Hepatotoxicity reports in the FDA adverse event reporting system database: A comparison of drugs that cause injury via mitochondrial or other mechanisms

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**Abstract**

Drug-induced liver injury (DILI) is a leading reason for preclinical safety attrition and post-market drug withdrawals. Drug-induced mitochondrial toxicity has been shown to play an essential role in various forms of DILI, especially in idiosyncratic liver injury. This study examined liver injury reports submitted to the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) for drugs associated with hepatotoxicity via mitochondrial mechanisms compared with non-mitochondrial mechanisms of toxicity. The frequency of hepatotoxicity was determined at a group level and individual drug level. A reporting odds ratio (ROR) was calculated as the measure of effect. Between the two DILI groups, reports for DILI involving mitochondrial mechanisms of toxicity had a 1.43 (95% CI 1.42−1.45; \( P < 0.0001 \)) times higher odds compared to drugs associated with non-mitochondrial mechanisms of toxicity. Antineoplastic, antiviral, analgesic, antibiotic, and antimycobacterial drugs were the top five drug classes with the highest ROR values. Although the top 20 drugs with the highest ROR values included drugs with both mitochondrial and non-mitochondrial injury mechanisms, the top four drugs (ROR values > 18: benzbromarone, troglitazone, isoniazid, rifampin) were associated with mitochondrial mechanisms of toxicity. The major demographic influence for DILI risk was also examined. There was a higher mean patient age among reports for drugs that were associated with mitochondrial mechanisms of toxicity [56.1 ± 18.33 (SD)] compared to non-mitochondrial mechanisms [48 ± 19.53 (SD)]

**Key words**

Mitochondrial toxicity; FAERS database; Adverse event reporting; Drug-induced liver injury; Hepatotoxicity

**Abbreviations:** AE, adverse event; CI, confidence interval; CNS, center nervous system; DILI, drug-induced liver injury; DNA, deoxyribonucleic acid; FAERS, FDA’s Adverse Event Reporting System; FDA, US Food and Drug Administration; MedDRA, Medical Dictionary for Regulatory Activities; NCTR-LTKB, National Center for Toxicological Research-Liver Toxicity Knowledge Base; NSAID, nonsteroidal anti-inflammatory drugs; ROR, Reporting Odds Ratio.

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1. Introduction

Severe drug-induced liver injury (DILI) is a rare, potentially life-threatening adverse event with an incidence of 10–15 cases per 10,000 to 100,000 patients per year. The clinical profile of DILI is challenging to diagnose as it can mimic almost any type of liver disease, and mild, asymptomatic transaminase elevations may mimic those caused by diet. Prediction of liver injury remains a challenge for the pharmaceutical industry, regulators, and clinicians. DILI symptoms range from non-specific mild elevations in liver enzymes (aminotransferases) to severe liver illnesses such as cirrhosis or acute hepatitis and there is no specific biomarker that links drug exposure as the contributing cause of liver injury.

There are two types of DILI: intrinsic (i.e., dose-dependent) and idiosyncratic (i.e., dose-independent). A well-known example of intrinsic DILI is acetaminophen-induced liver injury, as it is dose-dependent, the onset is hours to days, and predictable. On the other hand, idiosyncratic DILI is not dose-dependent, occurs in a small portion of drug-exposed individuals, its onset is days to weeks, and unpredictable. Idiosyncratic DILI is highly dependent on environmental and host factors that alter the susceptibility of individual patient responses to the drug. Hamilton et al. suggested that DILI is the convergence of three influencing risk factors: host factors, environmental factors, and drug-specific factors. Host-related risk factors include genetics, ethnicity, gender, comorbidities, alterations in drug transport, drug clearance capabilities, age, and mitochondrial function variability. Environmental risk factors include lifestyle, viral co-infection, co-prescriptions, diet, and alcohol consumption. Finally, drug-specific risk factors include the relationship of applied dose (exposure) and chemical structure with reactive metabolite formation, mitochondrial dysfunction, and lipophilicity. Therefore, mechanisms of DILI, whether intrinsic or idiosyncratic, are a multivariable, highly complex process that varies from patient to patient and is influenced by host, environmental, and drug-specific factors that influence the liver’s ability to adapt and recover from an injury caused by a drug.

