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Review article: Drug-induced liver injury in clinical practice

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SUMMARY

Background

Drug induced liver injury (DILI) is an important differential diagnosis in many patients in clinical hepatology. DILI is the leading cause of acute liver failure and is an important safety issue when new drugs are developed.

Aims

To provide a review of the recent data on DILI with particular focus on the most common and relevant issues seen in clinical practice.

Methods

A Medline search was undertaken in order to identify relevant literature using search terms including “drug-induced liver injury” and “hepatotoxicity”.

Results

The true incidence of DILI is unknown but incidence up to 14 cases per 100, 000 inhabitants and year have been reported. Antibiotics, analgetics and NSAIDs are the most common drugs causing liver injury. Idiosyncratic DILI has been shown to have a dose dependent component and drugs without significant hepatic metabolism rarely cause DILI. **Chronic elevation in liver enzymes can develop after DILI** but this is rarely associated with clinical morbidity or mortality.

Conclusions

Drug-induced liver injury remains a diagnostic challenge. Multicenter studies and international collaborative work with well characterized patients will increase our understanding of liver injury associated with drugs. New therapies for acute liver failure due to drugs are needed.

INTRODUCTION

Definitions and Epidemiology

Hepatotoxicity and drug-induced liver injury (DILI), are terms used interchangeably in this context. Drug-induced liver injury or DILI is the term **currently** used by most clinicians and scientists in this field (1). DILI can be defined as a liver injury induced by a drug or herbal medicines leading to liver test abnormalities or liver dysfunction with reasonable exclusion of other competing etiologies. Most cases of DILI are due to *idiosyncratic* or unexpected reactions. In contrast to acetaminophen induced hepatotoxicity which occurs with dose dependent overdose of the drug, *idiosyncratic* drug reactions have traditionally been considered to be dose independent. However drugs with well documented *idiosyncratic* DILI have been shown to have a dose dependent component (2). For most drugs, hepatotoxicity is extremely rare and have been estimated to occur from 1 in **10,000**- 1 in **100,000** of those exposed to the drug, and for other drugs the risk is probably even lower (3). The number of included patients in most clinical drug trials are less than **10,000** and hepatotoxicity has mostly been detected in the post-marketing phase (3). The frequency of DILI among users of most drugs is unknown and most epidemiologic studies in this context suffer from major methodological limitations. **There is uncertain accuracy in determining** the relationship

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3 between the liver injury and the drugs reported in these studies. Most
4
5 epidemiological studies are retrospective and lack standardized diagnostic work-
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8 up to exclude other potential causes of the liver injury. Moreover, most studies
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10 originate from tertiary referral centers and suffer from selection bias.

11
12 Underreporting of adverse drug reactions is well known and DILI is no
13
14 exception. Thus, the true incidence of DILI is largely unknown. **Up to date only**
15
16 **one prospective population based study has been undertaken to study the**
17
18 **incidence of DILIs in France, which revealed an incidence of 13.9 per 100,**
19
20 **000 inhabitants (4).** The results of the study might be considered a gold
21
22 standard for the true incidence of DILI (4). In retrospective studies from Sweden
23
24 and the UK, a crude incidence rate of 2-3 cases per 100, 000 inhabitants per year
25
26 was reported, **which was probably an underestimation (5-6).** Acute hepatic
27
28 injury due to drugs has been reported to occur in 2-10% of patients hospitalized
29
30 for jaundice (7-11). A total of 77/1164 (6.6%) patients in an outpatient
31
32 hepatology clinic in Sweden were due to DILI and half of these were new
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34 consults and the other half were followed up after hospitalization for DILI (5).
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36 In a recent study from Switzerland, the overall incidence of DILI was found to
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38 be 1.4% among hospitalized patients but the DILI was not included among the
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40 diagnoses or in the physician's discharge letter in a high proportion of patients
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42 (12).
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Presentation and clinical evaluation of DILI

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3 Patients who suffer from DILI have a wide variety of clinical presentations.
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5 Clinically, biochemically and histologically DILI can simulate almost all forms
6
7 of acute and chronic liver injury. Thus, these patients can present with acute
8
9 liver failure with severe encephalopathy, with acute hepatitis with or without
10
11 jaundice and chronic hepatitis with both symptomatic and asymptomatic
12
13 elevated liver tests. Table 1 shows the spectrum of liver disease, with examples
14
15 of drugs leading to different types of liver injury. Although rare, liver cirrhosis
16
17 has been reported to occur with long standing drug treatment suspected to have
18
19 caused DILI (14). A minority of patients with DILI (approximately 25-30%)
20
21 present with symptoms suggestive of immunoallergic drug reactions with fever,
22
23 rash and eosinophilia (15-16). In the initial assessment of patients presenting
24
25 with symptoms or signs of liver dysfunction, DILI needs to be considered. Most
26
27 *idiosyncratic* drug reactions occur roughly between 1-2 weeks and 2-3 months
28
29 from start of drug therapy (3). However, there are numerous exceptions with
30
31 exposure of the drug for many months, such as in liver injury due to
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33 nitrofuranton and ximelagatran (17-18).
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Although drugs with a well documented capacity to cause DILI can lead to a
different expression in different patients, most hepatotoxic drugs have a
“signature” toxicity. A hepatic pattern is typically observed in patients with
isoniazid, disulfiram and diclofenac associated hepatotoxicity whereas cholestatic
injury is seen most often with amoxicillin/clavulanic acid, macrolide antibiotics

