Antidepressant-Induced Liver Injury: A Review for Clinicians

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Objective: Antidepressant drugs can cause drug-induced liver injury (DILI). The authors review clinical data relevant to antidepressant-induced liver injury and provide recommendations for clinical practice.

Method: A PubMed search was conducted for publications from 1965 onward related to antidepressant-induced liver injury. The search terms were "liver injury," "liver failure," "DILI," "hepatitis," "hepatotoxicity," "cholestasis," and "aminotransferase," cross-referenced with "antidepressant."

Results: Although data on antidepressant-induced liver injury are scarce, 0.5%–3% of patients treated with antidepressants may develop asymptomatic mild elevation of serum aminotransferase levels. All antidepressants can induce hepatotoxicity, especially in elderly patients and those with polypharmacy. Liver damage is in most cases idiosyncratic and unpredictable, and it is generally unrelated to drug dosage. The interval between treatment initiation and onset of liver injury is generally between several days and 6 months. Life-threatening antidepressant-induced liver injury has been described involving fulminant liver failure or death. The underlying lesions are often of the hepatocellular type and less frequently of the cholestatic and mixed types. The antidepressants associated with greater risks of hepatotoxicity are iproniazid, nefazodone, phenelzine, imipramine, amitriptyline, duloxetine, bupropion, trazodone, tianeptine, and agomelatine. The antidepressants that seem to have the least potential for hepatotoxicity are citalopram, escitalopram, paroxetine, and fluvoxamine. Cross-toxicity has been described, mainly for tricyclic and tetracyclic antidepressants.

Conclusions: Although an infrequent event, DILI from antidepressant drugs may be irreversible, and clinicians should be aware of it. Aminotransferase surveillance is the most useful tool for detecting DILI, and prompt discontinuation of the drug responsible is essential. The results of antidepressant liver toxicity in all phases of clinical trials should be available and published. Further research is needed before any new and rigorously founded recommendations can be made.

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Drug-induced liver injury (DILI), the fourth leading cause of liver damage in Western countries, is a matter of concern in the context of increasing drug availability and prescription (1). DILI is the most frequent cause of market withdrawal of a drug and rejection of applications for a marketing license in the United States (2). The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) proposed guidelines for DILI in 2009 and 2010, respectively (3, 4).

The incidence of DILI is between 1 per 10,000 and 1 per 100,000 patient-years (5, 6), and therefore the first cases are generally described after commercialization of the drug, when a large number of patients have been exposed. In such situations, instances of DILI are often underdeclared, thus underestimating the true frequency (7, 8).

DILI can be classified as hepatocellular, cholestatic, or mixed, depending on the underlying liver injury. Hepatocellular injury is characterized by abnormally high serum alanine aminotransferase (ALT) titers with a small or no increase in alkaline phosphatase (ALP) titers; an associated high serum bilirubin level, found in cases of severe hepatocellular damage, is a marker of poor prognosis (9). Cholestatic liver injury is characterized by high serum ALP titers associated with only slightly higher than normal ALT levels; serum bilirubin concentrations may also be high. In cases of mixed injury, both ALT and ALP levels are abnormally high. Slightly higher than normal serum aminotransferase titers (less than 3 times the upper limit of normal; $<3\times$ULN) are found in 1%–5% of the general population (10). Therefore, ALT values $>3\times$ULN or ALP values $>2\times$ULN are indicative of DILI. These thresholds, however, are sensitive but not specific markers (11). To avoid unnecessary withdrawal of drugs erroneously identified to be hepatotoxic, a new threshold of $5\times$ULN for ALT has been proposed (9).

Two pathophysiological types of DILI have been identified. The most common type is idiosyncratic, dose independent, and unpredictable (12). It is the consequence

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either of immune-mediated liver damage (immuno-allergic idiosyncratic DILI) or of direct cellular injury (metabolic idiosyncratic DILI) (13). Intrinsic DILI, related to drug accumulation, has also been described; it is dose dependent and predictable and is generally observed during preclinical and clinical trials, leading to early drug withdrawal.

Our aim in this study was to review clinical data on antidepressant-induced liver injury and to provide recommendations for clinical practice against a background of increasing numbers of antidepressant prescriptions, increasing polypharmacy, a significant frequency of liver injury associated with antidepressants, and the potential risks of antidepressant-induced liver injury.

