American Journal of Gastroenterology

Published by Blackwell Publishing

ISSN 0002-9270
doi: 10.1111/j.1572-0241.2007.01456.x

Searching for a Needle in a Haystack: Use of ICD-9-CM Codes in Drug-Induced Liver Injury

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OBJECTIVES: The aim of our study was to compare three search strategies using a computerized administrative database to identify cases of idiosyncratic drug-induced liver injury (DILI) due to amoxicillin/clavulanic acid, phenytoin, valproic acid, and isoniazid.

METHODS: In search 1, electronic medical records from patients seen between 1994 and 2004 with an ICD-9-CM code of acute liver injury were identified and cross-searched for the specific drug names in the dictation text. In search 2, all patients with an ICD-9-CM code of drug poisoning/overdose due to one of the four study drugs were identified. In search 3, patients with a poisoning code as well as an acute liver injury code were identified.

RESULTS: Review of the records from the 7,395 search 1 patients yielded 51 DILI cases (0.7%). In contrast, the 566 search 2 patients yielded only three DILI cases (0.5%). Finally, search 3 provided the greatest specificity but a low rate of detection with only two patients (3.9%) having DILI due to one of the four drugs.

CONCLUSION: Acute liver injury ICD-9-CM codes combined with a text search of the dictated medical record yielded the greatest number of DILI cases but was less specific than crossing acute liver injury and poisoning codes. Use of ICD-9-CM codes to identify rare adverse events like DILI remains problematic and highlights the need for prospective surveillance networks.

(Am J Gastroenterol 2007;102:2437–2443)

INTRODUCTION

Drug-induced liver injury (DILI) is an infrequent but potentially serious adverse event (1). Liver injury may arise following the use of prescription drugs, over the counter medications, or complementary and alternative medicines including herbal products and weight-loss supplements (2, 3). DILI is frequently a diagnostic challenge for physicians due to substantial variation in the clinical manifestations and severity of liver injury from a given drug, the use of multiple medications, and the need to exclude other more common causes of liver injury (4). Furthermore, there are no objective laboratory tests to confirm a diagnosis of DILI, which frequently requires longitudinal follow-up to demonstrate improvement with drug cessation. Finally, idiosyncratic DILI is an unpredictable event that is independent of medication dose, duration, or other identifiable host risk factors and occurs in only a small proportion of exposed individuals (5). Although genetic variation in host metabolic, detoxification, and adaptation pathways has been implicated in the pathogenesis of DILI, confirmatory studies require the collection of biological samples from patients with a well-defined episode of DILI (5–7).

The National Institutes of Health recently established the Drug-Induced Liver Injury Network (DILIN), a multicenter prospective surveillance network, to improve our understanding of the risk factors, natural history, and biological basis of DILI in the United States (8, 9). In the retrospective protocol, four commonly used medications with characteristic phenotypes of hepatotoxicity have been targeted for further mechanistic studies (*i.e.*, phenytoin, isoniazid [INH], amoxicillin/clavulanate, valproate). To facilitate identification of patients with prior rare adverse events, some investigators have found that diagnostic codes used for billing and administrative purposes may be useful (10–12). However, other studies have shown that these diagnostic codes have limited accuracy compared to physician diagnosis (13–15). In the United States, the International Classification of Diseases-9th edition-Clinical Modification codes (ICD-9-CM) are used in most medical centers for tracking healthcare parameters in both the inpatient and outpatient setting. The aim of the current study was to explore the utility of various ICD-9-CM codes in a computerized administrative database to identify patients with DILI due to one of the four drugs targeted in the "Idiosyncratic Liver Injury Associated with Drugs" or ILIAD study. We also set out to determine the most useful search strategy to identify bonafide cases of DILI in patients seen at a large academic medical center.

