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Epidemiology of Idiosyncratic Drug-Induced Liver Injury

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Abstract

Idiosyncratic drug-induced liver injury (DILI) is a significant health problem because of its unpredictable nature, poorly understood pathogenesis, and potential to cause fatal outcomes. It is also a significant hurdle for drug development and marketing of safe prescription medications. Idiosyncratic DILI is generally rare, but its occurrence is likely underappreciated due to the lack of active reporting or surveillance systems and substantial challenges involved in its recognition and diagnosis. Nonetheless, DILI is a common cause of potentially serious and fatal acute liver failure in both children and adults. Population-based studies that accurately estimate the incidence and full spectrum of DILI are limited. However, using a prospective, population-based French study with an annual estimated incidence of 13.9 ± 2.4 DILI cases per 100,000 inhabitants, it has been extrapolated that nearly 44,000 individuals in the United States will suffer from DILI each year. Although increasing numbers of patients are also being seen with DILI due to herbal and dietary supplements, the epidemiology of this entity requires further investigation. In this article, the epidemiology of DILI, both in the general population and in potentially high-risk subgroups, is reviewed.

Keywords

Idiosyncratic; hepatotoxicity; acute liver failure; adverse drug reaction

Idiosyncratic drug-induced liver injury (DILI) is a common cause of acute liver failure (ALF), accounting for up to 13% of all ALF cases in the United States.¹ It is also the single most common adverse drug reaction (ADR) leading to a halt in the development of new medications by pharmaceutical companies, failure of new drugs to obtain regulatory approval, and withdrawal or restriction of existing drugs from the market.^{2–4} Although DILI is thought to account for a small proportion of all idiosyncratic ADRs, and there is a relatively low incidence of DILI with many approved drugs (i.e., only 1 per 10,000 to 100,000 treated patients), up to 10% of patients with drug-induced jaundice will die.³ As the use of prescription medications in the general population, especially the baby boomer generation, continues to increase, it is expected that the incidence of serious ADRs will also increase.⁵ Therefore, additional studies are required to define the mechanism and etiology of DILI so that improved means of diagnosing and preventing it can be developed.

The medication that most commonly causes DILI in the United States and other Western countries is acetaminophen. Hepatotoxicity due to acetaminophen poisoning is dose-dependent—ALF is more likely with doses > 150 mg/kg.⁶ Because it is readily available, intentional acetaminophen overdose is often used for suicide attempts in Western countries, and ~500 Americans die each year as a result of acetaminophen-associated ALF.^{7,8} In fact, the proportion

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of ALF cases caused by acetaminophen overdose has risen over the past decade, from 28% in 1998 to 50% in 2006, and more than half of these cases are unintentional overdoses.^{9,10} The majority of patients with acetaminophen-induced ALF are females and the median age is 36 years.⁹ Fortunately, treatments to replete glutathione stores and prevent further hepatocyte injury are available, and the majority of patients who receive prompt supportive care along with *N*-acetylcysteine will recover.^{6,11} Although acetaminophen overdose is the most frequently identified cause of DILI, the focus of this article is idiosyncratic DILI, which is unpredictable and not necessarily dose related. For the remainder of this article, idiosyncratic DILI will simply be referred to as “DILI.”

EPIDEMIOLOGY OF DILI IN WESTERN COUNTRIES

The epidemiology of DILI is poorly understood because of the limited active and passive reporting and surveillance systems in place and the lack of standardized criteria for its diagnosis. In clinical practice, DILI may present in many ways that closely resemble other known forms of both acute and chronic liver disease, and the severity can range from asymptomatic elevations in liver biochemistries to full-blown ALF.¹² Despite these challenges, several retrospective and prospective studies describing the incidence and risk factors for DILI have been reported.