Method

We conducted a PubMed search of articles published from 1965 through September 2013, using the search terms "liver injury," "liver failure," "DILI," "hepatitis," "hepatotoxicity," "cholestasis," and "aminotransferase," cross-referenced with "antidepressant." Case reports, letters, original articles, and reviews, in English and other languages, were identified. We also noted all relevant articles in the reference lists. We carefully analyzed a total of 378 articles, from which 158 (88 case reports, 38 original papers, and 32 reviews) were selected, by author consensus, as being suitable for review based on exclusion of other causes of liver injury and the use of validated scales for drug imputability assessment.

The available data on antidepressant-induced hepatic toxicity are mostly from reported cases and to a lesser extent from results of clinical trials and other studies, especially for the most recent drugs (nefazodone, venlafaxine, duloxetine, bupropion, and agomelatine). It is therefore difficult to draw conclusions about the prevalence and severity of antidepressant-induced liver injury. In our review, the potential for causing DILI was assessed for each antidepressant on the basis of five criteria: total number of published cases of antidepressant-induced liver injury, number of published cases of severe liver injury leading to death or liver transplantation, significant abnormalities of liver function tests in clinical trials, the existence of studies describing cases of antidepressant-induced liver injury, and hepatotoxicity demonstrated by published experimental studies.

Results

Epidemiology

Asymptomatic mild abnormal liver function is detected in 0.5%−1% of patients treated with second-generation antidepressants such as selective serotonin reuptake inhibitors (SSRIs) (14–16) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (17, 18), and up to 3% of patients treated with monoamine oxidase (MAO) inhibitors or tricyclic and tetracyclic antidepressants (19, 20). Results of clinical trials evaluating liver function during antidepressant treatment are available for duloxetine, venlafaxine, and agomelatine. For the other antidepressants, the estimated rates of asymptomatic mild abnormal liver function are based on data reported by the manufacturer or on empiric evidence. The incidence of DILI is estimated to be 4 per 100,000 patient-years for tricyclic/tetracyclic antidepressants (5, 14). Overall, the incidence of antidepressant-induced liver toxicity requiring hospitalization is only 1.28–4 cases per 100,000 patient-years, except for nefazodone, for which the incidence can be estimated to be 29 cases per 100,000 patient-years (6, 14).

Risk Factors

The risk factors for antidepressant-induced liver injury are poorly known. In particular, no gene polymorphisms associated with greater susceptibility to idiosyncratic DILI from antidepressant agents have been described.

Coprescription of more than one drug targeting the same cytochrome P450 (CYP450) isoenzyme pathway may increase the risk of DILI (Table 1). The CYP450 enzyme system is responsible for phase I oxidative reactions involving drugs (21). Some antidepressants can inhibit or induce CYP450 enzyme activity, thus affecting the serum concentrations of antidepressants or their metabolites and thereby potentially increasing the risk of hepatic toxicity. Furthermore, other therapeutic compounds may compete with antidepressants for the same CYP450 metabolic pathway. Caution is required when using such combinations of drugs because of the potential for hepatotoxic reactions. Case reports describing possible drug-drug interactions involving antidepressants are summarized in Table 1. It should be noted that cross-toxicity has been described for tricyclic/tetracyclic antidepressants (40, 41) and, to a lesser extent, for SSRIs (fluvoxamine and citalopram) (42). In the context of increasing polypharmacy in major depressive disorders, drug-drug interactions must be considered for possible liver toxicity.

Antidepressant-induced liver injury is generally considered to be dose independent. However, cases of hepatic toxicity following antidepressant dosage escalation have been reported for duloxetine, nefazodone, mianserin, and sertraline (30, 38, 43, 44) (Table 2); in one case report, reduction of the daily dose was followed by reversal of mianserin-associated liver injury (43) (Table 2). In clinical trials of agomelatine, aminotransferase values >3×ULN were observed in 1.4% of patients treated with 25 mg/day and 2.5% of those treated with 50 mg/day, compared with 0.6% of the placebo group (147, 151). Although idiosyncratic drug reactions tend to be dose independent, a retrospective analysis of reported cases of DILI in the United States found that drugs with daily doses ≥50 mg were associated with a higher risk of liver failure, liver failure leading to death, and liver transplantation than those with lower doses (12). Conversely, drugs administered at daily doses ≤10 mg rarely caused DILI (12). Moreover, a recent study indicated that the association of high daily doses and high lipophilicity is predictive of a risk of liver injury (152).

