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## Drug-Induced Liver Injury Module for Medical Students

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### Abstract

**Introduction:** No published curricula exist to introduce medical students to drug-induced liver injury (DILI). However, DILI is the most common cause of acute liver failure in the US, and drug-drug interactions are tested on the USMLE Step 1. **Methods:** We developed an independent study module to introduce students to DILI. This module consisted of a narrated PowerPoint introduction, a journal article, and four example cases. Students completed the module independently. To evaluate the effectiveness of the activity, exam data and responses to the cases were reviewed, and end-of-course survey data were used. These responses were used to modify questions for clarity and to develop a feedback rubric. **Results:** Mean scores on case-related questions in the module ranged from 44% to 73%. However, mean scores on test questions related to DILI ranged from 61% to 98%. It is possible that students learned from receiving feedback in the form of correct answers to the cases. On course evaluations, 52.4% of students agreed or strongly agreed that the online modules as a group (which included the DILI module) were an effective teaching method. **Discussion:** This module introduces students to DILI and enables them to interact with valuable resources. We hope that modifications will improve the learning experience and effectiveness of the module. Going forward, we plan to collect validity evidence for the feedback rubric and develop an advanced version of the module for gastroenterology fellows.

### Keywords

Preclinical Education, Drug-Induced Liver Injury, Asynchronous Instruction, Gastroenterology, Online/Distance Learning, Case-Based Learning, Virtual Learning

### Educational Objectives

By the end of this activity, learners will be able to:

1. Identify the major phenotypes of drug-induced liver injury.
2. Use a nomogram to predict the severity of acetaminophen toxicity.
3. Use the LiverTox web resource to determine the likelihood that a drug or drug class is causing liver injury.
4. Use a drug interaction checker to predict the consequences of altered drug metabolism.

### Introduction

Drug-induced liver injury (DILI) remains a challenging clinical problem.<sup>1</sup> Acetaminophen is the most common cause of acute liver failure in the United States and Western Europe.<sup>2</sup> Other drugs are known to cause liver injury in either a stochastic or

idiosyncratic manner. Still others are suspected to cause liver injury, but the relationship is difficult to prove. Clinicians should be trained to recognize potential offenders in order to prevent morbidity and mortality.

The USMLE Step 1 exam includes 5% to 9% of content covering gastroenterology.<sup>3</sup> Additionally, the *USMLE Physician Tasks/Competencies* list includes “Knows adverse effects of various drugs, or recognizes signs and symptoms of drug (and drug-drug) interactions resulting from polypharmacy in the therapeutic regimen and knows steps to prevent polypharmacy including lab studies to monitor drug therapy.”<sup>3</sup> While textbook chapters have been written on DILI,<sup>4</sup> no published curricula exist to the best of our knowledge. A literature search was performed, retrieving only one continuing medical education article for nurses,<sup>5</sup> which would not be appropriate for medical students. Within *MedEdPORTAL*, two curricula regarding different aspects of acetaminophen overdose were found.<sup>6,7</sup> The first is a simulation that focuses on patient safety and disclosure of a medical error, rather than the specifics of acetaminophen overdose. The second is useful for teaching this topic but is much narrower in scope and does not explore the other aspects of DILI.

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The Indiana University School of Medicine curriculum was recently revised. The new curriculum is systems based and more clinically focused. The content of the new curriculum was determined based on a multispecialty panel of clinicians and medical educators. DILI was not a topic that was addressed by the legacy curriculum. This content was developed for a session delivered to second-year medical students during a course that combined pathophysiology, pharmacology, pathology, and clinical medicine. The first version of this session was introduced in 2017 as a small-group, case-based session.