METHODS

University of Michigan Health System's Medical Record Computer Database

The University of Michigan Health System (UMHS) is a regional tertiary care referral center in Ann Arbor, Michigan that serves a population of over 1 million patients each year. The center includes a total of 865 inpatient beds located at the University Hospital, Mott Children's Hospital, and Women's Hospital as well as a large number of subspecialty and primary care outpatient clinics. The electronic medical records include an IDX (IDX Systems Corporation, Burlington, VT) database that is used to process professional fee billing transactions based upon ICD-9-CM codes. Another electronic database called HealthQuest (McKesson, San Francisco, CA) contains information obtained from several sources including patient management, patient accounting, and medical records that also use ICD-9-CM codes. A waiver of consent was obtained from the local Institutional Review Board to search the inpatient, outpatient, and emergency room electronic medical records in the IDX and HealthQuest databases.

ICD-9-CM Codes and Medical Record Search

The International Classification of Diseases, 9th edition, Clinical Modification (ICD-9-CM) codes indicative of acute liver injury or the codes used for specific drug overdose/toxicities were collated together. Individual patients with one of the ICD-9-CM codes entered between January 1, 1994 and March 31, 2004 were identified using one of the following search strategies:

SEARCH 1. All patients with at least one of the liver-related ICD-9-CM discharge diagnosis codes listed in Table 1 were identified. This list was crossed with a text search for one of the four study drugs of interest in their Dictated Medical Information documents. The medical records of the individual patients were then manually reviewed by a physician investigator (KJ) to identify patients with no other competing cause of acute liver injury and presumed DILI. Since there are no objective diagnostic laboratory tests for DILI, all patients with suspected DILI had to meet clinical criteria for presumed DILI that included: (a) exclusion of more common causes of acute liver injury (*e.g.*, hepatitis A, B, C, ischemia, alcohol, pancreaticobiliary disease); (b) temporal association between drug ingestion and onset of liver injury; (c) improvement of liver injury with discontinuation of suspect medication; (d) liver histology consistent with DILI if obtained; and (e) clinical presentation and phenotype consistent with known prior reports of DILI due to the suspect agent.

SEARCH 2. ICD-9-CM codes indicative of accidental, suicidal, or therapeutic use poisoning from one of the four study drugs were used in search 2. Specific poisoning codes included: 961.8 (isoniazid), 966.1 (phenytoin), 960.0 (antibiotic), 966.3 (anticonvulsant), whereas therapeutic use poisoning codes included: E930.0 (antibiotic), E936.1 (hydantoin derivative), E931.8 (isoniazid), and E936.3 (anticonvulsants).

Table 1. Frequency of Liver Injury Codes in Patients Identified in Search 1

ICD-9-CM Codes	Code Description	No. of Patients	No. of DILI Cases Due to Suspect Drugs	% of Total DILI Cases Due to Suspect Drugs
277.4	Jaundice, idiopathic	129	1	2 %
570	Liver failure, acute	495	15	29.4%
572.8	Liver failure, not otherwise specified	1,082	12	23.5%
573.3	Hepatitis, drug/ toxin induced	1,929	27	52.9%
573.8	Jaundice, hepatocellular	2,995	11	21.6%
576.8	Cholestasis	760	6	11.8%
782.4	Jaundice alone	1,971	10	19.6%
Total		9,361*	82†	

ICD-9-CM = International Classification of Diseases-9th edition-Clinical Modification.
*Actual number of individual patients is lower (*i.e.*, 7,395) because many had $\geq$1 diagnostic code.
†Twenty DILI patients had more than one ICD-9-CM acute liver injury code.

SEARCH 3. The electronic database was searched for patients who had at least one poisoning or therapeutic use poisoning code and one or more acute liver injury codes used in search 1.