Preexisting hepatic disease is usually not considered to be a risk factor for the development of antidepressant-induced liver injury, except in the case of duloxetine, for

TABLE 1. Potential Antidepressant Drug-Drug Interactions[a]

Interaction	CYP450 Metabolism	CYP450 Inhibition	Potential Enzymatic Mechanism	Reported Liver Toxicity	References
Moclobemide-fluoxetine	Moclobemide: 2C19; fluoxetine: 2D6, 2C	Moclobemide: 2D6, 2C9, 1A2; fluoxetine: 2D6, 2C9/19, 3A4	Inhibition	Death: 1	21, 22
Amitriptyline-diazepam	Amitriptyline: 2C19, 3A4, 1A2, 2C9, 2D6; diazepam: 2C19, 3A4	Amitriptyline: none; diazepam: 3A4	Competition and inhibition	Death: 1	23–25
Venlafaxine-trazodone	Venlafaxine: 2D6, 3A4; trazodone: 2D6	Venlafaxine: 2D6; trazodone: 3A4, 1A2	Competition and inhibition	Liver transplant: 1; spontaneous resolution: 1	21, 26–28
Duloxetine-mirtazapine	Duloxetine: 1A2, 2D6; mirtazapine: 1A2, 2D6	Duloxetine: none; mirtazapine: none	Competition	Death: 1; spontaneous resolution: 1	21, 29, 30
Duloxetine-fluoxetine	Duloxetine: 1A2, 2D6; fluoxetine: 2D6, 2C	Duloxetine: none; fluoxetine: 2D6, 2C9/19, 3A4	Competition and inhibition	Severe hepatocellular injury with spontaneous resolution: 1	21, 31
Duloxetine-clorazepate	Duloxetine: 1A2, 2D6; clorazepate: 3A4	Duloxetine: none; clorazepate: none	Competition and inhibition	Severe hepatocellular injury with spontaneous resolution: 1	21, 31
Duloxetine-trazodone	Duloxetine: 1A2, 2D6; trazodone: 2D6	Duloxetine: none; trazodone: 3A4, 1A2	Competition and inhibition	Fulminant hepatic failure with spontaneous resolution: 1	21, 32
Sertraline-donepezil	Sertraline: 2D6, 3A4, 2C9/19; donepezil: 2D6, 3A4, 1A2	Sertraline: 2D6, 3A4, 1A2; donepezil: none	Competition	Fulminant hepatic failure with spontaneous resolution: 1	21, 33, 34
Sertraline-diazepam	Sertraline: 2D6, 3A4, 2C9/19; diazepam: 2C19, 3A4	Sertraline; 2D6, 3A4, 1A2; diazepam: 3A4	Competition and inhibition	Death: 1	21, 24, 35
Paroxetine-trazodone	Paroxetine: 2D6; trazodone: 2D6	Paroxetine: 2D6; trazodone: 3A4, 1A2	Competition and inhibition	Spontaneous resolution: 1	21, 36
Nefazodone-clonazepam	Nefazodone: 3A4, 2D6; clonazepam: 3A4	Nefazodone: 3A4; clonazepam: none	Competition	Spontaneous resolution: 1	37, 38
Trazodone-thioridazine	Trazodone: 2D6; thioridazine: none	Trazodone: 3A4, 1A2; thioridazine: 2D6	Inhibition	Death: 1	21, 28, 39

[a] CYP450=cytochrome P450.

which DILI seems to be more frequent in patients with previous chronic liver disease or those who are at risk of liver disease (18, 31, 81). Furthermore, hepatic reserve is reduced in patients with cirrhosis or chronic hepatic failure, and when DILI occurs in such patients, it may be more severe (31, 153). Therefore, it has been suggested that agomelatine should be contraindicated in cases of preexisting liver disease (148).

Clinical Presentation and Diagnosis

Antidepressant-induced liver injury includes various biological and clinical presentations, ranging from isolated increases in liver enzyme levels to nonspecific symptoms such as fatigue, asthenia, anorexia, nausea, vomiting, and upper right abdominal pain, and also to more specific symptoms such as jaundice, dark urine or pale stool, progressive or even fulminant liver failure with hepatic encephalopathy, loss of hepatocellular functions, acute liver failure, and death. In most cases, however, patients are clinically asymptomatic and the biological alterations identified by abnormal results on liver function tests are the only elements that may raise a suspicion of antidepressant-induced liver injury.

Thus, the diagnosis of DILI often relies on the detection of an increase in ALT levels. In this context, it is important to note that there are physiological variations of ALT levels in healthy subjects. Indeed, in phase 1 clinical trials, aminotransferase activities between 1×ULN and 3×ULN can be observed in about 20% of patients treated with placebo during 2 weeks of follow-up (154). Also, although hospitalization is believed to eliminate confounding factors, it can itself be associated with an increase in ALT level (155). Similarly, changes in diet involving increased carbohydrate or fat intake can lead to a threefold increase in baseline ALT levels in only 3 days (156). Abnormal liver function test results for antidepressant-treated patients should therefore be interpreted with caution.