## Methods

This project was accepted by the Indiana University Institutional Review Board as exempt from full board review. The session was part of a course on gastrointestinal and liver disease delivered to second-year medical students. These students had already completed sessions on basic liver pathophysiology and pathology, and they had had some basic pharmacology during their first year of training. For the 2017 course, the session had been conducted as a small-group case-based discussion session. One of this curriculum's authors, Christen K. Dilly, developed the small-group session using hypothetical patient cases. The course development team, which consisted of another of this curriculum's authors, Jean P. Molleston, and several other clinical and basic science educators, reviewed the session and made edits for content and clarity. The end-of-course survey found that students disagreed that small-group sessions contributed to their understanding of course content, rating these sessions 2.01 on a scale of 1 to 4. Based on this feedback, Christen K. Dilly converted the session to an independent study module for the 2018 course. The session was modified to be accessed on Canvas (Instructure), our school's learning management system. We did not make any substantial changes to the content of the session when we converted it to an independent study module. In order to enable students to submit answers and receive immediate feedback in Canvas, the session was created as an ungraded quiz. While our students clearly stated a preference for lecture as an instructional strategy, our learning objectives included three skills that might be considered cognitive strategies. We therefore used an active learning strategy that guided the students through the resources we chose.

As the first step in the module, students viewed a narrated PowerPoint (Appendix A). This presentation provided an overview of the reading assignment, highlighting key points. It then clarified the difference between a stochastic (intrinsic) versus idiosyncratic drug reaction. It reviewed the biochemistry

of acetaminophen biotransformation and the benefit of N-acetylcysteine in acetaminophen toxicity. The presentation introduced students to the National Institutes of Health LiverTox website,<sup>8</sup> a resource they would later be expected to use while completing the module. Finally, as an attempt to emphasize the relevance of the material, we encouraged students to apply their knowledge during their clerkships.

For the next step, we asked students to read a review article on DILI.<sup>9</sup> This article was chosen for its clear writing and because the depth of information presented was appropriate for a medical student.

Next, we asked students to work through four cases (Appendix B). The first case described acetaminophen toxicity in a patient with chronic alcohol use. The second described cholestatic hepatitis in a young man who ingested anabolic steroids, and it required students to search the LiverTox database. The third described a classic presentation of a hypersensitivity or immunologic injury, and it required students to explore the categories of injury. The fourth presentation was the result of a drug-drug interaction that required students to use a resource that checked for interactions. After each case, the students submitted their answers to the questions and received feedback in the form of the correct answers (Appendix C). After submitting the last case, they also received a list of take-home points from the session.

We examined exam results from questions pertaining to DILI to determine how well students were able to use the knowledge they had gained. We tested this knowledge on an exam written by the course development team (course exam 2, three questions) and on an NBME subject matter exam that served as the final exam for the course (one question). We did not ask students to complete a session evaluation, as this was one of 70 sessions for the course. However, the end-of-course survey administered by the school provided some data regarding the students' satisfaction with the course in general. From this 18-question survey, we chose three questions that we believed most applied to the students' experience with this module.

As another means of evaluating the effectiveness of the session, we reviewed students' responses to the module questions. During this review, we aimed to determine whether students had attempted to answer the question (rather than submitting a blank response to receive the correct answer), whether there was evidence that the suggested resources were used, and whether the responses were correct. Based on the responses, the questions were edited for clarity, and a rubric was developed

for grading (Appendix D). In addition, the end-of-course feedback was reviewed and reported using descriptive statistics.

Based on students' responses to the cases in 2018, we again revised the cases. We made some of the questions more focused and clear. Where we had previously asked students to find resources such as an acetaminophen nomogram, we decided to include specific resources as part of the cases. A fifth case was added to highlight the complexities of diagnosing DILI in real life.

## Results

Of second-year medical students, 138 completed all four cases of the module; one student failed to complete the fourth case. Item analysis for the four DILI test questions is shown in Table 1. Data from the end-of-course survey are shown in Table 2. In this survey, 87.5% of students agreed or strongly agreed that the course engaged problem-solving skills. Of students, 52.4% agreed or strongly agreed that the online modules (which included the DILI module) were an effective teaching method. Also, 78.4% agreed or strongly agreed that the course provided an effective learning experience. We graded students' responses using the rubric we developed, with the results shown in Table 3.

## Discussion

To address the lack of curricula available to introduce DILI to medical students, we developed an independent study module. We found that students were able to complete the module and that the majority correctly answered related exam questions. By using the module, students were able to practice using valuable resources.