Medical Record Retrieval and Review

The medical records of all patients with liver injury thought to be due to one or more of the study drugs by the attending physician were pulled for further review. The inclusion criteria for the ILIAD protocol were total bilirubin $\geq$2.5 mg/dL for INH, phenytoin, and amoxicillin/clavulanic acid cases. For valproate hepatoxicity, inclusion criteria were a compatible clinical presentation severe enough to prompt hospitalization with evidence of liver dysfunction (*e.g.*, International normalized ratio [INR] $\geq$1.5 or serum alanine aminotransferase [ALT] > 3 × upper limit of normal [ULN], and/or characteristic liver biopsy). All potential DILI cases were further reviewed and verified by an experienced hepatologist (RJF).

Statistical Analysis

Baseline demographics and clinical features are described as the mean ± standard deviation or median and range for non-normally distributed parameters. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the various ICD-9-CM codes for DILI were calculated.

RESULTS

In the University of Michigan Health System between 1994 and 2004, 319,956 patients had emergency room visits,

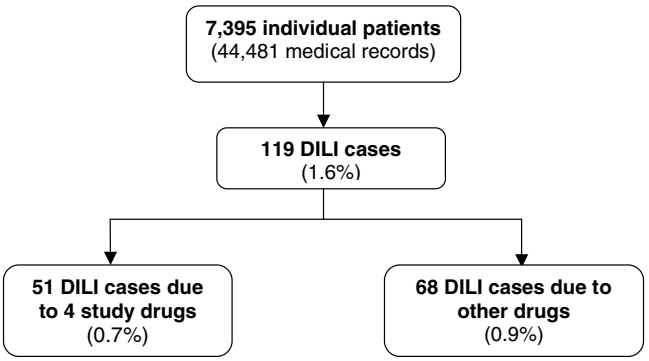

Figure 1. Results of search 1 combining liver injury codes and text search of the dictated medical record. Of the 119 DILI cases identified, 51 were due to one of the four study drugs of interest and 68 were due to other drugs.

284,199 patients had inpatient hospitalizations, and 881,400 patients had outpatient visits.

Acute Liver Injury Codes (Search 1)

During the study period, there were 7,395 individual patients with an ICD-9-CM code for acute liver injury and reference to one of the suspect medications in their dictated medical record. There were 6,076 individual subjects with a single ICD-9-CM code, 868 with two acute liver injury codes, and 449 with three or more codes. The ICD-9-CM codes for hepatocellular jaundice, drug-/toxin-induced hepatitis, and jaundice alone were most commonly identified and accounted for 40.5%, 26.1%, and 26.6% of the cases, respectively (Table 1). After manual review of the dictated medical record notes of these patients, 119 patients with suspected DILI were identified (Fig. 1). Further review of the medical records led to 51 subjects with DILI due to one of the four study medications of interest and 68 cases of DILI due to other drugs. Careful review of the 51 subjects' records led to 21 patients that met inclusion criteria for the retrospective ILIAD study. The remaining 30 patients had presumed DILI due to one of the four suspect medications but were excluded from the ILIAD protocol due to inadequate severity of biochemical liver injury (14 cases), multiple suspect hepatotoxic drugs (10 cases), medical conditions that confounded the diagnosis of DILI (4 cases), missing laboratory data (1 case), and vulnerable patient populations (*i.e.*, 1 prisoner). Of the 68 DILI cases due to other medications, 36 were attributed to acetaminophen overdose. Among the remaining 32 cases, 17 were due to various antibiotics, 3 due to lipid lowering agents, 2 due to nonsteroidal anti-inflammatory drugs, 2 due to carbamazepine, and 8 cases due to other individual drugs.

