LiverTox

• Website on drug-induced liver disease
• Collaborative effort between the National Library of Medicine (NLM) and the Liver Disease Research Branch, NIDDK.
• Source of reliable information on the clinical features, course and outcome of liver injury due to prescription and non-prescription drugs, herbals and dietary supplements
• Aims: advance knowledge and support research on drug induced liver injury

June 2017
SEARCH THE LIVERTOX DATABASE

Search for a specific medication, herbal or supplement:

Browse by first letter of medication, herbal or supplement:

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, herbs and dietary supplements. LIVERTOX also includes a case registry that will enable scientific analysis and better characterization of the clinical patterns of liver injury. 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.
LiverTox

• Three components
  • General introduction
  • Individual drug sections
  • Interactive component to enter findings from specific cases and provide comments
• Text is concise, formulaic, anonymous

June 2017
Drug Sections

- Overview of the drug (1-2 pages)
  - Background
  - Hepatotoxicity
  - Mechanism of injury
  - Outcome and Management
- Representative cases
- Chemical structure
- Link to product label (package insert)
- Annotated references with PubMed links
LiverTox

- Includes drugs that cause liver injury
- And those that do not
- Largely those in current use in the U.S.
- Prescription and Non-Prescription
- Herbal and Dietary Supplements
- Drugs or Substances of Abuse
- Metals, Trace elements, Minerals
LiverTox: Current Status

- Includes description of 1124 Agents
- More than 2 million words
- 23,000 annotated references
- 400 case descriptions
- Averages 170,000 unique visitors monthly

June 2017
Drugs described in LiverTox

Obtained: June 2010

- Drug Names in NLM Computerized Database: 23,270
- Number of Different Agents: 1884
- Topical Agents: 310
- Agents Approved in US: 1639
- Agents Appropriate for LiverTox: 909
- Master List of Agents for LiverTox: 1236
- In LiverTox (June 2017): 1124

- Special Agents: 420
  - Foods
  - Vaccines
  - Plasma Products
  - iv Solutions
  - Rarely used Agents
  - Veterinary Agents

Estimates: June 2017
LiverTox Status: 2017

Virtually all prescription medications in current general use in the United States that have systemic absorption. Also includes herbal medications, vitamins, nutritional supplements, metals, minerals, and illegal substances.

Masterlist of all potential agents: 1236

- Currently in LiverTox 1124 (91%)
  - Herbals -48
  - Nutritional supplements -28
  - Metals -15
  - Illicit drugs - 3
  - Prescribed drugs 1030
  - Groups of similar agents - 89
  - Different drugs 941

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LiverTox Activity: 2017

- Elements included in Masterlist
  - Generic ingredient
  - Brand name
  - Drug/Herbal/NS/Metal/Illlicit agent
  - Year of approval
  - Classification:
    - Primary (Organ System: CV, CNS, GI, Cancer)
    - Secondary (Indication: asthma, hypertension)
    - Tertiary (Class, Structure or Mechanism)
  - Likelihood score (A to E)
  - Number of cases, whether any fatal or rechallenge
LiverTox: Drug Classification

Diclofenac
1° Analgesic (CNS)
2° Mild-Moderate Pain
3° NSAID, Cox 1&2 inhibitor, acetic acid derivative

Imatinib
1° Antineoplastic
2° Chronic lymphocytic leukemia
3° Kinase inhibitor, BCR-ABL

Zafirlukast
1° Respiratory
2° Asthma
3° Leukotriene receptor blocker
Classes of Drugs in LiverTox

- **Antimicrobials**: 20%
- **Central Nervous System**: 18%
- **Antineoplastic**: 16%
- **Cardiovascular**: 11%
- **Endocrine**: 5%
- **Analgesic**: 4%
- **GI**: 4%
- **Respiratory**: 5%
- **Rheumat**: 2%
- **Other**: 17%

Total: 317

- **Antimicrobials**: Blue
- **CNS**: Pink
- **Antineoplastic**: Green
- **Cardiovascular**: Yellow
- **Endocrine**: Orange
- **Analgesic**: Orange
- **GI**: Yellow
- **Respiratory**: Orange
- **Rheumat**: Pink
- **Other**: Purple
Drug-induced liver injury: Likelihood

- Five categories (A to E)
  - A. 50 cases or more
  - B. 12 to 49 cases
  - C. 4 to 11 cases
  - D. 1 to 3 cases
  - E. No cases

