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Drug-induced liver injury and the urgent need for improved diagnostic test

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ABSTRACT

A review conducted by the National Library of Medicine has associated antibiotics, antidepressants, and other medications with liver damage. Researchers examined thousands of cases, investigating risk factors, diagnostic challenges, and the role of gut bacteria. They particularly focused on specific medications, including doxycycline and cyclophosphamide. There is an urgent need for the development of more accurate diagnostic tests for human Drug-Induced Liver Injury (DILI). The new findings underscore the necessity for improved diagnostic tools, such as biomarkers, to identify drug-induced liver injury effectively.

An extensive literature review was conducted on drug-induced liver injury (DILI), utilizing 2024 peer-reviewed publications from the National Library of Medicine, the world's largest and most trusted database [1]. A wide range of drugs can cause liver injuries, including, but not limited to, antibiotics, antivirals, nonsteroidal anti-inflammatory drugs (NSAIDs), herbal supplements, cholesterol medications, pain relievers, blood pressure regulators, and cancer treatments. Additionally, substances such as anabolic steroids, birth control pills, the antipsychotic chlorpromazine, the anesthetic halothane, and the heart medication amiodarone, have also been identified as potential contributors to liver damage. The findings of the review underscore the significance of practicing safe medication usage and routinely monitoring liver function.

The current diagnostic tests for Drug-Induced Liver Injury (DILI) provide valuable information, but they exhibit notable limitations. Many existing tests lack the specificity essential for distinguishing DILI from other liver pathologies, thereby presenting challenges in accurate diagnosis and management. Consequently, there is an urgent need for the development and implementation of more precise biomarkers and diagnostic methods to improve both the accuracy and timeliness of DILI diagnosis. Continuous advancements in this field are critical to enhancing patient outcomes and ensuring effective management of DILI cases.

DILI is a significant health concern in the US, often leading to hospitalization [2]. Diagnosing DILI is complex due to its varied clinical and histologic presentation, which can mimic other liver diseases [2]. A recent study included 1167 patients diagnosed with DILI between 2019 and 2021 [3]. The suspected drugs included antineoplastic agents, anti-infectives, and traditional Chinese medicines [3]. DILI can manifest as hepatocellular injury (30.08 %), cholestatic injury (8.31 %), mixed injury (2.31 %), or biochemical abnormalities only (59.30 %) [3]. Overall prognosis was favorable, with recovery in 23.99 % and improvement in 59.21 % of cases. Gender, age, malignancy, and other factors influence DILI risk. Clinicians should emphasize safe drug use and monitor liver function [3]. Cephalosporins can lead to cholestasis through mechanisms that impair bile flow, induce bile duct inflammation, and cause focal bile duct injury, rather than through bile duct blockage [4]. The incidence of DILI varies globally, with certain drugs like checkpoint inhibitors, COVID-19 vaccines, and green tea extract associated with liver injury [5]. DILI incidence varies globally, with an estimated annual occurrence of 14–19 cases per 100,000 persons exposed [5]. DILI accounts for approximately 10 % of acute hepatitis cases and is responsible for up to half of acute liver failure cases in Western countries [5]. DILI can be direct (dose-dependent), idiosyncratic (unpredictable), or indirect (immune system affected) [6]. According to the FAERS database, out of 324,588 cases involving the administration of antidepressants, 10,355 were classified as cases of DILI [7].

Among 42 antidepressants, nefazodone, fluvoxamine, and clomipramine had the highest reporting odds ratio for cholestatic injury, while mianserin, nefazodone, and maprotiline were associated with hepatocellular injury [7]. Antibiotics are a common cause of DILI globally [8]. A case study described a 28-year-old male patient who took doxycycline for Lyme disease [8]. After five days, he developed nausea, vomiting, fatigue, and significant transaminitis consistent with hepatocellular liver injury [8]. DILI is closely linked to gut microbiota [9].

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Cyclophosphamide, an antineoplastic medication, has been linked to DILI in animals and humans when used in high doses intravenously [10]. Lastly, numerous studies have demonstrated that the membrane vesicle assay possesses a modest predictive capability for human DILI, with a sensitivity around 50 % and a specificity ranging from 70 % to 80 % [11]. This fact suggests a significant number of DILI patients could be missed. Therefore, there is a clear need for the development of a more accurate diagnostic test for human DILI [11]. Liuzasulfapyridine or sulfasalazine contains both 5-aminosalicylic acid and sulfapyridine and the latter molecule is responsible for the toxic effects [12]. Sulfapyridine induces granulomatous liver diseases [13].

This concise review of DILI underscores the complexity of DILI and the need for continued research and improved diagnostic methods. It also highlights the role of various drugs and substances in inducing liver injuries, including antibiotics, antivirals, nonsteroidal anti-inflammatory drugs (NSAIDs), herbal supplements, cholesterol medications, pain relievers, blood pressure regulators, cancer treatments, and anticonvulsants. The review emphasizes the importance of safe drug use and regular liver function monitoring. The review concludes with a call for further investigation into new-generation antidepressants and their potential to cause DILI, as well as the unique aspects of cyclophosphamide-induced DILI.

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Yoshiyasu Takefuji: Writing – review & editing, Writing – original draft, Validation, Investigation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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