The mean age of the 51 DILI patients was 39.5 ± 23.2 yr and 51% were women (Table 2). More than 50% of the patients were hospitalized for the DILI episode and 5 (10%) died of liver failure or its complications whereas 1 additional patient required two liver transplants. All other patients recovered or were improving at last available follow-up. Forty-one of the cases were attributed to a single drug whereas 10 were attributed to multiple medications. Overall, 573.3 (hepatitis, drug/toxin induced) was the single most useful diagnostic code found in 27 of the 51 documented DILI cases (52.9%). The liver failure codes of 570 (liver failure, acute) and 572.8 (liver failure, not otherwise specified) were also present in 27 of the 51 documented DILI cases (52.9%). The code 782.4 (jaundice alone) was present in 10 of 51 DILI cases (19.6%) whereas code 277.4 (jaundice, idiopathic) was identified in only 1 patient (2%). Twenty of the 51 patients (39%) had two or more acute liver injury codes recorded during the DILI episode. The sensitivity, specificity, PPV, and NPV of the individual liver disease codes used in search 1 are displayed in Table 3.

All 11 patients with amoxicillin/clavunate hepatotoxicity were men with a mean age of 56.2 yr (median 60, range 21–77). Six of them required hospitalization and all subjects spontaneously recovered except for a 72-yr-old man who died of multiorgan failure during his DILI hospitalization. The most commonly identified ICD-9-CM code for amoxicillin/clavulanate hepatotoxicity was 782.4 found in 64% of the cases whereas 573.3 was present in only 18%. In contrast, the mean age for the 12 patients with valproate hepatoxicity was much lower at 23.8 yr (median 15, range 3–59) and 7 were under the age of 18. There was an equal proportion of men and women and children with valproate hepatotoxicity. Overall, the younger patients were more likely to be hospitalized (71.4%) compared to the adults (20%) with valproate hepatotoxicity. The most frequently identified ICD-9-CM code for valproate liver injury was 573.3 (hepatitis, drug/toxin induced). There were also three cases of DILI believed to be, in part, due to valproic acid and a second drug, which all occurred in pediatric patients with seizure disorders.

There were 9 DILI cases due to phenytoin alone. The mean age of these patients was 37.2 yr (median 39, range 2–70) and

Table 2. Bonafide DILI Cases Identified in Search 1

	Liver Injury Code						
Drug	570	572.8	573.3	573.8	277.4	782.4	576.8
Amoxicillin/clavulanate (11 patients)	3	1	2	3		7	3
Valproic acid (12 patients)	4	4	7		1		
Phenytoin (9 patients)	1	3	5	1			2
Isoniazid (9 patients)	2		6	5		1	
Multiple suspect drugs (10 patients)	5	4	7	2		2	1
Total	15	12	27	11	1	10	6

Table 3. Utility of ICD-9-CM Codes in 51 DILI Cases Identified in Search 1

ICD-9-CM Code	Sensitivity	Specificity	PPV	NPV	Accuracy
277.4 Jaundice, idiopathic	2.0%	98.3%	0.8%	99.3%	97.6%
570 Liver failure, acute	29.4%	93.5%	3.0%	99.5%	93.0%
572.8 Liver failure, not otherwise specified	23.5%	85.4%	1.1%	99.4%	85.0%
573.3 Hepatitis (drug/toxin induced)	52.9%	74.1%	1.4%	99.6%	73.9%
573.8 Jaundice (hepatocellular)	21.6%	59.4%	0.4%	99.1%	59.1%
576.8 Cholestasis	11.8%	89.7%	0.8%	99.3%	89.2%
782.4 Jaundice alone	19.6%	73.3%	0.5%	99.2%	72.9%

PPV = positive predictive value; NPV = negative predictive value.

only 2 (22.2%) occurred in children. There was an equal proportion of men and women and 4 (44%) required hospitalization. The most frequent ICD-9-CM code was 573.3 whereas 3 patients had 572.8. There were 9 DILI cases due to isoniazid hepatotoxicity alone. As expected, all of the patients were >40 yr of age with a mean age of 55.9 yr (median 54, range 44–76) and there was a female predominance (77.7%). Both 573.3 and 573.8 were the most frequently recorded ICD-9-CM codes for INH hepatotoxicity.