1
2
3 and estrogens (3, 17). The initial evaluation should include a thorough history of
4
5 drug exposure, duration of therapy, information about previously recognized
6
7 hepatotoxicity of the implicated drug and the severity of the reaction.
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11
12 In some patients who present with liver injury a short time after initiation of a
13
14 drug with well documented hepatotoxicity, the diagnosis of DILI is likely. If the
15
16 biochemical pattern is consistent with the “signature” of this drug, such as in
17
18 isoniazid, disulfiram and phenytoin induced DILI (19-21) it is supportive of the
19
20 diagnosis of DILI. However, in some cases it can be a very difficult task to
21
22 establish a relationship between a drug and liver injury. Given the heterogeneity
23
24 of presentations, the diagnosis relies on circumstantial evidence and “guilt by
25
26 association” (22). **In most DILI patients with new onset liver disease**, there is
27
28 a temporal relationship between starting the suspected drug and onset of DILI.
29
30 Also a temporal relationship between the discontinuation of the drug and
31
32 improvement of liver tests may be observed. However, there are a number of
33
34 pitfalls that the physician has to bear in mind in the causality assessment. For
35
36 some drugs there can be a significant delay between the discontinuation of
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38 therapy and development of elevated liver tests, which sometimes can take up to
39
40 2-3 weeks. Examples include trovafloxacin and amoxicillin-clavulanate induced
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42 liver injury (23-24). Thus, for some drugs causing hepatotoxicity liver injury
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44 may worsen initially for days or sometimes weeks between discontinuation of
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46 the drug and clinical presentation of liver injury. Another important question in
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3 this context is whether the drug treatment was started before the patient
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5 developed symptoms which might indicate liver disease such as severe lethargy,
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7 nausea and/or dark urine or pale stools. **Thus, it is conceivable that the patient**
8
9 **used the drug against symptoms associated with liver injury of other**
10
11 **etiology.** Thus, before the drug is “accused” of being responsible for the liver
12
13 tests **abnormality** a reasonable exclusion of other causes of liver diseases
14
15 should be undertaken (see below). Information about the latest liver tests before
16
17 the starting the implicated drug, should be obtained if possible. **Data on the**
18
19 duration of drug therapy is crucial in order to evaluate the time to onset of the
20
21 drug reaction. An important part of the causality assessment is in the best case
22
23 scenario to observe a rapid biochemical and clinical improvement after
24
25 discontinuation of the implicated drug, called positive dechallenge. However, in
26
27 patients with well characterized DILI with a classical “signature” presenting
28
29 with jaundice and/or liver failure, the condition can deteriorate despite
30
31 interruption of the drug at presentation and the patient dies or undergoes a liver
32
33 transplantation (25-26). **To complicate** matters further, it has been increasingly
34
35 recognized that for some drugs with a clear potential of hepatotoxicity, liver
36
37 tests can improve in some patients despite continuation of therapy, examples
38
39 being ximelagatran and tacrine (27). However, it is obvious that susceptible
40
41 individuals are unable to achieve such an “adaptation” to the liver injury and
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43 may go on to develop fatal hepatotoxicity (27). This was particularly well
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45 demonstrated in clinical trials with ximelagatran (18). **Improvement in liver**
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3 **tests is generally slower after cholestatic than hepatocellular reactions** (17).

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6 Information about the course of the disease after **drug** cessation is important
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9 which is typical for some drugs and also information about previously
10
11 documented hepatotoxicity of the drug, which may add to the evidence in favor
12
13 of a drug etiology in the reaction. A comprehensive list of hepatotoxic drugs was
14
15 recently made through combination of the largest series of DILI patients in
16
17 recent years in order to facilitate the causality assessment of DILI (28).

18
19
20 Although there is a strong suspicion of a drug etiology, exclusion of other causes
21
22 of liver disease is *sine qua non* for establishing a diagnosis of DILI. How
23
24 extensive this diagnostic work-up should be is dependent on the clinical context.
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28 Factors that may impact **are** the type of liver injury, age and symptomatology.
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32 With a typical cholestatic pattern, imaging plays a more prominent role (liver
33
34 ultrasound, **computed tomography** and cholangiography) whereas in case of
35
36 hepatocellular type of injury, infectious etiology is more important to rule out. In
37
38 most cases a reasonable imaging modality is an abdominal ultrasound. In
39
40 selected cases with negative viral serologies, a PCR screening may be necessary
41
42 in order to exclude a very recent viral infection. History of alcohol abuse should
43
44 be documented, as well as recent episodes of hypotension which can cause
45
46 hepatocellular liver injury. Instruments to evaluate causality have been
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48 developed, the most commonly used being the so called RUCAM method (29).
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52 This causality assessment method is rarely used in clinical practice but seems so
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3 far be the gold standard for research on DILI (30) and has been further
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5 developed by the DILIN network in the US (31).
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9 **Liver histology in the diagnosis and prognosis of DILI**