Retrospective Databases

Several retrospective studies have described the estimated incidence rates of DILI, which are summarized in Table 1. De Valle et al performed a retrospective analysis of all patients with a diagnosis of liver disease seen at a Swedish University outpatient hepatology clinic between 1995 and 2005.¹³ Of 1164 total cases of liver disease, 77 (6.6%) had a diagnosis of at least possible DILI. In a retrospective analysis of 800 patients participating in a jaundice referral system (The Jaundice Hotline) in the United Kingdom between 1998 and 2004, Hussaini et al reported that 28 of 347 (8.1%) patients with parenchymal liver dysfunction had suspected DILI.¹⁴ In another analysis using data from the SAS/CHDM (Stiftung für Arzneimittelsicherheit/ Comprehensive Hospital Drug Monitoring) pharmacoepidemiological database to monitor adverse drug events in a cohort of medical inpatients, Meier et al identified 57 DILI cases out of 4209 consecutive in-patients (1.4% frequency).¹⁵

In the United States, Russo et al estimated that DILI accounts for 15% of all the liver transplants performed for ALF annually.¹⁶ In their retrospective analysis of the United Network for Organ Sharing (UNOS) liver transplant database from 1990 to 2002, 357 of 2291 patients (15.6%) undergoing a transplant for acute hepatic necrosis were identified as having drug-induced ALF. Further analysis showed that acetaminophen toxicity accounted for 46% of the transplant recipients with drug-induced ALF, whereas DILI was responsible for the remaining 51% (the additional 3% was attributable to acetaminophen plus another drug). In another retrospective study of adult outpatients and inpatients with new-onset jaundice at a community hospital in Indiana, Vuppalanchi et al reported that of 732 eligible patients, drug hepatotoxicity accounted for 29 of these cases (overall incidence of 4.0%).¹⁷ In this study, most cases of drug hepatotoxicity (24 patients) were attributable to acetaminophen toxicity, and DILI occurred in only 5 of the 29 patients (0.7% of total study population). Using several different International Statistical Classification of Diseases (ICD)-9 codes and the names of specific medications (amoxicillin/clavulanate, phenytoin, valproic acid, and isoniazid), Jinjuvadia et al identified an overall DILI frequency of 1.6% (119 DILI cases out of 7395 total patients). Their study used the most sensitive combination of an acute liver injury ICD-9 code plus a medical record search of the University of Michigan Health System (UMHS) database.¹⁸ Importantly, 36 of these DILI cases (0.5%) were attributed to acetaminophen overdose, and the remaining 83 were due to other individual agents (1.1%). However, the different search techniques yielded highly variable results, and an important conclusion of this study was that use of ICD-9 codes may

not be an accurate method to study DILI epidemiology. In another study using ICD-9 codes to identify patients with acute liver enzyme abnormalities in the Fallon Community Health Plan (FCHP) database in Massachusetts, Duh et al reported that DILI was the most common cause of liver enzyme abnormalities (40.6 cases per 100,000 persons per year), but the overall incidence rate of DILI was low in this population.¹⁹ However, the authors point out that the incidence of drug-induced liver abnormalities may actually be much higher, as many of the cases of unknown etiology may have been unrecognized DILI.

In a large retrospective study of the General Practice Research Database (GPRD) in the United Kingdom, de Abajo et al reported an annual incidence rate of 2.4 cases per 100,000 persons for nonfatal DILI.²⁰ In this analysis, 1,636,792 individuals who registered in the GPRD database from 1994 to 1999 were followed for 5,404,705 person-years; 128 of these patients were deemed to have developed DILI. The high variability in the estimated frequency of DILI in these retrospective studies reflects not only the difficulty in diagnosing this condition, but also the need for prospectively designed clinical studies investigating DILI.

Prospective Registries

Over the last decade, there have been three prospective registries that significantly enhanced our understanding of DILI. These prospective efforts are the Regional Registry of Hepatotoxicity in southern Spain, the U.S. Acute Liver Failure Study Group (ALFSG), and the Drug-Induced Liver Injury Network (DILIN). These prospective, observational studies create a registry of patients with suspected DILI (ALF in the case of the ALFSG) and provide an opportunity to study the mechanisms, etiology, and prevention of these serious and potentially fatal ADRs. As an example, the inclusion and exclusion criteria for the DILIN prospective study are shown in Table 2.