The mechanism of liver injury associated with antidepressants is metabolic or immuno-allergic (Table 2). A hypersensitivity syndrome (fever, rash, eosinophilia, autoantibodies) and a short latency period (1 to 6 weeks) (13) suggests immune-mediated hepatic injury, whereas the absence of any hypersensitivity syndrome and a longer latency period (1 month to 1 year) suggests an idiosyncratic metabolic mechanism (157). In most cases, the onset of DILI is between several days and 6 months after the beginning of antidepressant treatment (Table 2). Note that some of the clinical symptoms of antidepressant-induced liver injury, particularly fatigue, asthenia, anorexia, and nausea, may be misdiagnosed as symptoms of

depression or anxiety and thus may lead to an increase in the antidepressant dosage or even to coprescriptions.

Antidepressant-related hepatic injury is an exclusion diagnosis: it can mimic almost all known liver diseases (viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease, autoimmune hepatitis, metabolic diseases, biliary tract obstruction, hepatic ischemia, vascular obstruction) and consequently is diagnosed by ruling out all other possible causes (9). Several criteria are used to assess drug imputability: the patient's age, the nature of the drug, previous case reports of antidepressant-induced liver injury, drug dosage, event chronology, description of first clinical signs, alcohol consumption, concomitant medication (including self-medication, phytotherapy products, and illicit drugs), other potential causes, and the results of liver function tests after drug withdrawal (a 50% decrease in liver enzyme levels following withdrawal of the suspected culprit drug is highly suggestive of DILI). Although drug rechallenge should be avoided because of the risk of severe hepatic failure, deliberate or inadvertent drug rechallenge resulting in a deterioration of liver function test findings provides strong evidence for drug imputability.

Outcome

Antidepressant-associated DILI is generally of the hepatocellular type and less frequently of the cholestatic or mixed types (Table 2). Generally, in the hepatocellular type, there is an increase in aminotransferase levels that can rapidly normalize with drug withdrawal. In severe cases, an increase in bilirubin concentrations associated with a decrease in prothrombin time is observed. In these rare cases, the drug must be withdrawn immediately because of the risk of fulminant hepatitis and liver failure. The cholestatic pattern of DILI occurs less commonly (20, 157, 158). The antidepressants most frequently associated with a cholestatic pattern are phenelzine, moclobemide, amitriptyline, mianserin, mirtazapine, and tianeptine. Regression of cholestatic DILI is slower than that of hepatocellular DILI (159). Cases of prolonged cholestasis and vanishing bile duct syndrome (disappearance of interlobular bile ducts) leading to biliary fibrosis have been described for amitriptyline (61) and imipramine (56).

For most patients, liver test results normalize after antidepressant withdrawal. However, in some cases there may be clinical symptoms and severe DILI, such as fulminant liver failure leading to death or liver transplantation. Data on the frequency of severe antidepressant-induced liver injury are not available except for nefazodone: the incidence of severe liver failure leading to death or liver transplantation is estimated to be 1 per 250,000–300,000 patient-years of treatment (6, 115, 116). Cases of fulminant hepatic failure leading to liver transplantation or death have also been reported for other antidepressants, including phenelzine, imipramine, amitriptyline, venlafaxine, duloxetine, sertraline, bupropion, trazodone, and agomelatine (27, 31, 35, 39, 50, 57, 62, 129, 149) (Table 2). In terms of prognosis, the presence of a hepatocellular pattern of DILI with jaundice (serum bilirubin level >2×ULN)—meeting the criteria of Hy's law on DILI—is associated with a mortality rate of at least 10% (20, 157, 158). When the criteria of Hy's law are met, the culprit drug should be withdrawn immediately. There is evidence suggesting that women and patients with concomitant stable chronic liver disease have more severe forms of DILI (160). However, there is currently no satisfactory method to assess the likelihood of developing liver failure.

Results for individual drugs are summarized in Table 2.

Discussion

Antidepressant liver toxicity has been underestimated in the scientific literature, and data on DILI from antidepressant agents are scarce. Nevertheless, cases of life-threatening hepatic failure and death have been reported in patients treated with antidepressants.