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12 The role of a liver biopsy in the diagnostic work-up of DILI is controversial. It is
13
14 a common misunderstanding that liver histology is essential for establishing a
15
16 diagnosis of a drug etiology. As there are no specific histological findings of
17
18 DILI liver biopsy is of unclear value in this context. There are no unique
19
20 histological features present in patients with DILI. Some histological features
21
22 such as prominence of eosinophils, granulomatous hepatitis and central
23
24 hepatocyte drop-out might suggest DILI but overlap exists with many other
25
26 acute and chronic liver diseases (32). At the best the histology can be
27
28 “compatible” with DILI. If the patient demonstrates a rapid improvement in
29
30 liver tests following cessation of drug therapy, a routine liver biopsy is not
31
32 indicated. Histology was considered to be particularly important in early studies
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34 on DILI (17). However, advances in methodologies to rule out potential
35
36 etiologies, such as viral infections, hemochromatosis, **Wilson’s** disease (33) and
37
38 also better imaging techniques, have decreased the need for a biopsy. If the
39
40 patient has an underlying liver disease and/or autoimmune hepatitis is suspected
41
42 despite negative serologies, a liver biopsy can be valuable. **In certain other**
43
44 **situations liver biopsy can be helpful. For example if the drug** has not been
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46 implicated previously causing liver injury, if the drug reaction has a very slow
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3 regression **or** other chronic liver diseases are difficult to rule out by appropriate
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5 serologies or imaging methods. Furthermore, liver biopsy can reveal specific
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7 histological features such as steatohepatitis that can be observed with
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12 amiodarone or valproate (34-35) or nodular regenerative hyperplasia seen with
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15 azathioprine and 6-thioguanine (36-37). **A liver biopsy can be helpful in cases**
16
17 **of DILI that have a particular associated histological pattern as**
18
19 **demonstrated in Table 1.**

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23 However, the impact of identifying **some of** these unusual histological patterns
24
25 on management is uncertain and the indication of liver biopsy depends on the
26
27 course of the liver injury as mentioned above.
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33 Limited data exist on the impact of histology on the clinical outcome in
34
35 DILI. Recently, in a study of patients with disulfiram-induced liver injury,
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37 eosinophilic infiltration was associated with a good short term prognosis
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39 whereas hepatocyte drop-out or necrosis was associated with a poor prognosis
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42 (20). Moreover, the presence of severe hepatic necrosis was also associated with
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44 a poor prognosis among patients with halothane- and isoniazid-induced liver
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47 injury (38-39). Drugs with well documented liver injury have a highly variable
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50 propensity to cause hepatic necrosis. Among 11 agents the proportion of
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53 reported hepatic necrosis ranged from 3% in amoxicillin/clavulanic acid to 89%
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56 in halothane- and 65% in isoniazid-induced liver injury (16). Patients with a
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59 liver biopsy showing severe hepatic necrosis had an 86% mortality (16). Hepatic
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3 necrosis was uncommon in patients with a cholestatic type of liver injury.

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6 Therefore, the lowest mortality rate was observed in patients with
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8
9 amoxicillin/clavulanate, sulindac and flucloxacillin associated DILI which
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11 typically present with a cholestatic/ mixed laboratory profile (16).
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17 **Causative drugs**

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19 A very large number of different drugs have been associated with liver injury
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21 (17). There is a clear difference in the documentation or the evidence for
22
23 hepatotoxicity associated with these drugs. For some drugs, only a single case
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25 report or a letter to the editor exists indicating DILI. If these drugs have been a
26
27 long time on the market, the hepatotoxic potential (if any) of these drugs is
28
29 unclear. Other drugs have well characterized hepatotoxicity, examples being
30
31 isoniazid, phenytoin, disulfiram, amoxicillin/clavulanate to mention a few (3,
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33 17). In early reports, halothane and chlopromazine were commonly reported to
34
35 be associated with hepatotoxicity (3, 17). More recently antibiotics, different
36
37 analgesics and NSAIDs are the most common type of drugs associated with
38
39 DILI (4-6, 13, 25-26, 31). The most common antibiotics implicated have been
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41 amoxicillin/clavulanate, erythromycin, flucloxacillin, trimethoprim-sulpha and
42
43 nitrofurantoin but antituberculous drugs such as isoniazid and rifampicin have
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45 also commonly been observed in these series (4-6, 13, 25-26). Type of drugs and
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47 specific drugs associated with DILI in different studies from the literature are
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49 shown in Table 2.
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3 In hospitalized patients heparins seem to commonly lead to DILI and are
4 probably underreported (12). The same is probably true for anti-neoplastic
5 agents which are usually not mentioned among drugs causing DILI in most
6 series (4-6, 13, 25-26, 31). However, a recent study of hospitalized patients in
7 Switzerland found anti-neoplastic agents to be one of the most common type of
8 drugs associated with DILI (12). **Several HIV drugs have been shown to lead**
9 **to DILI (40-41). Steatohepatitis has been associated with these drugs and**
10 **nodular regenerative hyperplasia has also been reported (42-44).**

