Drug Induced Liver Injury and Stevens Johnson Syndrome

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Drug-Induced Liver Injury

- ~3-10% of acute liver injury in the US
- Single, major cause of acute liver failure
- Common cause for a medication to be abandoned during development
- Common cause for withdrawal or restriction of use of an approved medication
- Frequently accompanies Stevens Johnson syndrome

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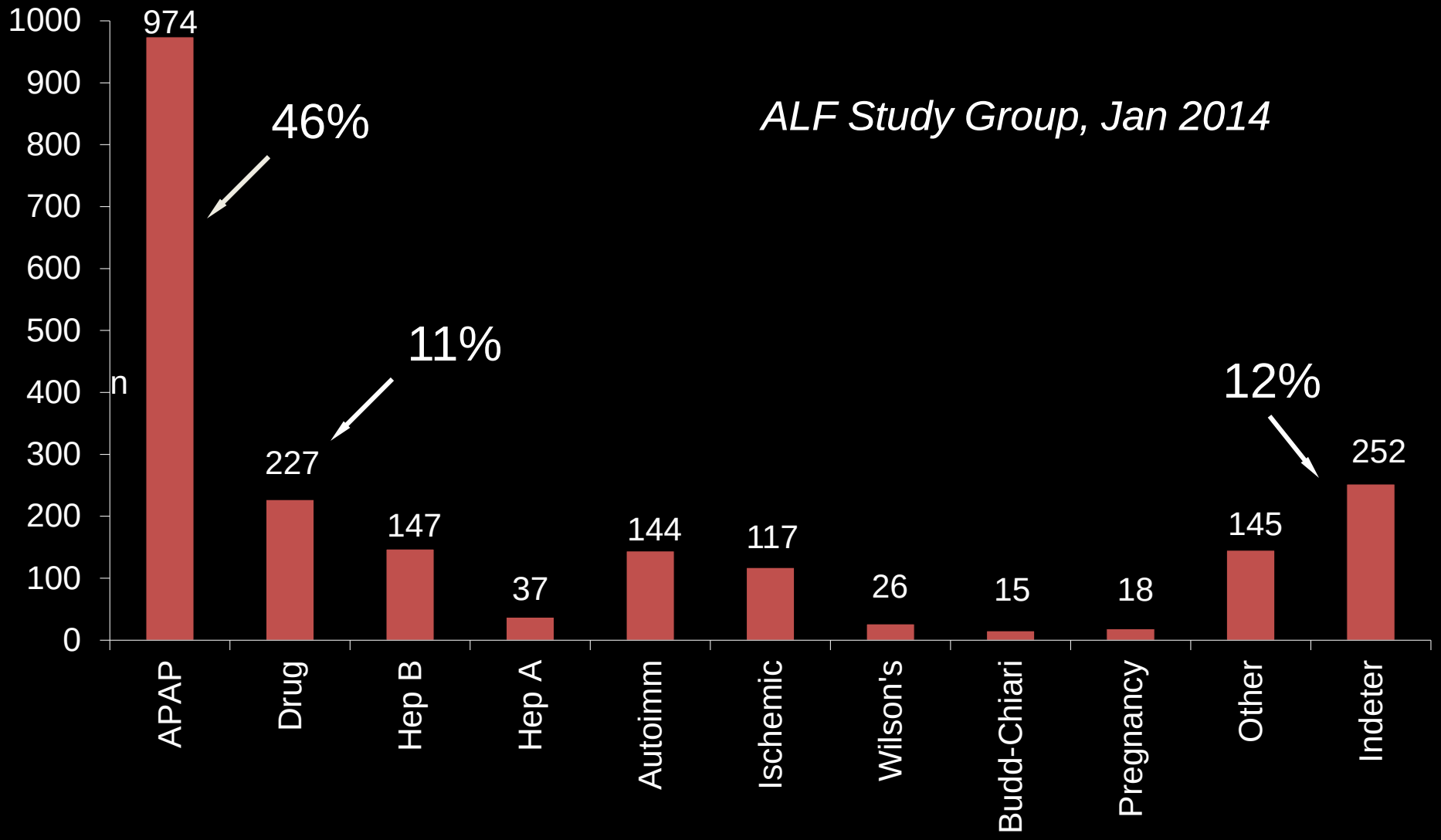
Etiology of Acute Liver Failure in the US