Number of published, verified cases were counted, unless >100
Case series were used only if formal causality was performed
All cases from agents in Category C and D were reviewed (RUCAM)
Likelihood Scores in LiverTox: 2017

- Five Categories based upon published reports
  - Category A (≥ 50 cases) 62 [7%]
  - Category B (12-49 cases) 84 [9%]
  - Category C (4-11 cases) 112 [12%]
  - Category D (1-3 cases) 157 [17%]
  - Category E (none) 364 [39%]
  - Category E* (suspected) 162 [17%]

Bjornsson & Hoofnagle: Hepatology 2015
Causes of Liver Injury

- Antimicrobials: 22%
- Central Nervous System: 19%
- Antineoplastic: 19%
- Cardiovascular: 12%
- Endocrine: 6%
- Analgesic: 5%
- GI: 3%
- Respiratory: 2%
- Rheumat: 7%
- Other: 7%

n = 317
Non-Causes of Liver Injury

- **Antimicrobials**: 18%
- **Central Nervous System**: 18%
- **Antineoplastic**: 14%
- **Cardiovascular**: 10%
- **Endocrine**: 5%
- **Analgesic**: 3%
- **Respiratory**: 2%
- **Gastrointestinal**: 6%
- **Rheumat**: 2%
- **Other**: 14%

n = 317
Proportion linked to Liver Injury
Proportion linked to Liver Injury [2]

- All: 45%
- Gastrointestinal: 17%
- Respiratory: 14%
- Urologic: 9%
- Dermatology: 17%
- Gynecology: 22%

*Note: The numbers in the table correspond to the percentages shown in the bar chart.*
Decline in New Hepatotoxic Agents

Explanation: Multiple Choice

- Industry is better at identifying agents that cause hepatotoxicity before seeking approval
- FDA is better at identifying agents that cause hepatotoxicity from pre-marketing studies
- It takes years before cases of idiosyncratic liver injury due are recognized and published
- All of the above

June 2017
Hepatotoxicity Likelihood

- FDA Assessment of Likelihood given in Product Label, in
  - Black box warning
  - Warnings and Precautions
  - Adverse events
  - Post marketing reports

June 2017
Hepatotoxicity Likelihood

- FDA assessment of degree of injury
  - Serum enzyme elevations
  - Hepatitis, jaundice, cholestasis
  - Hepatic failure, death

- Recommendations
  - REMS
  - Monitoring with schedule
  - Monitoring with no guidance

June 2017
## Most Commonly Implicated Agents in DILIN

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug</th>
<th>Year</th>
<th>No</th>
<th>Jaundice</th>
<th>Fatal</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amox/Clavulanate</td>
<td>1984</td>
<td>91</td>
<td>85</td>
<td>1</td>
<td>1%</td>
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<tr>
<td>2</td>
<td>Isoniazid</td>
<td>1974</td>
<td>48</td>
<td>36</td>
<td>9</td>
<td>25%</td>
</tr>
<tr>
<td>3</td>
<td>Nitrofurantoin</td>
<td>1953</td>
<td>42</td>
<td>23</td>
<td>4</td>
<td>17%</td>
</tr>
<tr>
<td>4</td>
<td>SMZ/TMP</td>
<td>1980</td>
<td>31</td>
<td>26</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>5</td>
<td>Minocycline</td>
<td>1971</td>
<td>28</td>
<td>16</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>Cefazolin</td>
<td>1973</td>
<td>20</td>
<td>18</td>
<td>0</td>
<td>0%</td>
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<tr>
<td>7</td>
<td>Azithromycin</td>
<td>1991</td>
<td>18</td>
<td>16</td>
<td>2</td>
<td>13%</td>
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<tr>
<td>8</td>
<td>Ciprofloxacin</td>
<td>1987</td>
<td>16</td>
<td>11</td>
<td>2</td>
<td>18%</td>
</tr>
<tr>
<td>9</td>
<td>Levofoxacin</td>
<td>1996</td>
<td>13</td>
<td>9</td>
<td>1</td>
<td>11%</td>
</tr>
<tr>
<td>10</td>
<td>Diclofenac</td>
<td>1988</td>
<td>12</td>
<td>7</td>
<td>1</td>
<td>14%</td>
</tr>
<tr>
<td>11</td>
<td>Phenytoin</td>
<td>1956</td>
<td>12</td>
<td>6</td>
<td>1</td>
<td>17%</td>
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<tr>
<td>12</td>
<td>Methyldopa</td>
<td>1962</td>
<td>11</td>
<td>9</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>13</td>
<td>Azathioprine</td>
<td>1968</td>
<td>10</td>
<td>7</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>
## Likelihood scores and FDA Warnings