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26 In outpatients, the single most common drug implicated in one series was
27 diclofenac (5). Among patients with acute liver failure due to drugs in the US
28 who underwent liver transplantation, acetaminophen was the most common
29 causative drug, followed by isoniazid, propylthiouracil, phenytoin and valproate
30 (45). The proportion of medicinal herbs out of all causes of toxic or drug
31 induced liver injury shows great geographical variation in previous series on
32 DILI. However, **herb-associated** hepatotoxicity has not been studied
33 systematically. In the prospective Spanish study of the DILI Registry, only 2%
34 of all cases were suspected to be due to herbal drugs (26) and only 5% of
35 patients attended an outpatient hepatology clinic in Sweden (5). Approximately
36 11% of patients who developed acute serious liver disease of unknown cause in
37 Spain had been using medicinal herbs (46). Among patients undergoing a liver
38 transplantation for acute liver failure in the US, a total of 11.7% of patients who
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3 had liver injury from drugs other than paracetamol were considered to be due to
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6 herbal substances and mushrooms (45). In a recent prospective study from the
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8
9 DILIN (drug induced liver injury network) multicenter group in the US, herbal
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11 and dietary supplements were implicated in 9% of the cases (31). In
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13
14 approximately 60% of the cases, the use of dietary or herbal supplements were
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17 intended for muscle building or weight loss (31). A study from Japan revealed
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20 that 10% cases of single agent DILI from 1997-2006 were attributed to dietary
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23 supplements, and 7% to Chinese herbal drugs (47).
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26 **Determinants of prognosis in DILI**

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30 The vast majority of patients with symptomatic **acute DILI** are expected to
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33 completely recover after discontinuation of the suspected drug. Although DILI
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36 patients with jaundice have worse prognosis than patients without drug induced
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39 jaundice (25-26, 31), the majority of jaundiced patients show a full recovery.
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42 For example, 712 of 784 (90.8%) DILI patients with jaundice recovered while
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45 72 (9.2%) died or underwent liver transplantation (25). The outcome is
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48 obviously dependent on the severity of liver impairment at presentation. For
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51 example, the prognosis of idiosyncratic DILI patients with acute liver failure
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54 (ALF), with coagulopathy (i.e. INR > 1.5) and encephalopathy, is usually poor
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57 without liver transplantation. Prognosis is generally better in acetaminophen-
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60 induced liver failure than ALF due to *idiosyncratic* drug reactions (i.e. 60 to
80% vs 20 to 40% transplant-free survival rates) (48). First described by Hy

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3 Zimmerman, clinical jaundice due to drugs (i.e. total bilirubin > 2.5 mg/dl) was
4
5 associated with a poor prognosis (i.e. a fatality rate of ~ 10%) for many drugs
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8 (17). This observation has been called Hy's Law and is used by the Food and
9
10 Drug Administration and other regulatory agencies in the evaluation of
11
12 investigational drugs showing potential hepatotoxic signals during clinical trials.
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14 Identifying cases fulfilling Hy's Law in clinical drug trials is considered to
15
16 predict serious safety problems in the post-marketing phase. Recent studies from
17
18 Sweden, Spain and the US have all confirmed the validity of Hy's Law by
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20 demonstrating a 9 to 12% rate of mortality/liver transplantation in patients with
21
22 severe hepatocellular DILI and jaundice (25-26, 31). Thus, all three of these
23
24 large studies show remarkably similar results in terms of the prognostic value of
25
26 jaundice in patients with severe hepatocellular DILI (17). Also patients with
27
28 cholestatic type of DILI have a significant mortality (25-26, 31). The prognosis
29
30 in patients with DILI is also dependent on the compound involved. In one series,
31
32 mortality ranged from 40% with halothane induced liver injury whereas all
33
34 patients with erythromycin induced liver injury survived (25). Patients with
35
36 erythromycin hepatotoxicity were significantly younger and had less severe liver
37
38 injury with lower serum AST, ALT and bilirubin levels at presentation than the
39
40 other patients (25). Thus, the specific drug implicated in the liver injury may
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42 influence the prognosis.
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3 The median duration between first exposure to the suspect drug and DILI onset
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5 was significantly longer in severe than in mild/moderate cases in univariate but
6
7 not in multivariate analysis in the DILIN study (31). The duration of treatment
8
9 prior to DILI onset was not found to be different between cases with and without
10
11 severe outcome in the European series (25-26). Longer duration of therapy
12
13 before the recognition of DILI and continuation of therapy despite liver
14
15 dysfunction, seems to increase the risk of developing chronic liver injury (14,
16
17 49-50) (see below). **Peripheral eosinophilia and hepatic infiltration of**
18
19 **eosinophils have been shown to have prognostic importance in DILI (20,**
20
21 **16). Support for the importance of eosinophilia comes from studies in Spain**
22
23 wherein eosinophilia was extremely rare in fatal DILI cases (26, 51).
24
25 Specifically, only one of the 18 (5.6%) Spanish patients who died or underwent
26
27 transplantation had signs of hypersensitivity features (peripheral eosinophilia)
28
29 whereas eosinophilia was observed in 23% of those who recovered (26). Also,
30
31 eosinophilia was reported in 49 of the 185 (26.5%) DILI patients in another
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33 series but was not present in any of the 12 patients who died or underwent liver
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35 transplantation (51).
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51 **Other important drug properties for the risk and outcome in DILI**