In recent years, drug-induced mitochondrial toxicity has been shown to play an essential role in intrinsic and idiosyncratic DILI.
Hepatotoxicity reports in the FDA adverse event reporting system database

adverse events, will be beneficial to this vulnerable patient pop-
ulation. Therefore, in this study, we evaluated the patient age and
gender associated with DILI reports (measured by reporting odds ratio) for hepatotoxicants with mitochondrial and non-
mitochondrial injury mechanisms.

Given that mitochondrial dysfunction is a common character-
istic of drugs that cause liver injury, a better understanding of the
association between the probability of liver injury induced by
drugs that are mitochondrial toxicants and the influence of pa-
tient’s age and gender would be beneficial for clinicians and drug
developers. If a drug is associated with mitochondrial mechanisms
of liver injury, clinicians could incorporate mitochondrial injury-
specific biomarkers into clinical trials. Additionally, the
development of clinically relevant animal models or study designs
may provide drug-induced mitochondrial toxicity risk translation
from animals to humans.

This study investigated liver injury reports submitted to the US
Food and Drug Administration (FDA) Adverse Event Reporting
System (FAERS) and compared the frequency of reports between
drugs that can cause hepatotoxicity via mitochondrial mechanisms
and those without mitochondrial mechanisms of toxicity. Addi-
tionally, we determined if there were age and gender differences
associated with DILI reports involving drugs with or without
mitochondrial toxicities.

2. Methods

2.1. Study design

2.1.1. Data source

FAERS database is the largest national repository of spontaneous
drug event reports, having accumulated over 28 million adverse
events reports. Healthcare professionals, patients, manufacturers,
and lawyers can submit potential drug-induced adverse events of
small and large therapeutic (biologics) classes and medical de-
tices to the FAERS database. The FAERS database has a vital role
in post-market drug surveillance in terms of detection and char-
acterization of drug and device-related adverse events.

We extracted adverse event reports from the FAERS database
database for the timeframe from January 1998 to May 2019. In this study,
the reports included severe adverse events, such as hospitalization,
disability, or death. The types of reports were classified by FAERS
as direct, expedited, or periodic. Direct reports were submitted to
FDA from consumer or health care professionals; whereas,
expedited reports were sent from the manufacturer within 15 days
of severe adverse events occurrence not included in the product
label. Adverse drug event reports considered periodic were
submitted from manufacturers, included in the label, and sent to
the FDA quarterly or annually. The main selection criterion was
“primary suspect” drugs. “Secondary suspect” drugs were
excluded because of the greater uncertainty of the association
between the drug and the reported adverse events. FAERS reports
were coded using the MedDRA (Medical Dictionary for Regula-
tory Activities) terms for DILI. Although DILI has complex
clinical symptoms, there has been documentation for the utiliza-
tion of the FAERS database to investigate emerging DILI adverse
events for newly marketed drugs.

2.1.2. Inclusion/exclusion criteria

Drugs that cause liver injury have been annotated using the United
States National Center for Toxicological Research Liver Toxicity
Knowledge Base (NCTR-LTKB), which utilizes hepatotoxic de-
scriptions from the FDA-approved drug labeling regulatory doc-
ments as well as evaluating causality evidence in the literature.

This database was created by the FDA to help clinicians, toxicolo-
gists, and researchers access information on DILI annotation of
various drugs. NCTR-LTKB serves as a centralized source to
study the mechanism of DILI and the development or validation
of emerging biomarkers and predictive models. This is the
largest publicly available annotated DILI dataset containing three
groups based on their potential to cause liver toxicity [Most DILI
concern (192 drugs), Lesser DILI concern (278 drugs), and No-
DILI concern (312 drugs)] with confirmed causal evidence connect-
ing a drug to liver injury. The FAERS database uses FDA
drug labeling information for the classification of drugs according
to their potential to cause DILI. This study utilized drugs with
“most-DILI concern”, which were defined based on hepatotoxicity
resulting in market withdrawal (in US and ex-US), black box
warning, or high severity of liver injury noted as part of the
warning and precautions label. Therefore, both mitochondrial
and non-mitochondrial mechanisms of toxicity groups are asso-
ciated with severe hepatic injury.