Adult Registry (n = 2,102)



Drug-Induced Liver Injury

- Two major forms: direct & idiosyncratic
  - Direct: intrinsically hepatotoxic agent; injury is frequent (1-100%), dose-related, reproducible in animal models, “expected”
  - Idiosyncratic: not inherently hepatoxic, rare (1:1,000-1:1,000,000), not dose related, not reproducible in animals, “unexpected”

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Idiosyncratic Hepatotoxicity

- Unexpected outcome, not dose-related, rare
  - Isoniazid (~1:500)
  - Amoxicillin/Clavulanic acid (~1:2,500)
  - Diclofenac (~1:30,000)
- Idiosyncrasy: immunologic or metabolic
- Phenotypes: acute hepatitis,
  Hepatocellular, Cholestatic or "Mixed"
- Etiology, generally unknown

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Idiosyncratic Drug-Induced Liver Injury: Immunoallergic hepatitis

- Acute liver injury with
  - Rash, fever, facial edema, lymphadenopathy,
  - Eosinophilia, atypical lymphocytosis
- Typically short latency, 1-30 days
- Rash and fever may precede hepatic manifestations
- Injury is usually hepatocellular initially, but may evolve into a cholestatic pattern

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Idiosyncratic Drug-Induced Liver Injury: Immunoallergic hepatitis: many names

- Hepatitis with simple drug rash
- Immunoallergic hepatitis
- Drug-induced hypersensitivity syndrome
- Anticonvulsant hypersensitivity syndrome
- DRESS
- Stevens Johnson syndrome
- Toxic epidermal necrolysis (TEN)

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Drug-Induced Liver Injury & SJS

- Have a lot in common
- Severe adverse events
- Rare
- Idiosyncratic, unexpected
- Sometimes overlap
- Clinical and Research Challenge

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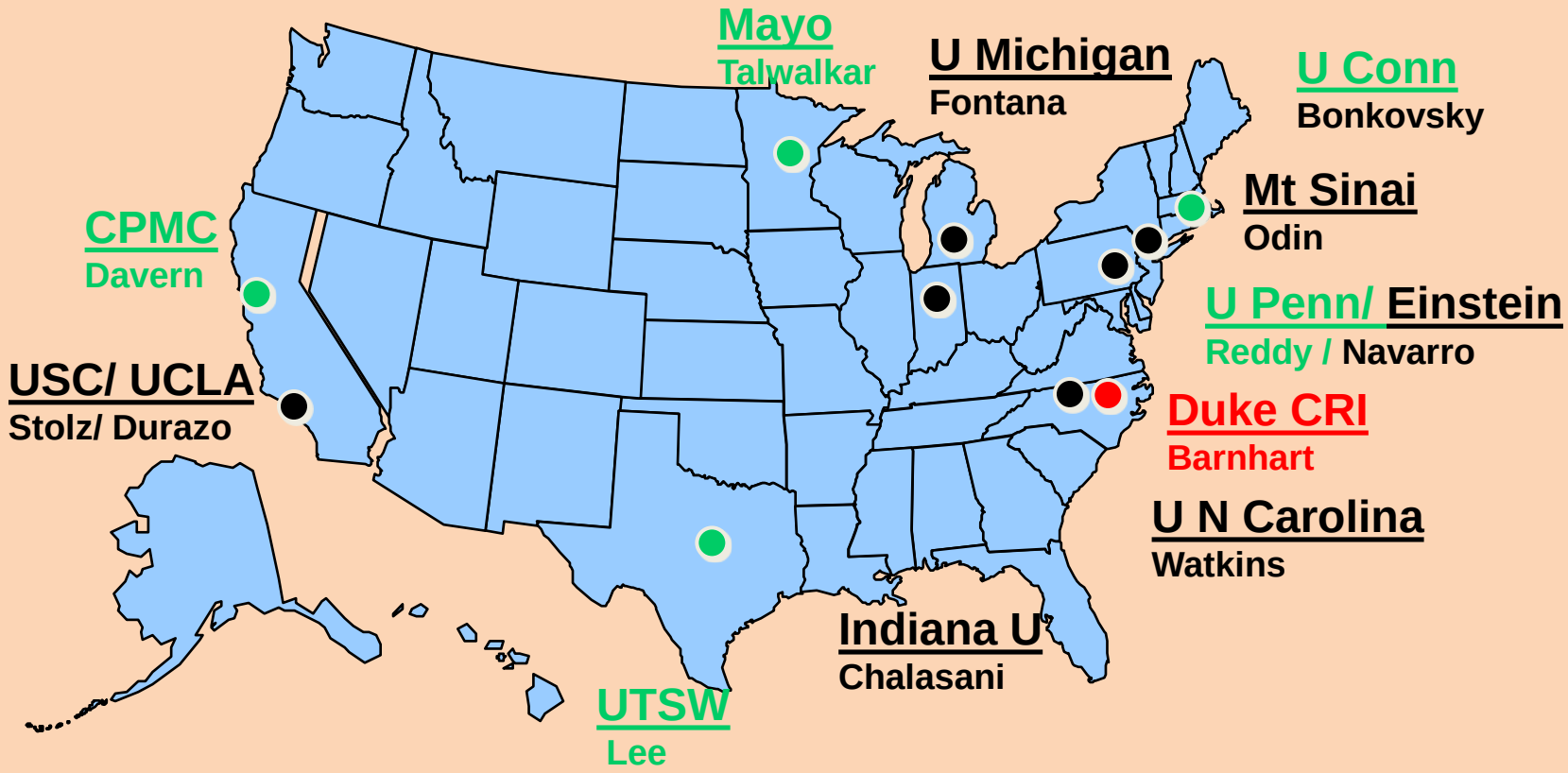
Drug-Induced Liver Injury: Mechanisms and Test Systems: NIH Research Symposium: October 17-18, 2000