An overview of the prospective studies that offer some details of DILI epidemiology are shown in Table 3. One of the first prospective studies was performed by Hartleb et al, who found that over a 3-year period at a single gastroenterology department in Poland, DILI was diagnosed in 14 patients.²¹ However, the total number of patients with acute liver injury over the same period was not reported, making these data of limited value. Data from the Regional Registry of Hepatotoxicity in Spain showed that from 1994 to 2004 461 cases of DILI were identified out of 570 patients submitted to the registry (109 cases were excluded due to unreliable chronological criteria or alternative causes of liver injury).²² Hepatocellular damage was the most common pattern observed (58%), and patients with drug-induced jaundice at presentation experienced worse outcomes—11.7% of patients required transplant surgery or died compared with only 3.8% of patients who were not jaundiced. This study estimated the overall annual incidence of DILI to be 34.2 ± 10.7 cases per 10^6 inhabitants, and the annual incidence of serious DILI was 16.6 ± 6.7 cases per 10^6 inhabitants. The main causative medications were anti-infectious (32%), followed by central nervous system (17%), musculoskeletal (17%), and gastrointestinal drugs (10%). It is noteworthy that amoxicillin/clavulanate was the individual drug responsible for the highest number of cases ($n = 59$).

Data regarding drug-induced ALF from the U.S. ALFSG have been summarized in two reports. In the first study, Ostapowicz et al described the incidence and causes of ALF at 17 tertiary care centers across the United States during the 4-year period from 1998 to 2001. They found that idiosyncratic drug reactions were responsible for 40 out of 308 ALF cases (13%), which was second only to acetaminophen overdose (39%).¹ In a later publication from the same group, covering the 6-year period from 1998 to 2003, the incidence rate of idiosyncratic drug-induced ALF was reported to be 12% (79 patients out of 662 total subjects), and the incidence of acetaminophen-induced ALF increased to 42% (275 patients).¹⁰

Recently, findings from the first 300 subjects enrolled in the ongoing DILIN prospective study were reported by Chalasani et al.²³ This study was created in 2003 as a cooperative network among the National Institutes of Health, five academic clinical centers, and a data coordinating center.²⁴ Data from this initial analysis showed that 73% of cases resulted from taking a single prescription medication, 9% of cases were attributed to herbal and dietary supplements, and 18% of DILI cases resulted from taking multiple agents.²³ Importantly, subjects with acetaminophen hepatotoxicity are not included in the DILIN prospective study. Subjects followed for at least 6 months showed the following results: 14% had persistent laboratory abnormalities and a reported mortality rate of 8%, although the cause of death was liver-related in only 44% of the cases. Among subjects with DILI caused by a single prescription drug, the major classes of implicated agents were antimicrobials (45.5%), central nervous system agents (15%), immunomodulatory agents (5.5%), analgesics (5%), and lipid-lowering agents (3.4%). Once again, amoxicillin/clavulanate was the individual drug responsible for the highest number of cases ($n = 23$).

In a population-based, prospective study of 81,301 individuals in France from 1997 to 2000, Sgro et al identified 34 patients as having DILI, resulting in an annual crude incidence rate of 13.9 ± 2.4 cases per 100,000 inhabitants.²⁵ The authors estimated that the number of hepatic ADRs in the French population would be 16 times greater than the number noted by spontaneous reporting to French regulatory authorities. Extrapolation of this data to the population of the United States suggests that there may be ~44,000 cases of DILI annually, resulting in at least 2700 deaths.¹¹ The main drugs implicated in France were anti-infectious, psychotropic, lipid-lowering agents, and nonsteroidal anti-inflammatory drugs.

Herbal and Dietary Supplements

Although prescription and over-the-counter medications are often implicated in DILI, there is growing concern over another important source of liver injury: dietary supplements and herbal compounds, either taken alone or in combination with drugs. Another article in this volume, "Herbal and Dietary Supplement Hepatotoxicity," is devoted to discussing the hepatotoxicity of dietary and weight-loss supplements. These products impact the epidemiology and etiology of DILI in different parts of the world, especially in Asia. For example, a large retrospective analysis of 1676 patients diagnosed with DILI in Japan between 1997 and 2006 revealed that in cases with one causative agent, dietary supplements were responsible for 10% of cases and Chinese herbal medicines were responsible for 7.1% of cases.²⁶ Interestingly, these numbers were markedly elevated from a previous survey from 1989 to 1998 by Tameda et al, in which they reported that only 0.7% of DILI cases were due to dietary supplements and 4.7% of cases were due to Chinese herbal medicines.²⁷ In a prospective study performed in Singapore, Wai et al identified 31 patients with DILI; 55% were attributed to use of traditional Chinese herbs, and 16% were caused by Malay complementary and alternative medications (CAMs).²⁸ These findings illustrate the impact of cultural influences on the etiologies of DILI on a global level.