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54 As mentioned earlier idiosyncratic adverse drug reactions were for decades
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56 considered to be dose independent (3, 17). However, analysis of DILIs found in
57
58 the general practitioners database from the UK revealed that there was dose-
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3 dependency for some drugs (6). Uetrecht pointed out that most drug associated
4
5 with severe liver injury were prescribed at a daily dose greater than 50 mg,
6
7 suggesting some dose-dependency at least for severe cases of DILI (52). This
8
9 hypothesis that *idiosyncratic* DILI may have a component of dose-dependency
10
11 was tested systematically recently (2). The relationship between daily dose of a
12
13 given drug and its propensity to cause liver injury was examined (2). By
14
15 analysing data from two pharmaceutical databases, **relationship between daily**
16
17 **dose of drugs** and reported frequency of ALT elevations, jaundice, liver failure,
18
19 liver transplantation and liver related deaths **was examined (2). In the same**
20
21 **study, DILIs with concomitant jaundice previously reported (25) were**
22
23 **analysed in terms of the daily dose of the drugs involved.** Among US
24
25 prescription drugs, a significant relationship was observed between daily dose of
26
27 oral drugs and reports of liver failure, liver transplantation and death caused by
28
29 DILI but not of ALT > 3 times upper limit of normal (ULN) or jaundice. Only
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31 9% of the Swedish DILI cases, belonged to the ≤ 10 mg/day group, 14% to the
32
33 11-49 mg/day group whereas almost 80% belonged to the ≥ 50 mg/day group.
34
35 Furthermore, analysis of patients who underwent liver transplantation for DILI
36
37 (45) and reported in the paper by Lammert et al. (2) revealed that 90% belonged
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39 to the ≥ 50 mg/day group. The results of this study consisting of different data
40
41 sets **support** a relationship between the daily dose of an oral medication and its
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43 propensity to cause serious liver injury (2). These results were recently
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45 confirmed by data from the Spanish Registry of Hepatotoxicity (53). Among
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3 approximately 600 cases, 77% were receiving daily doses of ≥ 50 mg/day,
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6 which was exactly the same percentage that was found in the Swedish dataset in
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8
9 the study by Lammert et al. (2). This dose dependency in *idiosyncratic* DILI
10
11 supports the reactive metabolite theory for the pathogenesis of idiosyncratic
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13 DILI. Further support for that hypothesis came from another study from the
14
15 same group recently published (54). This study examined the relationship
16
17 between hepatic metabolism of oral medications and *idiosyncratic* DILI. By
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19 using similar methodology, the metabolism characteristics of the 200 most
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21 prescribed drugs in the US were analyzed. Compounds with >50% hepatic
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23 metabolism were characterized as those with significant hepatic metabolism.
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25 Compared with compounds with lesser hepatic metabolism, compounds
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27 belonging to the significant metabolism group had significantly higher
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29 frequency of ALT > 3 times ULN, liver failure, and fatal DILI but not of
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31 jaundice or liver transplantation. Compounds (n=12) with no hepatic metabolism
32
33 had no reports of liver failure, liver transplantation, or fatal DILI. Compared
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35 with drugs without biliary excretion, compounds with biliary excretion had
36
37 significantly higher frequency of jaundice. Furthermore, an additive effect of
38
39 daily dose and hepatic metabolism was found (54). Drugs with >50% hepatic
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41 metabolism and also given at a dose of >50 mg/day had the highest risk of
42
43 hepatotoxicity compared with other groups. Supporting data for the reactive
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45 metabolite have been limited and if reproduced by others might facilitate the
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47 development of safer medications.
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3 In a recent study, Suzuki et al. found that certain co-administered medications
4 may negatively influence the outcome of acetaminophen induced liver injury
5 (55). This study aimed to analyse concomitant use of 9 drug classes using
6 multiple regression analyses. Concomitant use of statins, fibrates or NSAIDs
7 was associated with decreased likelihood of fatality in females, whereas
8 concomitant alcohol use increased the risk of fatality (55). In males concomitant
9 use of statins was associated with decreased likelihood, but use of sympathetic
10 stimulants or alcohol was associated with increased likelihood of fatality. The
11 results of this study supports experimental data showing that net tissue damage
12 is determined by the balance between injury and repair.
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35 **The course and the natural history of DILI after the acute episode: does**
36 **DILI lead to chronic liver disease?**
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41 The general view among hepatologists has been that if a patient with DILI
42 shows a clinical and biochemical recovery without liver transplantation, a full
43 recovery can be expected. However, chronic liver disease, even including the
44 development of liver cirrhosis have been reported with a number of different
45 drugs. A number of case reports have been published reporting chronic liver
46 injury following DILI (13, 38, 56-79) (Table 3).
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59 In the first study investigating the natural history of DILI, 13 out of 33 (39%)
60 patients with a median follow-up of 5 years had persistent abnormalities in their