Drug-Induced Liver Injury Network

- Created in 2003, Cooperative Agreement [NIDDK]
- Consortium of 5-8 Clinical Centers
- Data Coordinating Center
- Sample Repository, Genetics Core
- Aim: Collect and fully characterize cases of clinically apparent, drug-induced liver injury (phenotype) to allow for mechanistic studies into its etiology and potential prevention or treatment.

DILIN 2015


Mayo
Talwalkar
U Michigan
Fontana
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Bonkovsky
Mt Sinai
Odin
CPMC
Davern
U Penn/ Einstein
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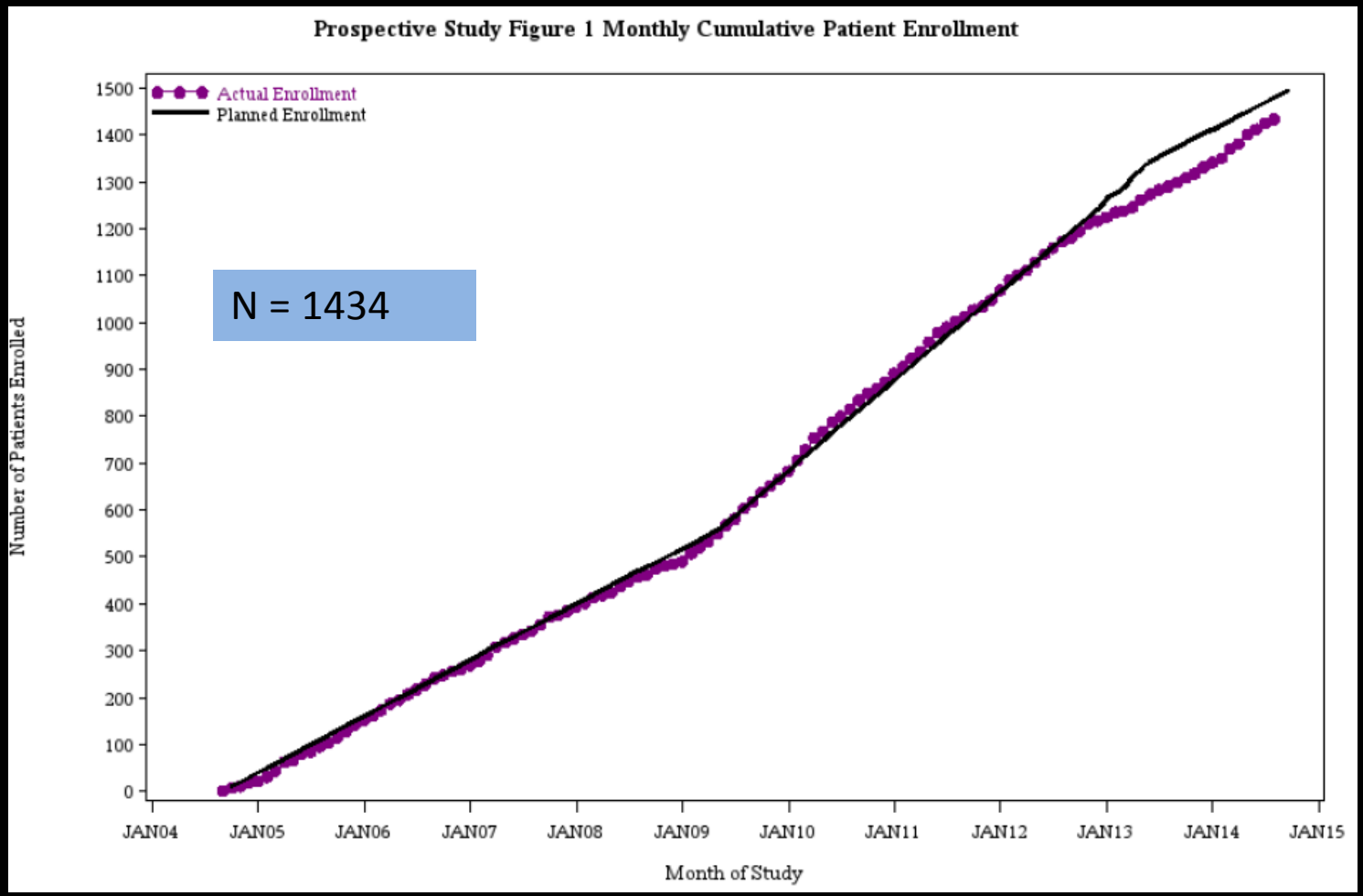
USC/ UCLA
Stolz/ Durazo
Duke CRI
Barnhart
U N Carolina
Watkins
Indiana U
Chalasani
UTSW
Lee
Previous site
Current site

