LiverTox Update

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FDA-Pharma

June 2017
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, herbas 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

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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

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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

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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

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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

Special Agents 420

Agents Appropriate for LiverTox 909

Foods
Vaccines
Plasma Products
iv Solutions
Rarely used Agents
Veterinary Agents

New Agents, HDS, Metals, Illicit Agents

Master List of Agents for LiverTox 1236

In LiverTox (June 2017) 1124

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

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Classification</th>
<th>Indication</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>1&lt;sup&gt;°&lt;/sup&gt;</td>
<td>Analgesic (CNS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2&lt;sup&gt;°&lt;/sup&gt;</td>
<td>Mild-Moderate Pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3&lt;sup&gt;°&lt;/sup&gt;</td>
<td>NSAID, Cox 1&amp;2 inhibitor, acetic acid derivative</td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>1&lt;sup&gt;°&lt;/sup&gt;</td>
<td>Antineoplastic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2&lt;sup&gt;°&lt;/sup&gt;</td>
<td>Chronic lymphocytic leukemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3&lt;sup&gt;°&lt;/sup&gt;</td>
<td>Kinase inhibitor, BCR-ABL</td>
<td></td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>1&lt;sup&gt;°&lt;/sup&gt;</td>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2&lt;sup&gt;°&lt;/sup&gt;</td>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3&lt;sup&gt;°&lt;/sup&gt;</td>
<td>Leukotriene receptor blocker</td>
<td></td>
</tr>
</tbody>
</table>
Classes of Drugs in LiverTox

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

n = 317
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%
- GI: 6%
- Analgesic: 3%
- Endocrine: 5%
- Respiratory: 2%
- Rheumat: 2%
- Other: 14%

n = 317
Proportion linked to Liver Injury

- Antimicrobials: 45% (A: 7%, B: 17%, C: 12%, D: 10%), 185 (8%)
- CNS: 46% (A: 5%, B: 11%, C: 15%, D: 14%), 171 (6%)
- Antineoplastic: 51% (A: 7%, B: 10%, C: 17%, D: 14%), 151 (5%)
- Cardiovascular: 49% (A: 7%, B: 10%, C: 17%, D: 14%), 105 (3%)
- Endocrine: 51% (A: 10%, B: 10%, C: 15%, D: 14%), 43 (8%)
- Analgesics: 56% (A: 12%, B: 17%, C: 22%, D: 14%), 36 (6%)
- Rheumatologic: 53% (A: 13%, B: 17%, C: 9%, D: 14%), 31 (9%)

Total: 18% (A: 45%, B: 19%, C: 16%, D: 14%)
Decade of Approval of Drugs in LiverTox

- **Before 1970** [n=156]
- **1970s** [n=82]
- **1980s** [n=119]
- **1990s** [n=211]
- **2000s** [n=188]
- **2010s** [n=167]

Total: n = 317
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

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## 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>
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<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>
</tr>
<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>Levofloxacin</td>
<td>1996</td>
<td>13</td>
<td>9</td>
<td>1</td>
<td>11%</td>
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<tr>
<td>10</td>
<td>Diclofenac</td>
<td>1988</td>
<td>12</td>
<td>7</td>
<td>1</td>
<td>14%</td>
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<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>
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</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>
<tr>
<td>Drug</td>
<td>Rate</td>
<td>LS</td>
<td>FDA</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>-------------------</td>
<td>------</td>
<td>----</td>
<td>------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amox/Clavulanate</td>
<td>1%</td>
<td>A</td>
<td>W: Monitor if hepatic impairment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>25%</td>
<td>A</td>
<td>BB: Monitor monthly, [&gt;35 yrs, ALT]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>17%</td>
<td>A</td>
<td>W: Monitor periodically</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMZ/TMP</td>
<td>4%</td>
<td>A</td>
<td>W: D/C for signs or symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minocycline</td>
<td>0%</td>
<td>A</td>
<td>W: Monitor periodically</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>0%</td>
<td>B</td>
<td>AE: D/C for signs or symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>13%</td>
<td>B</td>
<td>W: D/C for signs or symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>18%</td>
<td>B</td>
<td>W: D/C for signs or symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>11%</td>
<td>B</td>
<td>W: D/C for signs of symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>14%</td>
<td>A</td>
<td>W: ALT baseline &amp; periodically</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>17%</td>
<td>A</td>
<td>W: D/C for signs or symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyldopa</td>
<td>0%</td>
<td>A</td>
<td>W: Monitor periodically, first 6-12 wks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>0%</td>
<td>A</td>
<td>W: Monitor periodically</td>
<td></td>
<td></td>
<td></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.
LiverTox
Clinical and Research Information on Drug-Induced Liver Injury
www.livertox.nih.gov