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3 liver biochemistries and/or imaging (49). However, all of these patients were
4
5 identified through a histological database, leading to a potential selection bias
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7
8 (49). Whether these patients with residual liver disease developed clinically
9
10 significant liver related morbidity or mortality was unclear (49). In contrast, a
11
12 prospective follow-up of the Spanish Registry patients revealed development of
13
14 chronic liver injury in 5.7% of patients followed for a mean of 20 months (50).
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16
17 In this study, the definition of chronic liver injury was based on the presence of
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19 abnormal liver tests for a period of more than 3 months after DILI onset (50).
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Drugs most frequently associated with chronicity were amoxicillin/clavulanate, bentazepam and atorvastatin. Patients with cholestatic liver injury were more prone to develop chronic liver injury (50). A single center study from Sweden also found that only 3 of 50 (6%) patients diagnosed with DILI had persistently abnormal liver biochemistries after a median follow-up of 48 months (13). In the DILIN study, chronic DILI is defined at 6 months after DILI (without those with an underlying liver disease) by persistently elevated serum AST, ALT, alkaline phosphatase or bilirubin, levels on two separate occasions (1). Among the first 300 cases enrolled, the rate of chronic liver injury at 6 months was 14% (31). However, the long term outcome of these patients is unknown. A recent study was undertaken to determine the proportion and the long-term effects of chronic evolution after DILI (14). A mean follow-up of 10 years of DILI patients who originally all had jaundice revealed that development of clinically important liver disease after severe DILI was rare (14). A total of 23 of 685 (3.4%) DILI

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3 patients who had survived acute DILI were hospitalized for liver disease during
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6 the study period and 5 had liver-related mortality (14). Among these patients, 5
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9 of the 8 with cirrhosis did not have an alternative cause of liver disease (14). In
10
11 agreement with an early report (49), a significantly longer duration of drug
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13 therapy prior to the detection of DILI was observed in those who developed
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15 liver-related morbidity and mortality (14). Most cases with protracted courses
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17 (86%) were of the cholestatic type. In this subgroup of patients, all patients
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20 except one (with 6 years of follow-up) normalized their biochemical
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23 abnormalities at last follow-up and remained free of liver morbidity thereafter
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26 (14). Regular follow-up of patients who do not show complete normalization of
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29 laboratory, histological, and radiological parameters is recommended for clinical
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32 as well as legal implications.
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40 Management

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44 Once DILI is suspected in patients with new onset liver disease prompt cessation
45
46 of drug(s) implicated is usually the first step in their management. At the same
47
48 time severity assessment of the liver disease is of crucial importance. At the
49
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51 onset of the reaction, symptomatic patients with jaundice are in most cases
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53
54 hospitalized and obviously patients who also have coagulopathy and/or
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57 encephalopathy should be hospitalized. It is important to recognize the severity
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60 of the liver injury in a patient with jaundice and coagulopathy before the

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3 development of encephalopathy. Encephalopathy is a very late sign and after its
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5 development a rapid deterioration is often observed. Thus, an early contact
6
7 should be taken with a transplant center if the patient does not have an obvious
8
9 contraindication for liver transplantation. In acetaminophen-induced liver
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11 failure, N-acetylcysteine (NAC) should be given immediately (48). In a recent
12
13 study, the results of intravenous N-acetylcysteine to treat acute liver failure
14
15 caused by etiologies other than acetaminophen was reported (80). In this
16
17 prospective, double blind trial, patients with acute liver failure (non-
18
19 acetaminophen), were randomized to receive N-acetylcysteine (NAC) or
20
21 placebo infusion for 72 hours (80). Acute liver failure due to DILI (n=45)
22
23 represented the single largest group among 173 patients who were randomized.
24
25 Although the overall survival at three weeks was not significantly different
26
27 between the groups, the transplant free survival was significantly better among
28
29 those patients randomized to NAC (40% vs. 27%, p=0.043). The benefits of
30
31 NAC was primarily seen in patients with early course of the disease with coma
32
33 grade I-II (52% vs. 30% transplant free survival) but not in those with advanced
34
35 coma grade (III-IV) at randomization. Considering the overall and transplant
36
37 free survival of the 4 largest etiologic groups, patients with DILI and HBV
38
39 showed improved outcome in comparison with the AIH and indeterminate
40
41 groups (80). Transplant free survival among the DILI patients was 58% for
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43 those receiving NAC compared with 27% for those receiving placebo. The
44
45 results of this study suggest that therapy with intravenous NAC should be used
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3 in patients with acute liver failure due to *idiosyncratic* DILI. Steroids are
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6 sometimes used in patients with severe DILI (81). However, data supporting
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9 their efficacy and safety are lacking (82-83). The use of steroids may be justified
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12 when DILI is associated with hypersensitivity syndrome as can be the case with
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15 carbamazepine-induced hepatotoxicity (81). Steroids also seem useful when
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18 autoimmune hepatitis is considered to be induced by drugs such as
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21 nitrofurantoin and minocycline (84). Carnitine is recommended in valproate-
22
23
24 associated hepatotoxicity (85).