For the older drugs, notably MAO inhibitors, tricyclic/tetracyclic antidepressants, fluoxetine, and mianserin, data are scarce because the results of clinical trials are not available, and only case reports have been published. With more recent drugs, such as duloxetine, venlafaxine, bupropion, and agomelatine, data from both clinical trials and published case reports are available.

The available data show that all antidepressants are associated with a risk of hepatotoxicity. However, the evidence is insufficient for rigorous conclusions to be drawn about the prevalence and severity of antidepressant-induced liver injury (161). The drugs for which the frequency of reported DILI appears to be highest are MAO inhibitors, tricyclic/tetracyclic antidepressants, nefazodone, bupropion, duloxetine, and agomelatine. Those with apparently lower risks are citalopram, escitalopram, paroxetine, and fluvoxamine. Life-threatening or severe DILI has been reported for some antidepressants, including MAO inhibitors, tricyclic/tetracyclic antidepressants, venlafaxine, duloxetine, sertraline, bupropion, nefazodone, trazodone, and agomelatine.

In most cases, liver injury associated with antidepressants emerges between several days and 6 months after the beginning of treatment. Life-threatening DILI can occur, in some patients involving fulminant liver failure requiring liver transplantation and even leading to death. Cross-toxicity has been described for tricyclic/tetracyclic antidepressants and, to a lesser extent, SSRIs.

The main limitation of this review is related to publication biases that must be considered in the analysis of the literature. Any analysis involving case reports is subject to the inherent bias toward the publication of more severe cases. Also, the number of reported cases of DILI is inevitably higher for the most frequently used antidepressants, which may tend to indicate, falsely, a higher hepatotoxicity rate. By contrast, most clinical studies do not report the effects of antidepressant treatment on liver

TABLE 2. Hepatotoxicity of the Main Antidepressant Drugs[a]

Antidepressant Class and Agent	Epidemiology	Type of Lesion	Mechanism
MAO inhibitors			
Iproniazid	Abnormal LFT: 3% of treated patients (20)	Hepatocellular	Metabolic; immuno-allergic (autoantibodies: antimitochondrial type 6) (45)
Phenelzine	Abnormal LFT: 3% of treated patients (20)	Cholestatic cirrhosis	Metabolic
Moclobemide	Abnormal LFT: 3% of treated patients (20)	Cholestatic; hepatocellular	Immuno-allergic
Tricyclic and tetracyclic drugs			
Imipramine, desipramine	Cholestatic jaundice: 0.5%–1% of treated patients (53); no DILI in clinical trials (54, 55); DILI: 4/100,000 patient-years (5, 14)	Hepatocellular; cholestatic; VBDS	Immuno-allergic
Amitriptyline	Abnormal LFT: 3% of treated patients (19)	Cholestatic; hepatocellular; VBDS	Immuno-allergic
Maprotiline	Unknown	Hepatocellular; cholestatic	Metabolic
Clomipramine	Unknown	Hepatocellular	Immuno-allergic
Serotonin-norepinephrine reuptake inhibitors			
Venlafaxine	ALT >3×ULN: 0.4% of treated patients (17)	Hepatocellular; cholestatic	Metabolic; immuno-allergic
Duloxetine	ALT >3×ULN: 1.1% of treated patients (placebo: 0.3%) (18); ALT >5×ULN: 0.6% of treated patients (placebo: 0%) (79); ALT increase leading to discontinuation in 0.4% of treated patients (80); Hy's law: 0 (79); DILI: 26.2/100,000 patient-years (80, 81)	Hepatocellular; cholestatic; mixed	Metabolic; immuno-allergic
Selective serotonin reuptake inhibitors			
Sertraline	ALT >3×ULN: 0.5%–1.3% of treated patients (14); DILI: 1.28/100,000 patient-years (14); no DILI in clinical trials (86, 87)	Hepatocellular; cholestatic; mixed	Immuno-allergic; metabolic
Paroxetine	ALT >3×ULN: 1% of treated patients (16); no DILI in clinical trials (93, 94)	Hepatocellular; cholestatic; chronic hepatitis	Metabolic
Fluoxetine	ALT >3×ULN: 0.5% of treated patients (15); no DILI in clinical trials (100, 101)	Hepatocellular; mixed; cholestatic; chronic hepatitis	Metabolic
Citalopram, escitalopram	No difference in LFT versus placebo (107, 108)	Hepatocellular	Metabolic
Fluvoxamine	Unknown	Hepatocellular	Metabolic
Other antidepressants			
Nefazodone	DILI: 28.96/100,000 patient-years (14); severe DILI: 81.3% of cases (113); death or LT: 1/250,000–300,000 patient-years (6); no DILI in clinical trials (114)	Hepatocellular	Metabolic
Trazodone	Unknown	Hepatocellular; cholestatic	Immuno-allergic
Bupropion	ALT >3×ULN: 0.1%–1% of treated patients (127); no DILI in clinical trials (128)	Hepatocellular; cholestatic	Immuno-allergic
Mianserin	Unknown	Cholestatic; mixed; hepatocellular	Immuno-allergic
Mirtazapine	ALT >3×ULN: 2% of treated patients (136); no DILI in clinical trials (136)	Cholestatic; mixed; hepatocellular	Metabolic
Tianeptine	No difference in LFT versus placebo (140); no DILI in clinical trials (140)	Cholestatic; hepatocellular	Immuno-allergic
Agomelatine	ALT >3×ULN: 1.4% with 25 mg/day and 2.5% with 50 mg/day (placebo: 0.6%) (147, 151)	Hepatocellular	Unknown