The study drugs represented various drug classes such as analgesic,
anti-inflammatory, antidepressant, antibiotic, antidi-
betic, and antineoplastic agents. Most of these drugs had been
withdrawn, have boxed warnings, or have warnings and pre-
cautions for liver injury in their prescribing labels. The details of
DILI severity categories based on the DILI description are
included in the drug labeling: severity level 1; steatosis, level 2;
cholestasis and steatohepatitis, level 3; liver aminotransferases
increase, level 4; hyperbilirubinemia, level 5; jaundice, level 6;
acute liver failure, level 7; acute liver failure, level 8; hepatotox-
icity. Examples of withdrawn drugs include bromfenac, chlor-
zoxazo, troglitazone, and trovafloxacin, which have been
assigned a severity level of 8, suggesting evidence of fatal hepato-
toxicity. Drugs such as bosentan, danazol, ketoconazole, nef-
rozide, tolcapone, and valproic acid have box warning in their
product labeling and have severity categories ranging from 3 to 8.

2.1.3. Classification of drugs as mitochondrial toxicants

Drugs with mitochondrial mechanisms of toxicity were defined by
literature evidence of mitochondrial injury mechanisms (yes or
no) of in vitro or in vivo (e.g., cellular production of reactive oxygen species via oxidative stress, inhibition or uncoupling of respiratory complexes of electron transport chain, induction of mitochondrial membrane permeability transition pore, inhibition of mitochon-
drial fatty acid oxidation or mitochondrial DNA damage, etc.) or in vivo mitochondrial toxicity from animal studies
(evidence of impairment of oxidative phosphorylation complexes or histopathological alterations of mitochondria in vivo animal
models, etc.). Our classification was based on the parent drug-
induced toxicity (direct impact on mitochondria) and not the
metabolite. Possible drug effects on mitochondrial biogenesis or
respiratory capacity were not considered. Drugs with the non-
mitochondrial mechanisms of toxicity were defined by literature
evidence of the alternative mechanisms of injury or lack of evi-
dence. It is important to note that 8.2% of drugs had no literature
evidence of the type of toxicity mechanism, meaning it could be a
mitochondrial or non-mitochondrial mechanism. Furthermore, the
non-mitochondrial mechanisms of toxicity drugs are not proven to
have non-mitochondrial mechanisms. For these drugs, there is
simply no evidence of mitochondrial mechanisms of toxicity in-
formation that is publicly available yet.
2.2. Outcome

We determined the number of reports for hepatotoxicity at a group level and an individual drug level using the Reporting Odds Ratio (ROR). As shown in Table 1, we calculated total hepatotoxicity and all other adverse events for both the DILI groups. For ROR calculations, numerators are derived by multiplying the hepatotoxicity reports for mitochondrial mechanisms of toxicity drug group with all other adverse event reports of non-mitochondrial mechanisms of toxicity per drug group. The denominator is calculated by multiplying hepatotoxicity adverse event reports of non-mitochondrial mechanisms of toxicity with all the adverse events reported for mitochondrial mechanisms of toxicity per drug group. Therefore, the ROR for drugs associated with mitochondrial mechanism of toxicity was 1.43 [ROR = (40,343 × 1,342,486)/(586,989 × 64,358) = 1.43].

We also examined the RORs at the individual drug level, as shown in Table 2. A case (hepatotoxicity reports) or non-case (all other adverse event reports) disproportionality approach was utilized by creating a two-by-two contingency table, as demonstrated below using acetaminophen as an example. During this timeframe, a total of 383,540 hepatotoxicity reports and a total of 27,852,908 adverse event counts of any drug type were collected. For ROR calculations, numerators are derived by multiplying the hepatotoxicity reports for a drug of interest with all other adverse events reports. The denominator is calculated by multiplying hepatotoxicity adverse event reports of all other drugs (excluding acetaminophen) with all the adverse events reported with a drug of hepatotoxicity adverse event reports. The statistical significance of differences in categorical variables such as age group, DILI severity, drug label, and report type between two categories of DILI drugs was examined using the chi-square test. Whereas, differences in continuous variables such as mean patient age between the two categories of hepatotoxic drugs were compared with the two-tailed Student’s t-test for independent samples. The unadjusted association of age and gender with mitochondrial mechanisms of toxicity DILI group (against non-mitochondrial mechanisms of toxicity DILI group) was determined using univariate logistic regression analysis. ROR calculations were carried out using a two-by-two contingency table using OpenEpi (version 3.01; Centers for Disease Control and Prevention), which calculates 95% CI and P-values via Taylor series. Chi-square tests were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA), and two-sided t-tests were performed at the 0.05 significance level via GraphPad Prism version 8 (La Jolla, CA, USA). All statistical tests were two-sided with a significance level at 0.05.