25 26 **Acetaminophen**

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29 Similar to *idiosyncratic* drug reactions, symptoms of liver injury due to
30
31
32 acetaminophen are non-specific. Acetaminophen hepatotoxicity should be
33
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35 suspected in patients with extremely high aminotransferases and only mildly
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37
38 elevated bilirubin at presentation (86). Hepatic injury typically develops 12-72
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41 hours after suicidal intent and liver failure 72-96 after ingestion (86). Although
42
43
44 limited data exists on the prognosis of unselected patients with acetaminophen
45
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47 toxicity, it has been estimated that less than 5% of patients with overdose
48
49
50 develop acute liver toxicity (88-89). Recent data from the acute liver failure
51
52
53 study group in the US demonstrated that acetaminophen was responsible for
54
55
56 almost 50% of all cases of ALF (86). Unintentional overdoses accounted for
57
58
59 approximately half whereas intentional (suicide attempts) accounted for the rest
60
(86). Patients with acetaminophen toxicity with encephalopathy and/or signs of

1
2
3 kidney failure at presentation should in most cases be hospitalized in the
4
5
6 intensive care unit and liver transplantation assessment started immediately.
7
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9 Many of the principles of the diagnostic work-up and the causality assessment
10
11 **are** similar in cases of acetaminophen induced liver injury. However, blood
12
13 concentration of acetaminophen can be obtained at least early in the course of
14
15 the reaction and is an important part of the management of a patient with a
16
17 suspected and confirmed acetaminophen toxicity. Late in the course of the liver
18
19 injury, blood concentrations of the drug are not reliable. Moreover, patients with
20
21 unintentional acetaminophen overdose were found to have significantly lower
22
23 serum acetaminophen concentration than those with intentional overdose (86).
24
25 Also, false positive concentrations of acetaminophen have been observed in
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27 patients with acute liver failure, particularly in patients with high bilirubin
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29 concentrations (87).
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40 **Chronic analgesic use**

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42 Patients with unintentional acetaminophen toxicity have typically used over-the-
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44 counter drugs and narcotic pill combination with acetaminophen and the
45
46 attending physician should be aware of the possibility of such a “therapeutic
47
48 misadventure” (89-91). Due to the fact that unintentional acetaminophen
49
50 hepatotoxicity was responsible for approximately 50% of acute liver failure in
51
52 the US (86), chronic analgesic use is of concern. Interestingly, although only
53
54 13% of patients with acetaminophen overdose had unintentional toxicity in a
55
56 study from Canada, these patients had a 5-fold risk of hepatotoxicity and 13-fold
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3 risk of in-hospital mortality (89).The hepatic safety of chronic analgesic use
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5
6 (mostly acetaminophen) has not only come into focus due to the unintentional
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9 toxicity. Hepatotoxic effects have also been associated with therapeutic doses of
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11
12 acetaminophen (90-92). The safety of acetaminophen has also received renewed
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15 attention recently following a study showing hepatic enzyme elevations in
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18 approximately one third of healthy controls given 4 g daily for up to two weeks
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21 (93). The so called “therapeutic misadventures” have mostly been associated
22
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24 with chronic alcohol abuse (90-92), or fasting conditions (94). However,
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27 increased risk of hepatotoxicity with therapeutic doses in patients with chronic
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29
30 alcohol abuse, impaired nutritional status or in chronic liver disease remains
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33 controversial (95).

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35 The importance of alcohol abuse as a risk factor for acetaminophen
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38 hepatotoxicity seems to be better documented in acetaminophen overdose than
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41 with therapeutic use of acetaminophen (96). Chronic alcohol abuse was found to
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44 be an independent risk factor for acetaminophen-induced hepatotoxicity among
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46
47 patients admitted for single- dose acetaminophen poisoning (96). Alcohol use
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49
50 was associated with doubling effects of hepatotoxic effects independent of suicidal
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53 effects in another study (89). Administrative data for acetaminophen overdose
54
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56 and overdose intent is however problematic and data from retrospective studies
57
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59 on intent are perhaps not always reliable (89). A recent study found patients with
60
hepatitis C to be at increased risk of acute liver injury following acetaminophen

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3 overdose (97). However, as has been pointed out hepatotoxic effects of
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6 therapeutic doses of acetaminophen in chronic alcohol abusers (and increased
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9 risk with fasting) is based on retrospective reviews and case reports (95).
10
11 Controlled prospective randomized studies assessing the safety of
12
13 acetaminophen in alcoholics have not found increased risk of hepatotoxicity
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16 when therapeutic doses are consumed (99-100). To complicate matter further, it
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18
19 has been demonstrated that some individuals can develop tolerance towards the
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22 chronic effects of large daily doses of acetaminophen (101). Experimental study
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25 in mice has explained the mechanisms behind this development of tolerance for
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28 the hepatotoxic effects of acetaminophen (101).
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35 CONCLUSIONS