EPIDEMIOLOGY OF DILI IN POPULATION SUBGROUPS

Historically, the susceptibility to DILI across different population subgroups was thought to be influenced by multiple factors, including age, sex, concomitant medication use, environmental exposures and toxins, underlying disease states, and genetic predisposition. However, there is no conclusive evidence in the literature supporting the traditionally held beliefs that women, older individuals, or those who abuse alcohol are at an increased risk for developing DILI. A critical review of different causality instruments found that evidence is scant to support that any population subgroup (i.e., elderly, women) is consistently at higher risk for DILI caused by any medication.²⁹ An evolving view on host characteristics as risk factors for developing DILI is that they may confer susceptibility to certain compounds or may

lead to certain types of hepatic damage and differing outcomes, rather than an overall susceptibility to DILI.³⁰

As discussed previously, the epidemiology of DILI has not been well-studied due to the lack of active reporting and surveillance systems and the need for standardized diagnostic criteria. Furthermore, epidemiologic studies within specific patient subgroups historically suspected to increase the risk for developing DILI are lacking. Therefore, estimates of the incidence of DILI in particular patient subgroups are generally inferred from larger cohorts rather than investigations targeting a specific subgroup.

Female Sex

A general belief that female sex confers increased susceptibility to developing DILI is based partly on the observation of a preponderance of women in many published retrospective and prospective DILI cohorts,^{1,13,21,25} especially those caused by herbal and dietary supplements.^{31,32} However, a recent review by Shapiro and Lewis found that female sex was not a specific risk factor for developing DILI based on their critical analysis of published data.²⁹ Lucena et al analyzed 603 patients in the Spanish Registry of Hepatotoxicity from 1994 to 2007 and found a similar sex distribution across all DILI cases (49% women and 51% men).³⁰ In agreement with these findings are several other studies suggesting that female sex is not associated with the development of DILI.^{22,23,33} For example, in the French prospective study by Sgro et al, the crude annual incidence of DILI was 17.1 ± 3.6 per 100,000 women, which was not significantly different for men (10.4 ± 3.0 per 100,000 men).²⁵ Interestingly, in this study, the standardized female-to-male incidence ratio increased from 0.86 (0.26 to 2.90) in women younger than 50 years of age to 2.62 (1.0 to 6.92) after that age. However, this age-dependent sex disparity was not confirmed in a more recent report by Lucena et al.³⁰

Some studies have shown a relationship between female sex and DILI phenotype (hepatocellular pattern of liver injury),^{23,30} and also worse outcomes, including ALF requiring transplant surgery in some cases and death in others.^{16,22,30} A prospective study by Chalasani et al showed significantly more women in the hepatocellular DILI group than men (65% versus 35%, $P < 0.05$). Lucena et al showed that women ≤ 60 years of age had significantly more hepatocellular DILI than men ≤ 60 years of age (female-to-male ratio: 1.2), whereas women > 60 years of age had significantly lower likelihood of cholestatic DILI than men > 60 years (female-to-male ratio: 0.7). In the seminal article by Andrade et al, a strong relationship between DILI severity and female sex was seen: 89% of patients with fulminant DILI were women.²² But this association could not be reproduced in the DILIN prospective study, which showed no relationship between female sex and DILI severity (57% women in the mild to moderate DILI group versus 59% women in the severe DILI group, $P = 0.8$).

There is also rising concern for DILI caused by herbal and dietary supplements, especially those consumed for weight loss in women. The increasing frequency of this type of hepatotoxicity is likely due to the epidemic of obesity in developed countries, and one of the main concerns with the use of weight-loss supplements is that they are not regulated by governmental agencies, including the U.S. Food and Drug Administration (FDA). In addition to potentially causing direct liver injury, many supplements can interact with drugs via cytochrome P450 induction or inhibition, leading to additional increased risk for serious ADRs and development of DILI.³⁴ For example, Estes et al showed that in a group of adults with ALF, 50% of patients had recently taken potentially hepatotoxic herbs or supplements, including several known to induce weight loss.³⁵