3. Results

We included 192 drugs classified as having the highest DILI risk (“Most-DILI concern”) via the NCTR-LTKB database. Out of these 192 drugs, 134 drugs had searchable FAERS reports, while the remaining 58 drugs were either withdrawn before our study period or were withdrawn from the European market before US approval. Therefore, the final data set contained 134 drugs, which were categorized as 56 drugs causing hepatotoxicity via mitochondrial mechanisms, and 78 drugs were classified as causing hepatotoxicity via non-mitochondrial mechanisms.

Table 3 indicates the characteristics of the event reports included in the study. A total of 104,701 adverse event reports were extracted from FAERS for the period spanning January 1998 to May 2019. Of these, 40,343 (38.5%) reports of hepatotoxicity were for drugs that were associated with mitochondrial mechanisms of toxicity, whereas 64,358 (61.5%) reports of hepatotoxicity were for drugs associated with non-mitochondrial mechanisms of toxicity. Furthermore, drugs were categorized based on the NCTR-LTKB severity classification. There was a statistically significant difference in DILI severity (P < 0.0001) between the two groups of DILI drugs (mitochondrial mechanisms compared to non-mitochondrial mechanisms). There was a 5.5 percentage point difference in reports for more severe DILI (liver failure/hepatotoxicity) for drugs associated with mitochondrial

| Table 1 | Reporting odds ratio estimates for DILI drug groups (FAERS reports). |
|---------|---------------------------------------------------------------|
| DILI groups | Hepatotoxicity | All other adverse events | Total |
| Drugs associated with mitochondrial mechanisms of toxicity | 40,343 | 586,989 | 627,332 |
| Drugs associated with non-mitochondrial mechanisms of toxicity | 64,358 | 1,342,486 | 1,406,844 |
| Total | 104,701 | 1,929,475 | 2,034,176 |

Mitochondrial function declines with aging; therefore, we evaluated if reports of severe DILI were disproportionately associated with older patient age, indicating potential susceptibility to DILI from mitochondrial mechanisms of toxicity. Furthermore, since gender may play an important role in the sensitivity of DILI, we also evaluated the frequency of reports according to patient gender. The mean and standard deviation (SD) of patient age were calculated and compared between DILI reports caused by drugs associated with mitochondrial mechanisms of toxicity and DILI reports associated with non-mitochondrial mechanisms. Patient age was dichotomized into ≤65 years or >65 years for comparison. Other factors, including drug severity class, patient weight, report type, and label section, were examined in a descriptive analysis.

2.4. Statistical analysis

Descriptive statistics were used to compare the gender and age of reports for the DILI drug groups associated with mitochondrial mechanisms of toxicity and associated with non-mitochondrial mechanisms. The statistical significance of differences in categorical variables such as age group, DILI severity, drug label, and report type between two categories of DILI drugs was examined using the chi-square test. Whereas, differences in continuous variables such as mean patient age between the two categories of hepatotoxic drugs were compared with the two-tailed Student’s t-test for independent samples. The unadjusted association of age and gender with mitochondrial mechanisms of toxicity DILI group (against non-mitochondrial mechanisms of toxicity DILI group) was determined using univariate logistic regression analysis. ROR calculations were carried out using a two-by-two contingency table using OpenEpi (version 3.01; Centers for Disease Control and Prevention), which calculates 95% CI and P-values via Taylor series. Chi-square tests were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA), and two-sided t-tests were performed at the 0.05 significance level via GraphPad Prism version 8 (La Jolla, CA, USA). All statistical tests were two-sided with a significance level at 0.05.
mechanisms of toxicity compared to non-mitochondrial mechanisms (76.3% compared to 70.8%, respectively, \(P < 0.0001\)). As shown in Table 3, the FAERS reports were classified based on the drug label section for liver injury; there was a statistically significant difference in drug labels (\(P < 0.0001\)) between the two groups of DILI drugs (mitochondrial mechanisms compared to non-mitochondrial mechanisms). Additionally, 24.6% of mitochondrial mechanisms of toxicity drugs had a box warning label as compared to 19.8% of non-mitochondrial mechanisms of toxicity drugs. For drugs withdrawn due to hepatotoxicity, there were high numbers of reports (\(n = 4227, 10.5\%\)) for drugs that are associated with mitochondrial toxicity mechanisms, compared to a lower number of reports (\(n = 747, 1.2\%\)) for drugs with non-mitochondrial mechanisms of toxicity (\(P < 0.0001\)). Over 88% of reports were expedited, while the rest of the reports were either direct or periodic. In summary, there was a statistically significant difference between drug severity classification, label, and liver injury severity according to the drug’s ability to cause toxicity through mitochondrial mechanisms.