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38 Drug-induced liver injury remains a diagnostic challenge. Multicenter studies
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41 and international collaborative work with well characterized patients will
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44 increase our understanding of liver injury associated with drugs. New therapies
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47 for acute liver failure due to drugs are needed.
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<i>Spectrum of DILI</i>	<u>Examples of drugs</u>
Acute liver necrosis	Isoniazid, disulfiram, acetaminophen
Chronic hepatitis	Phenytoin, isonizid
Drug-induced AIH	Minocycline, nitrofurantoin
Granulomatous hepatitis	Carbamazepine, quinidine
Steatohepatitis	Amiodaron, valproate
Cholestatic hepatitis	Flucloxacillin, amoxicillin/clavulanate
Bland cholestasis	Estrogens, nimesulide
Ductopenia	Amoxicillin, Trimethoprim-sulpha
Fibrosis	Methotrexate
Nodular regenerative hyperplasia	Azathioprine, 6-thioguanine

Table 1. The most common types of liver injury that have been identified with drugs.
AIH=Autoimmune hepatitis.

Reference	Origin (time period) n=number	Specific drugs & Types of drugs
Aithal 1999 (reference 49)	UK (1978-1996) n=44	Antibiotics (29.5%), NSAIDs (25%), Dextropropoxyphene (9%), Chlorpromazine (6.8%)
Sgro 2002 (reference 4)	France (1997-2000) n=32	Antibiotics (19%), NSAIDs (16%), Antidepressants (12.5%), Nevirapine (9%),
Ibanez 2002 (reference 46)	Spain (1993-1998) n=103	#NSAIDs (38%), Analgesics (28%), Antibiotics (24%), H2-receptor antagonists (22%), benzodiazepines (16.5%), antidepressants (13.6%), herbs (11%), ACE inhib (11%), Antituberculous drugs (11%)
Russo 2004 (reference 45)	USA (1990-2002) n=270	Paracetamol (46%), isoniazid (17.5%), Anticonvulsants (15%), Propylthiouracil (7.3%), antibiotics (10.2%), herbs (5.1%), disulfiram (4.4%)
De Abajo 2004 (reference 6)	UK (1994-1999) n=128	Antibiotics (27%), paracetamol alone or combined (9%), diclofenac (8%), Chlorpromazine (4.7%), Metoclopramide (4%)
Meier 2005 (reference 12)	Switzerland (1996-2000) n=57	Heparins (45.6%), antibiotics (33%), anticancer drugs (12%)
Andrade 2005 (reference 26)	Spain (1994-2004) n=446	Amoxicillin/clavulanic acid (13%), Antituberculous drugs (7%), ebrotidine (5%), Ibuprofen (4%), Flutamide (3.8%), Ticlopidine (2.9%), Diclofenac (2.7%)
Bjornsson 2005 (reference 25)	Sweden (1970-2004) n=784	Antibiotics (27%), NSAIDs (4.8%), Disulfiram (3.4%), Carbamazepine (2.2%), Anesthetics (1.9%),
De Valle 2006 (reference 5)	Sweden (1995-2005)	Antibiotics (31%), Diclofenac (18%), Azathioprine (6.5%), Atorvastatin (5.2%)

	n=77	
Bjornsson 2006 (reference 40)	Sweden (1968-2003) n=4.690	Analgetics (8.9%), HIV drugs (6.5%), Anticonvulsants (3.9%), Antibiotics (3.6%)
Chalasani 2008 (reference 31)	USA (2003-2008) n=300	Antimicrobials (45.5%), CNS agents (15%), medicinal herbs (9%), Analgesics (5%), immunomodulatory agents (5%), Antihypertensives (5%),

Table 2. Type of drugs and specific drugs associated with DILI in different studies from the literature.

Drug	Type of drug	Reference
Dantrolene	Calcium blocker	62
Flucloxacillin	Antibiotic	63
Ebrotidine	H2-receptor antagonist	64
Ramipril	Antihypertensive	65
Amiodarone	Anti-arrythmic	66
Papaverine	Spasmolytic	67
Alpha-methyldopa	Antihypertensive	68
Sulphonamides	Antibiotic	69
Isoniazide	Anti-tuberculosis	70
Methotrexate	Anti-inflammatory	71
Diclophenac	NSAID	72
Halothane	Anesthetic	73
Acetyl-salicylic acid	Pain killer	74
Benzarone	Thrombolytic	75
Chlorpromazine	Antipsychotic	76
Fluoxetine	Antidepressant	77
Nitrofurantoin	Antibiotic	78
Practolol	Beta blocker	79

Table 3. Drugs with a suspect causality reported to have caused chronic liver disease, including the development of liver cirrhosis with references.

H2-receptor antagonist=Histamine 2 receptor antagonist, NSAID=Nonsteroidal anti-inflammatory drug.

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