The Elderly

Traditionally, it is believed that the incidence of DILI is greater in older individuals,⁴ and the prevalence of DILI in this population is of increasing interest as the large baby boomer generation continues to age. Support for this notion comes from the fact that pharmacokinetic factors associated with drug disposition may be altered with age, including drug absorption, distribution, metabolism, and elimination.³⁶ In fact, increased age (≥ 55 years) is one of the criteria included in the Council for International Organizations of Medical Science/Roussel Uclaf Causality Assessment Model (CIOMS/RUCAM). Regarding hepatotoxicity associated with individual drugs, there is clear evidence that older age is a risk factor for developing DILI by isoniazid.^{37,38} A recent study in Japan directly evaluated the clinical characteristics of DILI in a predominantly elderly population consisting of 142 hospitalized patients.³⁹ They found that older patients (≥ 75 years) had higher alkaline phosphatase levels, were taking a greater number of concomitant drugs at liver injury onset, and developed cholestatic liver injury more frequently. Indeed, an important consideration in the elderly is their use of multiple medications due to underlying illnesses, which may contribute to their increased risk of serious ADRs through alterations in cytochrome P450 expression and activity.⁴⁰

As in women, an emerging view is that older age is not necessarily a risk factor for DILI in general, but older individuals may be at increased susceptibility to DILI caused by certain compounds (i.e., isoniazid and amoxicillin/clavulanate). In addition, several studies have shown strong association between older age and cholestatic or mixed patterns of DILI.^{22,23,30,39,41}

Children

No population-based studies have systematically examined the epidemiology of DILI in children. Nonetheless, DILI is a significant clinical problem because it accounts for up to 20% of ALF cases requiring liver transplant surgery.⁶ In a report from the Pediatric Acute Liver Failure Study Group (PALF), of the first 348 children enrolled, 14% were found to have acetaminophen-induced ALF, and other drugs were responsible for 5% of ALF.⁴² In addition, Russo et al analyzed the number of ALF children who underwent liver transplant surgery for DILI, and found that 41 out of 270 total recipients were children < 18 years old and that acetaminophen toxicity was responsible for the majority of ALF cases (37%), followed by valproate (20%) and propylthiouracil (10%).¹⁶ Although the majority of DILI cases in children are mild, it is important to note that pediatric DILI patients have the potential to progress to ALF, resulting in the need for liver transplant surgery or in death.

As with the elderly, children do not appear to be more generally susceptible to DILI, but they undoubtedly have increased susceptibility to selected compounds. Unusual sensitivity of children with viral infections to aspirin (Reye's syndrome) is well known, and additional examples include an increased frequency of DILI in children receiving valproate and erythromycin estolate.⁴³ Unlike adults, in whom antimicrobial agents predominate, central nervous system agents (i.e., antiepileptics and psychotropics) are the single most common class of agents implicated in children with DILI.

Patients with HIV/AIDS

Infection with HIV is generally considered a predisposition to DILI. In addition, the antiretroviral drugs used to treat conditions such as HIV can induce liver injury on their own and are a significant source of morbidity, mortality, and discontinuation of treatment in affected populations.^{44,45} A large body of work is dedicated to understanding the relationships between HIV infection and the associated incidence of DILI, as well as the antiretroviral drug-related liver injury that is often seen in these patients. In a group of 102 African American and Hispanic patients with AIDS and jaundice (serum bilirubin > 3 mg/dL), Akhtar and Shaheen reported

that DILI was the most common cause (29%) of jaundice in this population.⁴⁶ In this group of subjects, 55% were receiving antiretroviral therapy, and the likely contributors to DILI were highly active antiretroviral therapy (HAART) drugs, isoniazid, rifampin, trimethoprim-sulfamethoxazole, and acetaminophen. These findings confirm previous studies demonstrating the increased incidence of DILI associated with the use of antiretroviral and antituberculosis drugs such as isoniazid in HIV-infected patients.^{44,47} Indeed, HIV infection is associated with an increased risk of development of antituberculosis drug-induced hepatotoxicity, which has an overall incidence rate that ranges from 2 to 28%.⁴⁸