We also examined patient bodyweight, but 79%-81% of the reports did not have this information documented. Among the 19%-21% of reports where the bodyweight data was present, the average difference between the two groups of DILI drugs (mitochondrial compared to non-mitochondrial mechanisms) was only 1.6 kg (68.6 \pm 20.8 compared to 70.2 \pm 23.4; \(P < 0.0001\)). In this case, the small \(P\)-value may be because the large sample size overpowered the comparison. As large numbers of the reports

### Table 3  Characteristics of patients and hepatotoxic drugs associated with mitochondrial mechanisms of toxicity compared to non-mitochondrial mechanisms.

| Characteristics                          | Hepatotoxicity via mitochondrial mechanism (56 drugs) | Hepatotoxicity via non-mitochondrial mechanism (78 drugs) |
|------------------------------------------|------------------------------------------------------|---------------------------------------------------------|
| FAERS report counts \((n)\)              | 40,343 (38.5%)                                        | 64,358 (61.5%)                                          |
| Reports based on NKTR drug severity classification |                                                      |                                                         |
| 3 - Liver aminotransferases increase     | 0 (0%)                                               | 3048 (4.7%)                                             |
| 4 - Hyperbilirubinemia                   | 1958 (4.9%)                                          | 2292 (3.6%)                                             |
| 5 - Jaundice                             | 7526 (18.7%)                                         | 13,392 (20.8%)                                          |
| 6 - Liver necrosis                       | 0 (0%)                                               | 35 (0.05%)                                              |
| 7 - Acute liver failure                  | 4581 (11.3%)                                         | 17,207 (26.7%)                                          |
| 8 - Fatal hepatotoxicity                 | 26,278 (65%)                                         | 28,384 (44.1)                                           |
| Reports combined based on less and severe DILI |                                                      |                                                         |
| Less severe injury                       | 9484 (23.5%)                                         | 18,767 (29.2%)                                          |
| Liver failure/hepatotoxicity             | 30,839 (76.5%)                                       | 45,591 (70.8%)                                          |
| Reports based on drug label section      |                                                      |                                                         |
| Warning & precautions                    | 26,177 (64.9%)                                       | 50,898 (79.1%)                                          |
| Box warning                              | 9939 (24.6%)                                         | 12,713 (18.8%)                                          |
| Withdrawn                                | 4227 (10.5%)                                         | 747 (1.2%)                                              |
| Report type                              |                                                      |                                                         |
| Direct                                   | 1992 (4.9%)                                          | 2393 (3.7%)                                             |
| Expedited                                | 35,569 (88.2%)                                       | 57,119 (88.8%)                                          |
| Periodic                                 | 2782 (6.9%)                                          | 4846 (7.5%)                                             |
| Patient characteristics                  |                                                      |                                                         |
| Weight (kg)                              |                                                      |                                                         |
| FAERS report counts \((n)\)              | 7666 (19%)                                           | 13,532 (21%)                                            |
| Weight missing                           | 32,677 (81%)                                         | 50,826 (79%)                                            |
| Weight Mean \(\pm\) SD                   | 68.6 \pm 20.8                                        | 70.2 \pm 23.4                                           |
| Gender                                   |                                                      |                                                         |
| Male                                     | 19,818 (49.1%)                                       | 24,353 (37.8%)                                          |
| Female                                   | 17,711 (43.9%)                                       | 34,690 (53.9%)                                          |
| Gender missing                           | 2814 (7%)                                            | 5315 (8.3%)                                             |
| Age (year)                               |                                                      |                                                         |
| FAERS report counts \((n)\)              | 30,324 (75.2%)                                       | 46,310 (71.9%)                                          |
| Age missing                              | 10,019 (24.8%)                                       | 18,046 (28%)                                            |
| Age Mean \(\pm\) SD                      | 56.1 \pm 18.3                                        | 48 \pm 19.5                                             |