As we changed instructional strategies from a small-group discussion session to an independent online module, we learned that some of the questions needed to be more specific and the instructions more directive; the cases have been modified accordingly. Because the responses suggested that many students had not used a nomogram to predict liver damage from the overdose, we provided a nomogram in the question stem.

**Table 1.** Exam Item Results for Drug-Induced Liver Injury Questions

Exam <sup>a</sup>	Question Topic	Percent Correct
Course exam 2	Acetaminophen and N-acetylcysteine	96%
Course exam 2	P450 enzyme induction	61%
Course exam 2	Phenotypes of drug-induced liver injury	79%
NBME final exam	Drug-drug interaction	98%

<sup>a</sup>Course exam 2 was an exam written by our team. This exam covered material from approximately 3 weeks of our course. The NBME final exam was composed of questions provided by the NBME subject matter exam in gastroenterology.

**Table 2.** End-of-Course Survey Data

Question <sup>a</sup>	M	SD	Percent Agree or Strongly Agree
1. The course engaged my problem-solving skills.	4.19	0.85	87.5%
2. The online modules improved my understanding of course content.	3.22	1.27	52.4%
3. The course provided an effective learning experience.	4.02	0.82	80.5%

<sup>a</sup>Level of agreement rated on a 5-point scale (1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, 5 = strongly agree).

The scores for students' submissions were calculated using the rubric and the students' responses to the previous version of the questions, so we expect that scores will be higher for next year's students who will use the revised questions.

Course developers can use this module in a number of ways. As a low-technology option, students can view the PowerPoint, read the article, and then complete the case worksheets. Instructors can then give feedback in three ways: First, the answers and key points (Appendix C) can be provided, and the students can compare these with their own answers after submitting, as we did with this module. Second, the responses can be graded by an instructor using the rubric provided (Appendix D). A third option would be for an instructor to provide detailed feedback for each student response. Administering the module using a learning management system is not necessary, but it can simplify integrating the module into student workflow, collecting responses, and providing feedback. Additionally, interactive software (such as Canvas or Adobe Captivate) that enables learners to receive detailed feedback on each response as it is submitted can be used. The choice of how to administer the module would depend on available resources and on whether the instructor chooses to use the module as a self-guided resource or a graded assignment. The module could also be useful to learners at other levels, such as residents or fellows.

There are several important limitations to this module. This module is an introduction to the topic. As such, it is not intended

**Table 3.** Analysis of Student Responses to Case Questions

Case	Average Score	SD	Modifications Made Based on Responses
1	4.0/8 (50%)	1.6	Questions were made more specific. Nomogram was included as part of the question, instead of asking students to find a nomogram.
2	3.5/8 (44%)	1.7	Questions were made more specific.
3	2.7/4 (68%)	1.1	Questions and instructions were made more specific.
4	4.4/6 (73%)	2.0	Question 1 was made more specific.

to provide a comprehensive understanding of DILI. Our evaluation approach was limited due to our inability to survey students at the end of the module. Survey questions at the end of the course referred to a group of online modules, so responses may have been skewed by strong opinions about other sessions. The rubric provided does not have validity evidence, so it should only be used for formative assessment. The choice of when to provide feedback will likely impact the amount of effort that students put into answering the questions. For example, when we provided correct answers immediately after submission and the assignment was not graded, some students submitted blank responses or just guessed. Providing some credit for effort might help ensure that students take the opportunity to explore resources that could help them during clinical work.

Going forward, we will use the rubric to grade next year's class submissions and collect validity evidence. We will also build an advanced version of the module that can be used for a more in-depth study of the subject or with more advanced learners.

## Appendices

- A. DILI Presentation.pptx
- B. DILI Cases.docx
- C. DILI Cases with Answers & Key Points.docx
- D. DILI Case Rubrics.docx

All appendices are peer reviewed as integral parts of the Original Publication.

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## Ethical Approval

The Indiana University School of Medicine Institutional Review Board approved this study.

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