Prospective Study Enrollment
Target: 2 patients/ center/ month



Causality in Drug Induced Liver Injury

- DILI is a diagnosis of exclusion
- Compatible history
- Negative tests for hepatitis A, B, C and E
- Absence of alcoholism, shock, autoimmunity
- Imaging studies of liver and biliary tree
- Known cause and compatible signature
- No specific tests to prove causality

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Drug-Induced Liver Injury Causality Assessment

Score	Causality	Percent	Legal Description	
1	Definite	≥95%	Beyond a reasonable doubt	Yes
2	Very Likely	75-94%	Clear and convincing	
3	Probable	50-74%	Preponderance of the evidence	
4	Possible	25-49%		No
5	Unlikely	<25%		

Each case is reviewed and scored by 3 DILIN hepatologists independently; discordances are resolved by email or telephone discussions.

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DILIN: First 1,068 Cases

- 899 were adjudicated as definite, highly likely or probable (83%)
- Caused by ~250 different agents
- Prescription drugs: 84%
- Herbals and Dietary Supplements: 16%
- Top 10 most common: 36%
- Top 25 most common: 50%

13% possible, 5% unlikely

Chalasani et al Gastro 2015, in press

Prescription Drug-Induced Liver Injury
Twenty most common causes

Rank	Agent	No		Rank	Agent	No
1	Augmentin	91		11	Phenytoin	12
2	Isoniazid	48		12	Methyldopa	11
3	Nitrofurantoin	42		13	Azathioprine	10
4	TMP/SMZ	31		14	Hydralazine	9
5	Minocycline	28		15	Lamotrigine	9
6	Cefazolin	20		16	Mercaptopurine	9
7	Azithromycin	18		17	Atorvastatin	8
8	Ciprofloxacin	16		18	Moxifloxacin	8
9	Diclofenac	15		19	Allopurinol	7
10	Levofloxacin	13		20	Amoxicillin	7