Hepatotoxicity related to the use of antiretroviral drugs has become an important research topic due to the increased use of HAART and the negative impact DILI has on patient outcomes, including cessation of suppression of HIV viral load due to drug discontinuation. Most episodes of antiretroviral liver injury are mild and resolve spontaneously; however, in some cases DILI induced by antiretroviral therapy can be severe. Overall, the incidence of DILI after initiation of HAART therapy is between 2 and 18%.^{44,49–58} Not surprisingly, DILI is more common in HIV-infected patients that are co-infected with hepatitis B virus (HBV) or hepatitis C virus (HCV),^{49–58} especially those infected with HCV genotype 3.^{59–61} Other factors associated with an increased incidence of DILI in HIV/AIDS patients include advanced age,⁴⁹ alcohol use,⁴⁹ female sex,⁵⁶ first exposure to antiretroviral therapy,⁵⁷ and elevated liver enzymes before initiation of HAART therapy.^{52,54–56} Finally, Aranzabal et al suggested that there is a correlation between the incidence of HAART-induced hepatotoxicity and the histological stage of liver fibrosis.⁶²

Patients with Chronic Hepatitis B or C Infection

In general, chronic liver diseases such as HBV and HCV infection are thought to be associated with an increased incidence of hepatotoxicity induced by several specific drugs. Furthermore, patients with underlying liver disease potentially have poorer outcomes than healthy individuals if they do, in fact, develop DILI.⁶³ For example, the presence of underlying chronic HBV or HCV has been shown to increase the risk of DILI caused by antituberculosis drugs, isoniazid, and rifampin.^{64,65} Other medications that may be associated with an increased incidence of DILI in the presence of underlying HBV and HCV infection include ibuprofen and methimazole.⁶⁶

As previously discussed, HIV-infected individuals with HCV or HBV co-infection are at higher risk for DILI. In a recent study, Labarga et al demonstrated that sustained HCV clearance after interferon-based therapy in a group of 132 HIV patients with HCV co-infection was associated with a lower incidence of DILI during antiretroviral therapy.⁶⁷ These important findings suggest that the incidence of antiretroviral hepatotoxicity is reduced by successful treatment of HCV. However, in patients without HIV co-infection, the importance of excluding possible underlying liver conditions such as acute or chronic HCV, HBV, and hepatitis E virus (HEV) in the causality assessment of DILI is critical. For example, of the first 300 patients enrolled in the prospective DILIN study, acute HCV infection was the final diagnosis for four out of nine cases that were determined “unlikely” to be DILI.²³ In addition, Dalton et al recently reported that 6 out of 47 British patients with suspected DILI actually were infected with HEV, which has a clinical presentation that can closely mimic the nonspecific features of DILI.⁶⁸

Patients with Obesity and Nonalcoholic Fatty Liver Disease

It does not appear that individuals with obesity and nonalcoholic fatty liver disease (NAFLD) are systematically at increased risk for developing DILI. Perhaps the most investigated agents in this context are statins, which are widely used in individuals with obesity and NAFLD. Several studies have shown that these individuals are not at increased risk to develop DILI from statins.^{69–71} However, an Italian study has made a provocative observation that patients

with NAFLD may have higher risk of DILI. In this study, Tarantino et al prospectively followed 248 patients with chronic liver disease (174 patients with HCV and 74 age- and sex-matched patients with NAFLD) for 6 years. During the 6-year follow-up, six patients developed “certain” DILI (2.4%) with all cases occurring in the NAFLD group.⁷² Notwithstanding their sample size, the authors concluded that NAFLD is an independent risk factor of DILI with an odds ratio 3.95 (95% confidence interval [CI], 1.35 to 11.48). However, this has not been the experience of the senior author (N.C.) who has followed more than 500 NAFLD patients over the last decade (personal observation). Although obesity may have an adverse effect on the outcome of patients with ALF,⁷³ there is no indication that body mass index (BMI) has significant influence on the pattern, severity, or outcome of DILI.^{22,23} In the study by Chalasani et al, BMI was nearly identical among hepatocellular, cholestatic, and mixed forms of DILI and also in mild to moderate and severe DILI.²³

