

**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 – chloropromazine |
| Atipical antipsychotics – olanzapine (40%), quetiapine |

**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] | Hepatocelular, cholestatic | Immuno-allergic |
| Amitriptiline | ALT transient elevation-10%[45]  Abnormal LFT: 3%[48]  Fatal/Trxp DILI:1[39] | Hepatocelular, cholestatic | Immuno-allergic |
| Clomipramine | Severe DILI: 2 reports[42,49] | Hepatocelular | Immuno-allergic |
| **MAO inibitors** | | | |
| Moclobemide | Abnormal LFT: 3%[50]  Fatal DILI: 1[51] | Hepatocelular, cholestatic | Immuno-allergic |
| **Serotonin-norepinephrine reuptake inhibitors** | | | |
| Venlafaxine | ALT > 3ULN: 0.4%[52]  Severe DILI:6[53-56]  Fatal DILI/Trxp: 1[57] | Hepatocelular, 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] | Hepatocelular, cholestatic, mixed | Immuno-allergic, metabolic |
| **Serotonin- reuptake inhibitors** | | | |
| Sertraline | ALT > 3ULN: 0.5%-1.3%[46]  DILI: 1.28/100,000 patient-years[46]  Severe DILI:4[62-65]  Fatal/Trxp DILI:2[66,67] | Hepatocelular, cholestatic, mixed | Immuno-allergic, metabolic |
| Paroxetine | ALT > 3ULN: 1%[46]  Severe DILI:4[68-71] | Hepatocelular, cholestatic, chronic hepatitis | Metabolic |
| Fluoxetine | ALT > 3ULN: 0.5%[46]  Severe DILI: 6[72-77] | Hepatocelular, cholestatic, chronic hepatitis | Metabolic |
| Fluvoxamine | Unknown[38]  DILI: 3[78-80] | Hepatocelular | Metabolic |
| Citalopram, Escitalopram | No difference in LFT *vs* placebo[81,82] | ? | ? |
| **Other Antidepressants** | | | |
| Nefazodone | DILI: 28.96/10000 patient-years[38]  Severe DILI-35[83]  Fatal-20[83] | Hepatocelular, cholestatic, mixed | Metabolic |
| Trazodone | ALT > 3Unknown[38]  Severe DILI- 7[84]  Fatal/Trxp DILI- 2[57,85] | Hepatocelular, 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] | Hepatocelular |  |
| Mirtazapine | ALT > 3ULN: 2%[95]  Severe DILI 2: reports[96] |  |  |

DILI: Drug-induced liver injury; ALT: Alanine aminotransferase.

**Table 3 Antipsychotics and liver toxicity**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Epidemiology | Type of lesion | Mechanism |
| **Typical** | | | |
| Cloropromazine | Jaundice: 0.16%-0.3%[99]  S Severe DILI: > 350[100,101,115-124]  Fatal Injury: 8[102-109] | Cholestatic | Immuno-allergic |
| Haloperidol | 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] | Hepatocelular  Cholestatic  Chronic esteatosis | Immuno-allergic  Chronic estatosis. |
| Olanzapine | ALT > 3ULN: 6%[143]  Severe DILI: 7[139,144-149] | Hepatocelular  Cholestatic  Chronic esteatosis | Immuno-allergic,  Chronic estatosis. |
| Risperidone | ALT > 3ULN: 3%[150]  Severe DILI: 13[150-162] | Hepatocelular  Cholestatic  Chronic esteatosis | Immuno-allergic  Chronic estatosis. |
| 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 |  |  |
| Amissulpride | Not reported |  |  |

DILI: Drug-induced liver injury; ALT: Alanine aminotransferase.

**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] | Hepatocelular, cholestatic | ++Hypersensitivity  -- Metabolic |
| Valproate | Transient ALT, AST elevations: 10%-15% patients[170]  Hyperrubillirubinemia-44%[170]  DILI: 3%-44%[173]  Fatal DILI: 0.02% (0.2% children < 2a)[1] | Hepatocelular | Metabolic  (Toxic metabolites through w-oxidation)  Statosis |
| Lamotrigine | Transient ALT, AST elevations < 1%  Rare hepatotoxicity[170]  (4 severe DILI)[174] | Hepatocelular | Metabolic |
| Topiramate | Transient ALT, AST elevations < 1%[1]  Rare hepatotoxicity  (2 severe DILI)[174] | Hepatocelular | Metabolic |
| Gabapentine; Pregabaline | Rare hepatotoxicity[1] | ? | ? |
| **Benzodiazepines** | | | |
| Chlordiazepoxide, diazepam, flurazepam | Rare  hepatotoxicity [171,172] | Cholestatic | Hypersensitivity |
| **Litium** | | | |
|  | Very rare hepatotoxicity[1] | ? | ? |

DILI: Drug-induced liver injury; ALT: Alanine aminotransferase.

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

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