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## LiverTox:

### A Web Site on Drug Induced Liver Injury

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Drug-induced liver injury is one of the more challenging forms of liver disease; both in diagnosis and management. Several hundred drugs, nutritional supplements and herbal medications have been implicated in causing liver injury. Their clinical presentation can be highly variable and mimic almost any form of liver disease. The literature on drug-induced liver injury is large, but spread among many journals in many different specialties and languages. Excellent textbooks are available, but they are rapidly out-of-date and not always easily accessed. Drug induced liver injury is also a challenging area of research, in that most cases are unpredictable, idiosyncratic and rare and thus difficult to study. As a consequence, there have been few advances in the understanding, control or prevention of drug induced liver injury in the last 50 years.

As a part of a long-term initiative in promoting basic and clinical research on drug-induced liver injury, the Liver Disease Research Branch of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in collaboration with the National Library of Medicine (NLM) has created the *LiverTox* website ([www.livertox.nih.gov](http://www.livertox.nih.gov)) (Figure). LiverTox is a multilayered, informational and interactive website with comprehensive and evidence-based information on drug, dietary supplement and herbal-induced liver injury that is freely accessible to physicians, researchers and the public. The website is particularly designed for use by physicians and health care professionals who might rarely see patients with drug-induced liver injury, including family practitioners, internists, pediatricians, psychiatrists, surgeons, specialists and subspecialists in all areas of medicine. The website will also be helpful to hepatologists and experts in hepatotoxicity by providing a complete

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and accurate summary of information about the clinical features of liver injury for each medication along with a complete and annotated list of references. Finally, LiverTox will be helpful to patients seeking information on liver injury due to drugs.

LiverTox consists of three major components: (1) an introductory and background section, (2) separate records on the hepatotoxicity of individual drugs, and (3) an interactive section that allows for submission and assessment of cases.

The introductory and background section includes an overview and detailed discussion of the problem of drug-induced liver injury: its frequency, major causes, epidemiology, natural history, diagnosis, and management. The section provides a description of the principal clinical and histologic patterns of liver injury (phenotypes), standardized definitions of terms used, and discussion of methods to diagnose and judge severity and causality in drug induced liver injury. This section includes specific and detailed information about formal causality assessment instruments such as the Roussel Uclaf Causality Assessment Method (RUCAM), the Maria and Victorino Clinical Scale (M & V), the Naranjo Adverse Drug Reaction Probability Scale, and the Drug Induced-Liver Injury Network (DILIN) Causality Process. The website provides printable copies of the actual instruments, discussion of their relative strengths and weaknesses, and detailed instructions on their completion (manual of operations).

The bulk of the LiverTox website consists of individual records on approximately 650 different medications, dietary supplements and herbals. The specific agents are searchable using both generic and trade names. The agents discussed include all of the major known causes of drug-induced liver injury as well as the most commonly used medications in the United States (prescription and nonprescription and whether or not they cause liver injury). Limited numbers of the many drugs, herbals and nutritional supplements available only outside of the United States are discussed in LiverTox based upon whether they have been implicated in cases of hepatotoxicity. Each drug record is a concise summary (200–400 words) about the drug class, mechanism of action, indications, dose-regimens, frequency of use and common side effects. This introduction is followed by a concise description of the hepatotoxicity associated with the agent, including its frequency, clinical patterns and course followed by a brief overview of the known or suspected mechanisms of injury from the medication. A final paragraph summarizes the prognosis and outcome of liver injury from the agent and a brief discussion of management. This overview is followed by one to four actual case reports taken from the published literature or from the DILIN Network. The drug record also includes chemical information with the drug structure and specific internet links to the approved product labeling (package insert). Each drug record concludes with a comprehensive list of scientific articles and publications on hepatotoxicity of the medication prepared by the NLM and annotated by NIDDK staff.

The final component of LiverTox is an interactive section that allows clinicians to submit a case report or to make suggestions and comments about the website. Submission of a case requires registration and assignment of a password. The submission uses a highly structured method with cues to enter the specific information necessary to fully assess the liver injury and judge severity and causality. Information sought includes the name of the drug, dates it

was started and stopped, dates of onset of the drug-induced liver injury, pertinent demographic and medical history, initial and serial laboratory tests, and specialized testing and imaging results. The LiverTox website then produces a computer-generated history, a table of serial laboratory results, a graphic display of the course of the illness, and calculations of latency, time to recovery, severity, causality (RUCAM score) and data completeness. The submission can also generate an official MedWatch report, if requested so as to include the case in the official Food and Drug Administration's (FDA) Adverse Event Reporting System (AERS). Unlike the typical MedWatch report, however, submissions made through LiverTox will be specific for liver-related adverse events and will provide all of the information necessary to adequately assess liver-related adverse drug events. The submitted cases will be maintained in a searchable database available to the registrants for analysis. This database will provide a means of monitoring the frequency and secular trends in incidence of drug induced-liver injury and permits analysis of clinical features and outcomes of the submitted cases. Finally, LiverTox allows for submission of comments regarding the content of the website which will aid in the updating and improvement in the information provided.

LiverTox became available on line in April 2012 and was released officially as of October 1, 2012. At the time of release, the text of LiverTox contained over one million words, provided information on more than 650 medications, and included over 12,000 annotated references. LiverTox is a work-in-progress and will continue to add new drug records, references and information in the years ahead. Comments about the accuracy and completeness of LiverTox and suggestions for improvement are welcomed. The creators of LiverTox hope that the website will be a practical and widely used tool for improving diagnosis, management, prevention and treatment of drug-induced liver disease. The ultimate purpose of LiverTox is to provide a stimulus and structured basis for future clinical and basic research into this important but often neglected cause of liver disease.

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## Abbreviations

<b>DILIN</b>	Drug-Induced Liver Injury Network
<b>NIDDK</b>	National Institute of Diabetes and Digestive and Kidney Diseases
<b>NLM</b>	National Library of Medicine

## Biographies

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**Figure.**  
The LiverTox website

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