Chalasani et al: in press 2015

Drug-Induced Liver Injury
9 Cases of Stevens Johnson Syndrome

No	Agent	SJS	Jaundice	Fatal
1	Lamotrigine	EM vs SJS	Yes	No
2	Lamotrigine	DRESS vs SJS	Yes	Yes*
3	Lamotrigine	SJS	No	No
4	Azithromycin	SJS	Yes	Yes
5	Azithromycin	TEN	Yes	No
6	Carbamazepine	SJS/TEN	Yes	Yes
7	Moxifloxacin	SJS	Yes	No
8	Diclofenac	SJS/TEN	Yes	Yes
9	Nitrofurantoin	SJS	Yes	No
All			89%	44%

**** Death from hepatic failure***

Drug-Induced Liver Injury and SJS

Feature	SJS Cases (9)	All DILI Cases (899)
Mean age	32 years	49 years
Sex (female)	78%	59%
Race: White African American Asian American	44% 33% 22%	79% 12% 7%
Median time to onset	14 days (1-58)	36 days (1 day-10 yrs)
Jaundice	89%	70%
Fatal	44%	11%*

Liver Transplantation in 4%

Drug-Induced Liver Injury & SJS

Feature	Chalasani et al Indianapolis, US 2004-2012 (n=899)	Devarbhavi et al India, Bangelore 1997-2013 (n=670)
SJS/TEN	9 (1%)	32 (5%)
Mean age	32 years	31 years
Female sex	78%	56%
Jaundice	89%	62%
Latency	3-58 days	< 60 days
Drugs	Lamotrigine (3)	Phenytoin (8)
	Azithromycin (2)	Dapsone (4)
	Carbamazepine (1)	Carbamazepine (4)
	Moxifloxacin (1)	SMZ/TMP (3)
	Diclofenac (1)	Nevirapine (3)
	Nitrofurantoin (1)	Allopurinol (2)

Lamotrigine

- Accounted for 12 of the 899 cases of DILI
- 11 had DRESS (7), SJS (3) or drug rash (1)
- Median age, 26 years; 75% women
- 63% white, 25% Afr Am, 13% Asian
- Median latency 23 days (8-117 days)
- Jaundice 83%
- Fatality 8%

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Spectrum of Drug Induced Liver Injury

Acute Liver Failure

Liver Injury with Jaundice

Symptomatic Liver injury without Jaundice

Asymptomatic rise in Serum Enzymes

Severe clinically apparent cases represent the "tip of the iceberg"

Spectrum of Drug Hypersensitivity Syndromes

SJS/TEN

DRESS

Immunoallergic injury

Drug Rash

Drug Fever

Hypersensitivity without symptoms (Eosinophilia)

Perhaps SJS & TEN represent the "tip of the iceberg"

Drug-Included Liver Injury & SJS

- The 9 patients with SJS were often exposed to multiple other medications some of which have been implicated in SJS
- Number of other agents, 0-14, mean = 5
- Anticonvulsants: clonazepam, levetiracetamin, phenytoin, pregabalin, valproate
- Analgesics: acetaminophen, ibuprofen, meloxicam
- Antibiotics: cephalosporins, clindamycin, doxycycline, erythromycin, fluoroquinolones, penicillin, piperacillin
- Psychotrophic: alprazolam, amitryptyline, aripiprazole, escitalopram, fluoxetine, lithium, lorazepam, methylphenidate, quetiapine, trazodone, ziprasidone

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LiverTox

Clinical and Research Information on Drug-Induced Liver Injury

www.livertox.nih.gov

United States National Library of Medicine

NIDDK National Institute of Diabetes and Digestive and Kidney Diseases

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Clinical and Research Information on Drug-Induced Liver Injury

SEARCH THE LIVERTOX DATABASE

Search for a specific medication:

Search

Browse by first letter of medication:

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

LiverTox provides up-to-date, accurate, and easily accessed information on the diagnosis, cause, frequency, patterns, and management of liver injury attributable to prescription and nonprescription medications and herbals. The LiverTox Website provides a comprehensive resource for physicians and their patients, and for clinical academicians and researchers who specialize in idiosyncratic drug-induced hepatotoxicity. For complete information, see About

LiverTox

Drug Sections (~750 currently)

- Overview of the drug (1-2 pages)
  - Background
  - Hepatotoxicity
  - Mechanism of Injury
  - Outcome and Management
- Representative cases
- Liver Histology
- Chemical structure
- Link to Product label (package insert)
- Annotated references with links

DRUG RECORD

DICLOFENAC

OVERVIEW
Diclofenac

Introduction

Diclofenac is a commonly used nonsteroidal antiinflammatory drug (NSAID) used for the therapy of chronic forms of arthritis and mild-to-moderate acute pain. Therapy with diclofenac in full doses is frequently associated with mild serum aminotransferase elevations and, in rare instances, can lead to serious clinically apparent, acute or chronic liver disease.