<table>
<thead>
<tr>
<th>Drug</th>
<th>No</th>
<th>Jaundice</th>
<th>Fatal</th>
<th>Rate</th>
<th>LS</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amox/Clavulanate</td>
<td>91</td>
<td>85</td>
<td>1</td>
<td>1%</td>
<td>A</td>
<td>W-h</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>48</td>
<td>36</td>
<td>9</td>
<td>25%</td>
<td>A</td>
<td>BB-f</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>42</td>
<td>23</td>
<td>4</td>
<td>17%</td>
<td>A</td>
<td>W-h</td>
</tr>
<tr>
<td>SMZ/TMP</td>
<td>31</td>
<td>26</td>
<td>1</td>
<td>4%</td>
<td>A</td>
<td>W-f</td>
</tr>
<tr>
<td>Minocycline</td>
<td>28</td>
<td>16</td>
<td>0</td>
<td>0%</td>
<td>A</td>
<td>W-h</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>20</td>
<td>18</td>
<td>0</td>
<td>0%</td>
<td>B</td>
<td>AE-h</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>18</td>
<td>16</td>
<td>2</td>
<td>13%</td>
<td>B</td>
<td>W-h</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>16</td>
<td>11</td>
<td>2</td>
<td>18%</td>
<td>B</td>
<td>W-f</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>13</td>
<td>9</td>
<td>1</td>
<td>11%</td>
<td>B</td>
<td>W-f</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>12</td>
<td>7</td>
<td>1</td>
<td>14%</td>
<td>A</td>
<td>W-f</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>12</td>
<td>6</td>
<td>1</td>
<td>17%</td>
<td>A</td>
<td>W-f</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>11</td>
<td>9</td>
<td>0</td>
<td>0%</td>
<td>A</td>
<td>W-f</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>10</td>
<td>7</td>
<td>0</td>
<td>0%</td>
<td>A</td>
<td>W-E,SoS</td>
</tr>
</tbody>
</table>

*June 2017*
## FDA Recommendations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rate</th>
<th>LS</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amox/Clavulanate</td>
<td>1%</td>
<td>A</td>
<td>W: Monitor if hepatic impairment</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>25%</td>
<td>A</td>
<td>BB: Monitor monthly, [&gt;35 yrs, ALT]</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>17%</td>
<td>A</td>
<td>W: Monitor periodically</td>
</tr>
<tr>
<td>SMZ/TMP</td>
<td>4%</td>
<td>A</td>
<td>W: D/C for signs or symptoms</td>
</tr>
<tr>
<td>Minocycline</td>
<td>0%</td>
<td>A</td>
<td>W: Monitor periodically</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>0%</td>
<td>B</td>
<td>AE: D/C for signs or symptoms</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>13%</td>
<td>B</td>
<td>W: D/C for signs or symptoms</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>18%</td>
<td>B</td>
<td>W: D/C for signs or symptoms</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>11%</td>
<td>B</td>
<td>W: D/C for signs of symptoms</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>14%</td>
<td>A</td>
<td>W: ALT baseline &amp; periodically</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>17%</td>
<td>A</td>
<td>W: D/C for signs or symptoms</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>0%</td>
<td>A</td>
<td>W: Monitor periodically, first 6-12 wks</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>0%</td>
<td>A</td>
<td>W: Monitor periodically</td>
</tr>
</tbody>
</table>
LiverTox

- Meant as an aid to the community
  - Source of unbiased information
  - Can be helpful in diagnosis
  - Increasingly referenced in publications
- Meant to encourage research and improvement in management of DIL
  - Can be used in clinical research

June 2017
The most common causes of DILI are agents that have been in use for decades.

Some are associated with severe and sometimes fatal outcomes.

There remains a need to standardize warnings, terminology and recommendations for monitoring for agents of greatest concern.

June 2017
LiverTox
Clinical and Research Information on Drug-Induced Liver Injury
www.livertox.nih.gov