The 10 patients with DILI due to multiple suspect drugs were relatively young with a mean age of 32.4 yr (median 25.5, range 10–88 yr) and 90% were women. All of these patients were hospitalized and three of them died as a result of DILI. The most frequently identified ICD-9-CM code in cases with multiple suspect medications was 573.3 (hepatitis, drug/toxin induced), present in seven cases (70%), whereas 570 (liver failure, acute) was present in five cases (50%).

Poisoning Codes (Search 2)

Among the 566 individual patients with a therapeutic poisoning code diagnosis, there were only four identified DILI cases including three due to one of the study drugs (2 isoniazid, 1 phenytoin) and one patient with DILI due to a nonstudy drug (sulfasalazine) (Table 4, Fig. 2). All identified patients were women and 50% were hospitalized but none of them died. None of these patients were previously identified in search 1. One of the isoniazid cases, a 22-yr-old woman, had acute liver failure and met criteria for enrollment into the ILIAD protocol whereas the other two DILI cases had milder liver injury. The two isoniazid cases and the one sulfasalazine case had an "E" code modifier in their ICD-9-CM codes (*i.e.*, classified as having therapeutic use poisoning).

Table 4. Frequency of Therapeutic Use Poisoning/Overdose Codes in Patients Identified in Search 2

ICD-9-CM Code	Code Description	No. of Patients
961.8*	Isoniazid	3
966.1*	Phenytoin	189
960.0*	Antibiotic	33
966.3*	Anticonvulsant	265
E930.0†	Antibiotic	28
E936.1†	Hydantoin derivative	28
E931.8†	Isoniazid	0
E936.3†	Anticonvulsant	20
Total		566

ICD-9-CM = International Classification of Diseases-9th edition-Clinical Modification.
*Poisoning codes.
†Therapeutic poisoning codes.

Acute Liver Injury and Poisoning Codes (Search 3)

Among the 51 patients who had both an acute liver injury and poisoning code, three were identified as having DILI. Two of these three DILI cases were due to study drugs (1 phenytoin, 1 isoniazid) and one was due to a nonstudy drug (sulfasalazine) (Fig. 3). Interestingly, all three of these cases had been previously identified in search 2 but not in search 1. The acute liver injury code for all three cases was 573.3.

DISCUSSION

Our study results demonstrate that crossing acute liver injury codes with a text search of the suspect drug name in the dictated medical record (*i.e.*, search 1) appears to be the most sensitive means of identifying potential DILI cases. In contrast, crossing acute liver injury codes with a poisoning code (*i.e.*, search 2) was the most specific strategy but had a low net yield. Of the three search strategies employed, search 1 yielded the largest number of potential DILI cases. However, to identify those 51 DILI cases, the medical records of 7,395 patients had to be manually reviewed. Therefore, only 0.7% of the patients identified in search 1 truly had DILI due

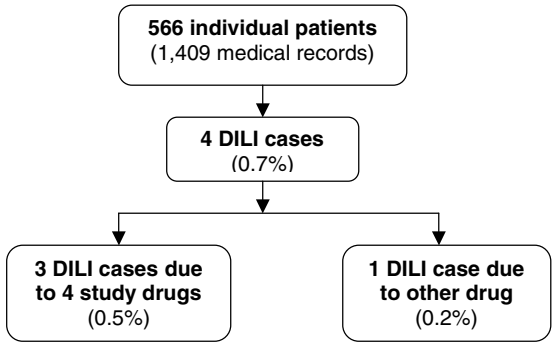

Figure 2. Results of search 2 using therapeutic use poisoning and overdose codes. There were four DILI cases identified including three due to one of the study drugs of interest and one case attributed to sulfasalazine.