[a] DILI=drug-induced liver injury; FDA=U.S. Food and Drug Administration; LFT=liver function tests; LT=liver transplantation; recovery=full recovery; ULN=upper limit of normal; VBDS=vanishing bile duct syndrome.

Latency	Coprescriptions	Outcome	Other	Risk of Liver Injury
4 days–6 months	Fluoxetine	Death or LT in 20% of patients developing jaundice (45–48)	Hepatic focal necrosis in rats (100–400 mg/kg) (49); withdrawn in 1978 due to hepatotoxicity (available in France until 1999)	++++
2–4 months		LT: 2; cirrhosis: 1 (50, 51)		+++
1–3 weeks	Fluoxetine	Death: 1; recovery: 1 (22, 52)		++
1 week–5 months		Death: 1; LT: 1; VBDS: 1; recovery: 4; (53, 56–60)	Cross-toxicity between tricyclic/tetracyclic drugs (6, 40, 41)	+++
1–8 months		Deaths: 3; VBDS: 1; recovery: 4; (25, 61–65)	Cross-toxicity between tricyclic/tetracyclic drugs (6, 40, 41)	+++
25 days–4 years		Recovery: 5 (66–70)		+
~1 month		Recovery: 2 (40, 71)	Cross-toxicity between tricyclic/tetracyclic drugs (6, 40)	+
10 days–6 months	Trazodone	LT: 1; recovery: 9 (26, 27, 72–78)	Non-dose-dependent abnormal LFT in clinical trials (17); 1 case of DILI following venlafaxine dosage escalation (75)	++
2 weeks–3 months	Mirtazapine and fluoxetine	Death: 1; recovery: 12 (29–32, 80–82)	Dose-dependent abnormal LFT in clinical trials (80); 1 case of DILI following duloxetine dosage escalation (32); risk factor for DILI: preexisting chronic liver disease (18, 81–83) (cautious use in the U.S. [84] and contraindication in Europe [85])	+++
2 weeks–6 months		Death: 1; recovery: 10 (34, 35, 44, 88–92)		++
1 day–10 months		Recovery: 12 (36, 95–99)		+
2.5 months–1 year		Chronic hepatitis: 1; recovery: 5; (102–106)		+
4 days–8 weeks		Recovery: 4 (109–112)		+
9 days		Recovery: 1 (42)		+
4 weeks–8 months		Deaths: 2; LT: 3; severe liver dysfunction: 2; recovery: 2 (14, 38, 115–119)	Discontinuation of branded formulation in 2003, but generic formulations available; FDA black box warning regarding hepatotoxicity	++++
4 days–18 months	Thioridazine	Death: 1; chronic hepatitis: 1; recovery: 5 (39, 120–126)		++
20 days–6 months	Paroxetine	Deaths: 2; recovery: 5 (127, 129–133)	DILI possible after bupropion discontinuation (134)	+++
12–28 days		Recovery: 4 (43, 135)	1 case of DILI following mianserin dosage escalation (43); positive drug rechallenge (43)	++
2 weeks–3 years	Duloxetine	Recovery: 4 (137–139)		++
6 days–2 months		Recovery: 4 (141–145)	Major metabolic: beta oxidation; microvesicular steatosis in mice (146)	++
First months of treatment		LT: 1; recovery: 1 (148–150)	Assessment of LFT recommended before treatment and then after 3, 6, 12, and 24 weeks of treatment (151); dose-dependent abnormal LFT in clinical trials (147); postmarketing settings: normalization of LFT in most cases (148)	+++

function or liver function markers, and the numbers of patients exposed to antidepressants in these studies are mostly insufficient to detect any potential liver toxicity.