CASE REPORTS
Diclofenac

Case 1. Elevations in serum aminotransferase levels during first month of diclofenac therapy. [Modified from a case in the database of the Drug-Induced Liver Injury Network]

A woman in her 30s with ankylosing spondylitis was started on diclofenac in a dose of 75 mg twice daily. One week later, although asymptomatic, she was found to have raised serum aminotransferase levels and the drug was discontinued. Viral and autoimmune hepatitis serologies were negative. Ultrasound was normal. During the following month, her ALT levels returned to baseline. She had previously tolerated ibuprofen and nabumetone without difficulty.

Key Points

Medication: Diclofenac 75 mg orally twice daily
Pattern: Hepatocellular (R=9)
Severity: 1+ (never jaundiced, never hospitalized)
Latency: Several days
Recovery: Complete recovery 1 month after stopping the medication
Other medications: Ibuprofen

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Comments
Pre		49			
0					Diclofenac started
7 days		255	79	0.7	
9 days		253			
10 days	0				Diclofenac stopped
16 days	6 days	275	84	0.5	
4 weeks	17 days	71	89	0.4	
6 weeks	1 month	37	73	0.3	
Normal Values		**<42**	**<115**	**<1.2**	

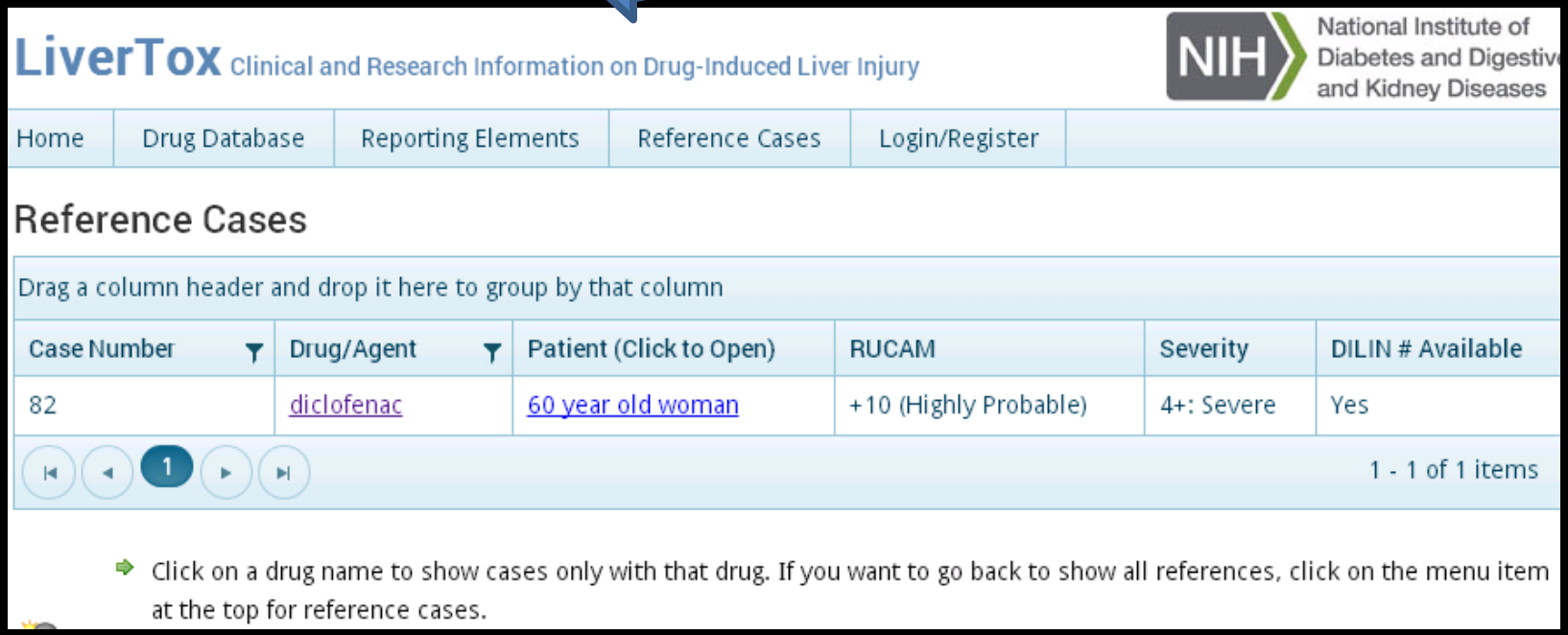
Comment

CASE REPORTS SUBMITTED TO LIVERTOX
Diclofenac

Clinical cases of drug-induced liver injury that have been submitted to LiverTox ("Submit a Case Report") are available for review. Most of these reference cases are from the Drug-Induced Liver Injury Network, but others are from users of LiverTox who have submitted data from an actual clinical case. All cases have been reviewed and cleared of personal identifiers and a brief comment added by the LiverTox editors. Click on the following link to view the submitted case reports that have been made publically available.

Submitted Cases on Diclofenac

Top of page



LiverTox Clinical and Research Information on Drug-Induced Liver Injury

NIH National Institute of Diabetes and Digestive and Kidney Diseases

Home | Drug Database | Reporting Elements | Reference Cases | Login/Register

Reference Cases

Drag a column header and drop it here to group by that column

Case Number	Drug/Agent	Patient (Click to Open)	RUCAM	Severity	DILIN # Available
82	diclofenac	60 year old woman	+10 (Highly Probable)	4+: Severe	Yes

1 - 1 of 1 items

Click on a drug name to show cases only with that drug. If you want to go back to show all references, click on the menu item at the top for reference cases.