A statistical difference between two DILI groups across categorical variables was performed using a chi-square test. Comparisons of continuous variables were performed using \(t\)-tests; \(P\) values were <0.0001 for all the variables (\(P < 0.05\) was considered significant); \(n\) is number of instances.
were missing bodyweight, further analysis was not performed. As shown in Table 3, a higher percentage of males were the subjects of hepatotoxicity reports via mitochondrial mechanisms compared to the subjects of reports involving hepatotoxicity via the non-mitochondrial mechanisms (49.1% compared to 37.8%, \( P < 0.0001 \)). About 7%—8.3% of reports were missing information about the patient’s gender.

Table 3 presents the difference in the mean and distribution of age among the two groups. The patient’s age was recorded in more than 71% of the reports from both the groups. As shown in Table 3, there was a statistically significant difference (\( P < 0.0001 \)) between the mean age of patients with hepatotoxicity in drugs that are associated with mitochondrial mechanisms [56.1 ± 18.33 (SD)] compared to non-mitochondrial mechanisms of toxicity [48 ± 19.53 (SD)]. In other words, reports involving drugs associated with mitochondrial mechanisms of hepatic toxicity displayed a higher mean age than reports for drugs associated with non-mitochondrial mechanisms of hepatic toxicity.

Fig. 1 indicates the ROR values of drugs associated with mitochondrial mechanisms of toxicity; benzbromarone, troglitazone, isoniazid, rifampin, and nimesulide had the highest ROR values in the group. Fig. 2 indicates the ROR values of drugs associated with non-mitochondrial mechanisms of toxicity; telithromycin, gemtuzumab ozogamicin, mexiletine, dactomycin, and disulfiram had the highest ROR values in the group. Table 4 indicates the top 20 drugs with the highest ROR values in both groups of hepatotoxicants. The top 20 drugs with the highest ROR values included drugs with either mitochondrial or non-mitochondrial injury mechanisms. The top four drugs, which had ROR values higher than 18 (benzbromarone, troglitazone, isoniazid, rifampin), were associated with mitochondrial mechanisms of toxicity. Furthermore, the top two drugs, benzbromarone, and troglitazone were withdrawn from the market.

Table 5 indicates the RORs between the two groups of drugs that caused liver injury via mitochondrial compared to non-mitochondrial mechanisms. Between the two DILI groups, reports for DILI involving mitochondrial mechanisms of toxicity had a 1.43 (95% CI 1.42—1.45; \( P < 0.0001 \)) times higher odds compared to drugs associated with non-mitochondrial mechanisms of toxicity. The univariate logistic regression model was used after dichotomizing age and gender. Table 6 indicates a statistically significant risk association of age or gender with hepatotoxic drugs with mitochondrial toxicity mechanisms. Reports of liver injury were 2.2 (odds ratio: 2.2, 95% CI 2.12—2.26) times more likely to be associated with older patient age, as compared with reports involving patients under 65 years of age. On the other hand, female patients were 37% less likely to be subjects of liver injury reports for drugs associated with mitochondrial mechanisms of toxicity compared to males (Odds Ratio 0.63, 95% CI 0.61—0.64). Supporting Information Tables S1—S7 contain DILI reports, all adverse event reports, ROR, and 95% Confidence Interval (CI) for all the drugs evaluated in the study.

Fig. 3 indicates the totality of all ROR scores of DILI drugs with mitochondrial or non-mitochondrial mechanisms of toxicity. Drugs from the antineoplastic, antiviral, analgesic, antibiotic, and antimycobacterial classes were the top five drugs classes associated with higher ROR scores. Drugs from the antidiabetic,
antiretroviral, anti-inflammatory, anti-Parkinson, vasoactive, neuroprotective, and antihyperlipidemic drug classes were primarily associated with mitochondrial mechanisms. Alternatively, leukotriene pathway modulators, alcohol antagonists, CNS stimulants, and platelet inhibitor drug classes were the drugs with non-mitochondrial mechanisms having higher RORs. Figs. 4 and 5 categorize these two groups of drugs based on the drug label section and severity class. We did not observe any notable trend between mitochondrial and non-mitochondrial mechanisms and drug label section, or severity class.