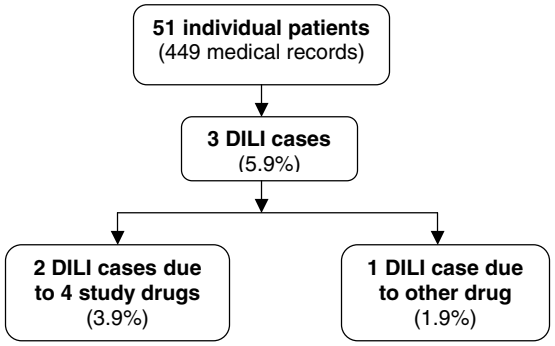

Figure 3. Results of search 3 using liver injury and therapeutic use poisoning/overdose codes. The three DILI cases had been previously identified in search 2 and included two DILI cases due to one of the study drugs of interest.

to one of the four study drugs. The low overall incidence of DILI cases may, in part, be due to the low incidence of DILI in the general population compared to other more common causes of acute liver injury such as alcohol, viral hepatitis, and pancreaticobiliary disease, as demonstrated in a recent study (16). In addition, there is a potential referral bias in our study since the University of Michigan is a liver transplant center and may attract a large number of patients with acute liver injury due to other causes. Therefore, additional studies using various search strategies in other hospital systems are needed to confirm our results.

Review of the medical records of the 566 patients identified in search 2 yielded three patients (0.5%) with presumed DILI due to one of the four study drugs. The majority of the non-DILI cases identified in search 2 had drug toxicity due to therapeutic medication overdose (*e.g.*, high blood levels of phenytoin with neurological toxicity) rather than idiosyncratic adverse events such as DILI. This observation highlights the low incidence of DILI compared to other more common adverse events with these widely prescribed medications. Interestingly, search 3 also yielded only three potential DILI cases and all three had previously been identified in search 2. However, since only 51 total cases were identified in search 3, this strategy was more efficient than search 2 (3.9% *vs* 0.5%). The lack of overlapping cases between search 3 and search 1 suggests that these two search strategies may be complementary (17). The search 1 results also demonstrate that groups of ICD-9-CM codes can improve the detection of uncommon disease conditions such as DILI (12, 18). For example, although code 573.3 (hepatitis, drug/toxin induced) was the single most useful diagnostic code, failure to include the other codes would have missed nearly half of the DILI cases. Overall, the liver injury codes 573.3, 570, 572.8, and 573.8 were most commonly identified, with one or more present in 49 of the 51 cases. Therefore, it seems reasonable to recommend using multiple disease-related ICD-9-CM codes when attempting to identify patients with a rare clinical phenotype/adverse event such as DILI. However, further refinement of search strategies may prove useful because the three other acute liver injury codes (277.4, 576.8, 782.4) were uniquely identified in only two DILI cases but accounted for nearly 20% of the charts that required manual review.

Our study demonstrates the utility of ICD-9-CM codes for identifying DILI cases due to specific agents with differing clinical phenotypes. For example, DILI due to amoxicillin/clavunate frequently presents several days to weeks after drug cessation with new onset cholestatic hepatitis and jaundice in older men (19, 20). A delay in diagnosis of amoxicillin/clavulanate hepatotoxicity is commonly encountered whereas other more common etiologies of new onset jaundice are being evaluated (*e.g.*, choledocholithiasis, malignancy). Therefore, it is not surprising that the code 782.4 (jaundice alone) was the most commonly assigned code in cases of amoxicillin/clavulanic acid DILI whereas 573.3 was used in only 27%. In comparison, 573.3 was identified in 75% of valproate cases, 88% of phenytoin cases, and 88% of the isoniazid cases which tend to present with acute hepatocellular injury and characteristic clinical features (1).

A substantial discrepancy between the assigned ICD-9-CM codes and the suspected or confirmed diagnosis was noted in a large proportion of search 1 patients (Table 1). This may, in part, have been due to limited medical knowledge of the diagnostic coding staff or financial incentives based upon diagnostic-related group reimbursements as reported in prior studies (21–23). Prior studies have also shown that diseases with distinct and observable signs and symptoms are more likely to be coded correctly compared to conditions that are more difficult to recognize and diagnose (10, 24). Therefore, diseases like DILI that are rare and largely a diagnosis of exclusion are expected to be incorrectly coded more frequently than other more common liver diseases such as acute hepatitis A virus infection. Finally, although typing or data entry errors could have led to erroneous coding of DILI, it is unlikely that this would explain the large number of incorrectly coded cases.