SUMMARY AND FUTURE DIRECTIONS

DILI is a rare cause of acute liver injury in clinical practice, but it poses significant problems for the pharmaceutical industry, regulators, clinicians, and patients. The epidemiology of DILI is poorly understood, and it is difficult to conduct population-based epidemiological studies due to its rarity and challenges in recognizing and diagnosing patients with bona fide DILI. Recent efforts to establish prospective registries have greatly enhanced our understanding of the characteristics of patients with well-defined DILI but have not provided population-based epidemiological data. Particularly challenging is to investigate the epidemiology of DILI caused by herbal and dietary supplements. Although population-based studies will be quite difficult to conduct without a federally mandated active reporting system, pharmacoepidemiological studies should be conducted at organizations such as large health maintenance organizations and Veterans Affairs healthcare systems to further our understanding of DILI epidemiology. Similarly, unpublished clinical trial data possessed by pharmaceutical companies and regulators might serve as a rich source for investigating clinical aspects of DILI, including genetic polymorphisms.

ABBREVIATIONS

DILI	drug-induced liver injury
ALF	acute liver failure
ADR	adverse drug reaction
AIDS	acquired immunodeficiency syndrome
ALFSG	Acute Liver Failure Study Group
BMI	body mass index
CAM	complementary and alternative medicine
CHDM	Comprehensive Hospital Drug Monitoring
CI	confidence interval
CIOMS/RUCAM	Council for International Organizations of Medical Science/Roussel Uclaf Causality Assessment Model
DILI	drug-induced liver injury
DILIN	Drug-Induced Liver Injury Network
FCHP	Fallon Community Health Plan
FDA	U.S. Food and Drug Administration

GPRD	General Practice Research Database
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
ICD-9	International Statistical Classification of Diseases code
NAFLD	nonalcoholic fatty liver disease
PALF	Pediatric Acute Liver Failure Study Group
SAS/CHDM	Stiftung für Arzneimittelsicherheit/Comprehensive Hospital Drug Monitoring
UMHS	University of Michigan Health System
UNOS	United Network for Organ Sharing

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Table 1

Summary of Retrospective Drug-Induced Liver Injury (DILI) Studies

Reference	Setting	Time Period	Number of Patients	Number of Patients with Idiosyncratic DILI	DILI Frequency	Comments
de Valle et al (2006) ¹³	Swedish outpatient hepatology clinic	1995–2005	1164	77	6.6%	DILI occurred more often in women (56%) Most common causative agents were antibiotics
Hussaini et al (2007) ¹⁴	The Jaundice Hotline, a jaundice referral center in England	1998–2004	347	28	8.1%	Most common causative agents were antibiotics
Meier et al (2005) ¹⁵	Swiss SAS/CHDM inpatient pharmacoepidemiological database	1996–2000	4209	57	1.4%	Most common causative agents were antineoplastic and antituberculosis medications in these hospitalized patients
Russo et al (2004) ¹⁶	U.S. UNOS liver transplant database	1990–2002	2291	137	6.0%	Numbers are for drug-induced liver transplants, which occurred more often in women (76%) Most common causative agents were isoniazid, propylthiouracil, phenytoin, and valproate Additional 133 patients had acetaminophen hepatotoxicity for total of 270 DILI cases (11.8% of liver transplants attributable to overall DILI)
Vuppalanchi et al (2007) ¹⁷	Inner-city primary care clinics and nonreferral hospital in Indiana	1999–2003	732	5	0.7%	Numbers are for drug-induced jaundice Drugs taken by patients in the DILI group included Metabolife, HAART, and valproate Additional 24 patients had acetaminophen hepatotoxicity for total of 29 DILI cases (4.0% of jaundice cases attributable to overall DILI)
Jinjuvadia et al (2007) ¹⁸	ICD-9 codes and medication search of the UMHS database	1994–2004	7395	83	1.1%	Patients were identified using ICD-9 liver injury codes, medication searches, and text searches of the dictated medical record Different searches yielded highly variable results Additional 36 patients had acetaminophen hepatotoxicity for total of 119 DILI cases (1.6% incidence rate of overall DILI)
Duh et al (1999) ¹⁹	ICD-9 codes and medication search of the FCHP database in Massachusetts	1992–1993	219	50	22.8%	Numbers are for drug-induced liver enzyme abnormalities Patients were identified using ICD-9 hepatic disorder codes and medication searches (only prescription drugs with hepatotoxicity warnings in the package insert were considered) Drug-induced liver enzyme abnormalities were the most common type of liver enzyme abnormalities (incidence rate of 41/100,000 persons per year)
de Abajo et al (2004) ²⁰	Population-based case-control study using data from the GPRD in the UK	1994–1999	1,636,792	128	2.4/100,000 persons per year	Most common causative agents were chlorpromazine, azathioprine, and sulfasalazine

DILI, drug-induced liver injury; SAS/CHDM, Stiftung für Arzneimittelsicherheit/Comprehensive Hospital Drug Monitoring; UNOS, United Network for Organ Sharing; HAART, highly active antiretroviral therapy; ICD-9, International Statistical Classification of Diseases; UMHS, University of Michigan Health System; FCHP, Fallon Community Health Plan; GPRD, General Practice Research Database.