The strengths of this review include the exhaustive analysis of published cases of DILI from antidepressant drugs and the evaluation of liver function test anomalies reported in clinical trials.

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 antidepressant clinical trials (6–12 weeks) relative to the latency of DILI (54, 55). Therefore, indicators of the potential for severe DILI have been proposed by the FDA: an excess of aminotransferase values increasing to >3×ULN in the treatment group relative to the placebo group; any marked elevations of aminotransferase values to >5×ULN in the treatment group without a corresponding increase in the placebo group; and one or more cases of bilirubin levels increasing to >2×ULN associated with aminotransferase levels >3×ULN (Hy's law) with no other explanation (3). The presence of one of these criteria may indicate a significant risk of DILI (at least 1 per 10,000 patient-years); consequently, shortly after marketing approval, cases of severe DILI may appear as the number of patients exposed increases. For newer antidepressants, such as agomelatine, the EMA recommends regular monitoring of liver function. Although serum aminotransferase activities are probably a poor indicator of DILI for most antidepressants, it remains the gold standard that should be used to monitor patients. Studies of various individual gene polymorphisms may allow the identification of more reliable indicators of the risk of DILI for use in the future.

Recommendations for Clinical Practice

Risk factors for DILI include age and polypharmacy. These risk factors should be checked systematically before prescribing antidepressants. It remains unclear whether existing liver damage favors, or is a risk factor for, antidepressant-induced liver injury.

Antidepressants suspected to have a higher potential for hepatotoxicity should be used with caution in elderly patients, in patients with coprescriptions, and in patients with substantial alcohol use, illicit substance use, or evidence of chronic liver disease, because in these patients the development of a severe form of DILI could have devastating consequences.

Although no dose-response relationship has been clearly demonstrated, the prescription of minimum effective dosages of antidepressant should be recommended to reduce the risk of DILI. Similarly, coprescriptions with antidepressants should be avoided as far as possible, to decrease the risk of DILI and especially the risk of severe DILI. Cases of possible drug-drug interaction have been described, so it would be advisable to avoid coprescriptions that may target the same CYP450 pathway in patients treated with antidepressants.

Ordinarily, treatments presumed to be associated with a greater risk of hepatotoxicity (iproniazid, nefazodone, tianeptine, phenelzine, imipramine, amitriptyline, duloxetine, bupropion, trazodone, and agomelatine) should not be initiated in individuals with preexisting liver failure. Although there is no clear evidence that preexisting chronic liver disease increases the likelihood of developing liver toxicity, baseline abnormalities can complicate monitoring of the patient. Moreover, in patients with a history of DILI associated with tricyclic/tetracyclic antidepressants, it is recommended that clinicians avoid prescribing these agents or other therapeutic compounds with a similar tricyclic structure, such as phenothiazines (41).

DILI is difficult to prevent, and consequently its early detection is a major goal. Physicians should therefore be aware of the possibility of antidepressant-associated liver injury. For antidepressants with a high potential for hepatotoxicity and for patients with known risk factors, systematic pretherapeutic screening and regular assessment of hepatic enzymes while under treatment may be useful. Baseline assessment of ALT, ALP, and bilirubin levels can provide an estimation of reference values and identify any liver disease. Given the physiological variations of ALT levels, a single determination of ALT before or during treatment may not be sufficiently informative. Moreover, an increase in ALT level (before any antidepressant treatment or even during treatment) may be related to an underlying liver disease, not necessarily severe, such as weight gain (nonalcoholic fatty liver disease) or active hepatitis C virus infection, that does not contraindicate antidepressant treatment. Patients with alcohol abuse may also have increased ALT levels and need antidepressants. Overall, baseline ALT values are useful as they help in the interpretation of abnormal liver function test results during antidepressant treatment; such abnormal results may be a manifestation of either underlying liver disease or antidepressant-induced hepatotoxicity.

For safety reasons, when using an antidepressant associated with a greater risk of hepatotoxicity (iproniazid, nefazodone, phenelzine, imipramine, amitriptyline, duloxetine, bupropion, trazodone, tianeptine, or agomelatine) or prescribing an antidepressant for a patient with an underlying liver disease, regular monitoring of serum ALT should be discussed, even though there is no formal recommendation for such investigations. For agomelatine, assessment of liver function is recommended for all patients before treatment and again after 3, 6, 12, and 24 weeks of treatment (151). Nevertheless, further studies are needed both to confirm the efficacy of follow-up liver function tests for the early detection of DILI and to identify patients at greater risk of DILI.