An important limitation regarding the current study is that not all institutions may have the capability to search for selected keywords in the dictated medical record. We were fortunate to have this capability so that the number of records requiring manual inspection was more manageable (*e.g.*, in search 1, 7,395 *vs* 21,109 patients if text searching was not available). Alternative strategies to text searching include cross-searching patients with an acute liver injury code with a pharmacy database, which was not possible in our medical center. However, the computerized administrative database allowed us to search both the primary discharge diagnosis codes and up to 13 secondary ICD-9-CM codes, which may not be possible in other centers. When we looked at the distribution of discharge diagnoses from search 1, we noted that 15,109 of the liver injury codes were primary and 5,622 were secondary. Therefore, the inability to search for secondary ICD-9-CM codes may lead to substantially fewer cases of DILI.

In conclusion, a strategy combining ICD-9-CM codes for acute liver injury with a text search of drug names in the

dictated electronic medical record provided the largest number of potential DILI cases due to four commonly used medications. However, the lack of a consistent and specific diagnostic code for DILI precludes the use of ICD-9-CM codes for the purpose of estimating the incidence of this rare adverse event. It is possible that the implementation of the ICD-10 coding system with more precise diagnostic codes for uncommon diseases such as DILI will improve the utility of this method (25). Nonetheless, incorrect coding will likely continue to be encountered due to the difficulty in establishing a diagnosis of DILI. Going forward, multicenter surveillance networks such as DILIN that prospectively capture cases of rare adverse events may prove to be of greater value in improving our understanding of the genetic, immunological, and environmental basis for this rare but increasingly important cause of liver injury (8, 26, 27).

STUDY HIGHLIGHTS

What Is Current Knowledge

- Idiosyncratic drug-induced liver injury (DILI) is a rare but potentially serious adverse event of growing importance to the medical, regulatory, and pharmaceutical sectors.
- Idiosyncratic DILI also poses substantial diagnostic challenge to practitioners due to the lack of an objective confirmatory laboratory test, variable phenotype, and the need for longitudinal follow-up to exclude other more common causes of liver injury.
- International Classification of Diseases-9th edition-Clinical Modification codes recorded in administrative databases can be used to track the incidence of various medical conditions including rare adverse events due to medications.

What Is New Here

- A strategy combining a text search of the electronic medical record with ICD-9-CM codes for acute liver injury identified 51 patients with DILI due to four commonly used medications over a 10-yr period in a large academic medical center. Although a large number of potential DILI cases were identified, the sensitivity of this method was low at 0.7%.
- A strategy that crossed ICD-9-CM codes of acute liver injury with drug poisoning/overdose codes was more efficient but yielded only three DILI cases due to four commonly used medications over the same time period.
- There is a high degree of diagnostic inaccuracy in inpatient and outpatient medical encounters coded as potential DILI cases presumably due to the difficulty with establishing a diagnosis. Therefore, administrative databases using ICD-9-CM codes may have limited utility in tracking trends in the incidence of a rare adverse event such as DILI in the United States.

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Received November 6, 2006; accepted February 15, 2007.

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CONFLICT OF INTEREST

Guarantor of the article: Robert J. Fontana, M.D.
Specific author contributions: Robert J. Fontana was responsible for the overall design, conduct, analyses, and drafting/editing of the manuscript. Wendy Kwan was involved in conducting the database searches and drafting/editing the manuscript. Kartik Jinjuvadia reviewed the individual medical records and assisted with drafting/editing the manuscript, tables, and figures.
Financial support: This work was supported in part by an NIDDK research contract to RJF (NIH U01 DK065184-01).
Potential competing interests: None.