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Diclofenac in LiverTox

REFERENCES
Diclofenac

References Last Updated: 16 April 2014

1. Zimmerman HJ. Drugs used to treat rheumatic and musculospastic disease. The NSAIDS. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 517-41. (Review of hepatotoxicity of NSAIDs published in 1999 mentions that more than 60 cases of diclofenac hepatotoxicity have been appeared in the literature and 180 were known to the FDA; clinical features resemble acute hepatitis with hepatocellular enzyme elevations; a disproportional number of cases occur in women with osteoarthritis).
2. Lewis JH, Stine JG. Nonsteroidal anti-inflammatory drugs and leukotriene receptor antagonists: pathology and clinical presentation of hepatotoxicity. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd Edition. Amsterdam: Elsevier, 2013. pp. 370-402. (Expert review of liver injury caused by NSAIDs mentions that diclofenac has been implicated in more than 250 cases of hepatocellular damage with a case fatality rate of ~10%; metabolic idiosyncrasy is suspected to be the cause).
3. Grossner T, Smyth EM, Fitzgerald GA. Anti-inflammatory, antipyretic, and analgesic agents: pharmacotherapy of gout. In, Brunton LL, Chabner BA, Knollman BC. Goodman & Gilman's The pharmacological basis of therapeutics, 12th ed. New York: McGraw-Hill, 2011. p. 959-1004. (Textbook of pharmacology and therapeutics).
4. Ciccolunghi SN, Chaudri HA, Schubiger BI, Reddrop R. Report on a long-term tolerability study of up to two years with diclofenac sodium(Voltaren). Scand J Rheumatol Suppl 1978; 22: 86-96. PubMed Citation (Among 286 patients treated with diclofenac, elevation in liver tests in occurred in 38 [13%] and was reason for stopping therapy in 2 [1%]; no mention of hepatitis or jaundice).
5. Dunk AA, Walt RP, Jenkins WJ, Sherlock SS. Diclofenac hepatitis. Br Med J(Clin Res Ed) 1982; 284: 1605-6. PubMed Citation (52 year old man developed jaundice 4 months after starting diclofenac [bilirubin 7.4 mg/dL, AST 1375 U/L] with partial resolution on stopping, but recurrence [bilirubin 11.8 mg/dL, AST 1150 U/L] on restarting drug, then resolving within 6 weeks).

LiverTox Status: 2015

- Official release: October 2012
- Current web activity: 115,000 unique visitors per month
- 750 agents described
- 1.3 million words
- 13,000 annotated references
- 1,000 clinical cases

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