Patients should also be informed that antidepressant therapy can be associated with liver abnormalities ranging from asymptomatic reversible increases in serum aminotransferase levels to signs and symptoms of liver dysfunction

(jaundice, anorexia, gastrointestinal complaints, malaise, and so on) and even liver failure resulting in death or liver transplantation. They should be informed that the risk of severe liver abnormalities may be increased by alcohol consumption, illicit drug use, and over-the-counter medications. Consumption of such agents should be discouraged in patients receiving antidepressants. Patients should be encouraged to refer to their primary care physician or psychiatrist should any clinical symptoms emerge suggesting the possibility of DILI, and to stop treatment if jaundice develops.

Indeed, antidepressants should be discontinued immediately in any patient with suspected DILI. It has been suggested that these drugs should be promptly discontinued when serum ALT levels are >3×ULN (or >5×ULN, as recently suggested) (9) or if there is an unexplained increase in bilirubin levels to >2×ULN. For patients with high baseline ALT levels, drug discontinuation is recommended when serum ALT levels are >3 times the baseline value. In patients with a concomitant increase in ALT and bilirubin, treatment continuation (particularly of imipramine/desipramine, amitriptyline, paroxetine, trazodone, or agomelatine) despite hepatotoxicity could lead to severe hepatic failure or chronic hepatocellular dysfunction that may progress to liver cirrhosis.

Investigations should be performed to exclude potential causes of liver injury and to confirm the diagnosis of DILI, including serological tests for hepatotropic viruses (hepatitis A, B, C, and E viruses, Epstein-Barr virus, cytomegalovirus, and herpes simplex virus), autoantibody tests, iron and copper levels, and abdominal ultrasonography. Alcohol consumption should also be evaluated, as alcoholism is common among depressed patients and may be the cause of liver injury in some cases. A recent study showed that acute hepatitis E is the cause of some cases of liver disease that were initially suspected to be DILI (162). Hepatitis E testing should therefore be performed in all cases of suspected antidepressant-induced liver injury, particularly if the clinical features are compatible with acute viral hepatitis. Abdominal ultrasonography should also be carried out to search for fatty liver, bile duct lithiasis, and permeability of the portal vein and suprahepatic veins.

As many antidepressants may lead to weight gain, an increase in ALT levels during antidepressant treatment may be related to an antidepressant-induced metabolic syndrome (nonalcoholic fatty liver disease), but not to a direct antidepressant-induced liver toxicity. Moreover, the depression itself may be associated with a metabolic syndrome (163, 164). Studies are needed to explore the relationship between metabolic syndrome (nonalcoholic fatty liver disease), antidepressant-induced weight gain, and abnormal liver function tests in antidepressant-treated patients.

Evaluation of liver function (ALT, ALP, and bilirubin tests) is essential once DILI is suspected and until normalization or return to baseline values. Liver function in most cases improves after drug discontinuation, but hepatic injury may persist for several months, particularly in cases with the cholestatic pattern.

Finally, patients with antidepressant-induced liver injury should be presumed to be at increased risk of liver injury if the same antidepressant is reintroduced. Accordingly, such patients should not be considered for retreatment with the same antidepressant or with any other antidepressant that may display cross-toxicity.

Conclusions

All antidepressant drugs may potentially cause liver injury, even at therapeutic doses. Nevertheless, DILI from antidepressant agents is a rare event, although in some cases it is irreversible. As there is still no strategy available to prevent antidepressant-induced adverse hepatic events, early detection and prompt drug discontinuation remain critical. Surveillance of liver function in clinical trials and careful evaluation of reported abnormalities could make a major contribution to the early detection of antidepressants associated with a high risk of causing DILI. Finally, further research is required before rigorously founded recommendations can be established for clinical practice.

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Clinical Guidance: Antidepressant-Induced Liver Injury

Liver dysfunction related to antidepressant use is rare, but it is unpredictable and not always reversible. Liver damage is generally unrelated to dosage and can occur with any antidepressant, but higher risks are associated with iproniazid, nefazodone, phenelzine, imipramine, amitriptyline, duloxetine, bupropion, and trazodone. In most cases, onset occurs between several days and 6 months after the beginning of antidepressant treatment. Most affected patients are clinically asymptomatic, and symptoms overlap with those of depression, e.g., fatigue, asthenia, and anorexia. If liver toxicity is suspected, Voican et al. recommend discontinuing antidepressants and conducting liver function tests. In most cases, liver function improves after antidepressant treatment is stopped.