Table 2**Eligibility Criteria for the Drug-Induced Liver Injury Network (DILIN) Prospective Study**

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • Adults or children >2 y • Evidence of liver injury known or suspected to be related to a drug or herbal/dietary supplement within the previous 6 mo • Written informed consent • Clinically significant DILI, as shown by any of the following: <ul style="list-style-type: none"> – Jaundice or serum bilirubin >2.5 mg/dL and any elevation in ALT, AST, or alkaline phosphatase – Elevations in serum ALT or AST ($>5 \times$ ULN) or elevations in alkaline phosphatase ($>2 \times$ ULN) on 2 consecutive occasions – Persons with known preexisting liver disease (e.g., chronic HBV or HBC), elevations in ALT or AST $>5 \times$ baseline values, or elevations in alkaline phosphatase $>2 \times$ baseline values 	<ul style="list-style-type: none"> • Other known preexisting liver diseases such as sclerosing cholangitis, autoimmune hepatitis, or primary biliary cirrhosis • Acetaminophen hepatotoxicity • Liver transplantation prior to DILI onset

DILI, drug-induced liver injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; HBV, hepatitis B virus; HBC, hepatitis C virus.

Adapted from the DILIN Physicians Brochure: <https://diln.dcri.duke.edu/>.

Table 3

Summary of Prospective Studies of Drug-Induced Liver Injury

Reference	Setting	Time Period	Number of Patients	Number of Patients with Idiosyncratic DILI	Frequency of DILI	Comments
Hartleb et al (2002) ²¹	Polish gastroenterology department	1997–1999	—	14	—	DILI occurred more often in women (57%) Most common causative agents were amoxicillin/clavulanic acid, lipid-lowering agents, and antituberculosis medications
Andrade et al (2005) ²²	Spanish Registry of Hepatotoxicity	1994–2004	—	461	—	109 cases were excluded due to unreliable chronological criteria or identification of alternative causes of liver injury Factors associated with worse outcomes were female sex, hepatocellular pattern of damage, and high bilirubin levels at baseline Most common causative agent was amoxicillin/clavulanic acid (12.8% of all DILI)
Ostapowicz et al (2002) ¹	U.S. ALFSG	1998–2001	308	40	13.0%	Numbers are for drug-induced ALF Additional 120 patients had acetaminophen hepatotoxicity for total of 160 DILI cases (51.9% of ALF attributable to overall DILI)
Larson et al (2005) ¹⁰	U.S. ALFSG	1998–2003	662	79	12.0%	Numbers are for drug-induced ALF Additional 275 patients had acetaminophen hepatotoxicity for total of 354 DILI cases (53.5% of ALF attributable to overall DILI)
Chalasani et al (2008) ²³	U.S. DILIN	2004–2007	—	300	—	DILI was caused by single prescription medication in 73%, dietary and herbal supplements in 9%, and multiple agents in 18% Most common causative agents were antimicrobials and central nervous system medications After 6-mo follow-up, 14% of patients had persistent laboratory abnormalities and 8% died
Sgro et al (2002) ²⁵	French population-based study	1997–2000	81,301	34	13.9 ± 2.4 cases/ 100,000 persons	Most common causative agents were antibiotics, psychotropics, lipid-lowering agents, and nonsteroidal anti-inflammatory drugs The number of hepatic ADRs would be 16 times greater than the number actually reported to French regulatory authorities 1 case of DILI was attributable to acetaminophen hepatotoxicity

DILI, drug-induced liver injury; ALFSG, Acute Liver Failure Study Group; ALF, acute liver failure; DILIN, Drug-Induced Liver Injury Network; ADR, adverse drug reaction.