4. Discussion

Prediction and characterization for DILI during preclinical drug development and post-approval remains a challenge for the pharmaceutical industry, toxicologists, clinicians, physicians, health authorities, and regulators. Characterizing DILI has been a challenge due to its unpredictability, lack of accurate biomarkers, poorly defined pathogenesis, and its potential to cause fatal liver failure. In the past two decades, drug-induced mitochondrial dysfunction has been established as an important contributing mechanism associated with liver, muscle, heart, kidney, and central nervous system toxicity. Mitochondrial dysfunction is one of the reasons known to cause muscle toxicity by HMG-CoA reductase inhibitor (cerivastatin), cardiovascular toxicity by anthracyclines (daunorubicin, doxorubicin, idarubicin), and DILI by an antidepressant (nefazodone), antibiotics [isoniazid, ketoconazole (oral)], and anxiolytic (panadipol) drugs.

We calculated the ROR for reports of severe hepatotoxicity adverse events among drugs with the highest risk for DILI, for drugs having mitochondrial or non-mitochondrial mechanisms of toxicity. Brinker et al. indicated that various measures of disproportionate reporting of adverse events such as Proportional Reporting Ratio, Multi-item Gamma Poisson Shrinker, and the Bayesian Confidence Propagation Neutral Network had been used in analyses of surveillance databases. Each of these methods may have different strengths and limitations and may lead to different sensitivity and specificity for a drug’s risk reporting. Various health regulatory authorities use different statistical measures for reporting. For example, the European Medicines Agency uses Proportional Reporting Ratio; FDA and UK’s Medicines and Healthcare products Regulatory Agency uses Multi-item Gamma Poisson Shrinker. Whereas, the World Health Organization has utilized the Bayesian Confidence Propagation Neutral Network method for reporting. These reporting measures have been used to generate hypotheses and do not infer adverse event—causal associations. It has been suggested that there is not one single measure of effect that is superior to the others. Our study utilized reporting odds ratios to characterize the frequency of liver

### Table 4

Top 20 drugs with the highest reporting odds ratio in both DILI groups.

| Drug class            | Drug name        | Severity class | Label section | Mitochondrial toxicity | ROR   |
|-----------------------|------------------|----------------|---------------|------------------------|-------|
| Antigout agent        | Benzbromarone    | 8              | Withdrawn     | Yes                    | 36.31 |
| Antidiabetic agent    | Troglitazone     | 8              | Withdrawn     | Yes                    | 31.02 |
| Antimycobacterial     | Isoniazid        | 8              | Box warning   | Yes                    | 20.79 |
| Antimycobacterial     | Rifampin         | 8              | Warnings and precautions Yes | 18.64 |
| Antibiotics           | Telithromycin    | 8              | Warnings and precautions No | 18.33 |
| Antineoplastics       | Gemtuzumab ozogamicin | 8            | Box warning   | No                     | 18.08 |
| Antiarrhythmics       | Mexiletine       | 3              | Box warning   | No                     | 17.8  |
| Antineoplastics       | Dactinomycin     | 8              | Warnings and precautions No | 17.25 |
| Anti-inflammatory agent | Nimesulide     | 8              | Withdrawn     | Yes                    | 15.07 |
| Antialcoholics        | Disulfiram       | 8              | Warnings and precautions No | 14.82 |
| Antivirals            | Didanosine       | 8              | Warnings and precautions Yes | 14.38 |
| Stimulants; central nervous system | Pemoline | 8            | Withdrawn     | No                     | 14.24 |
| Platelet inhibitors   | Ticlopidine      | 4              | Warnings and precautions No | 13.51 |
| Antibiotics           | Trovafloxin mesylate | 8            | Withdrawn     | Yes                    | 13.48 |
| Antithyroid agents    | Propylthiouracil | 8              | Box warning   | No                     | 13.33 |
| NSAIIDs               | Bromfenac        | 8              | Withdrawn     | No                     | 13.01 |
| Antiretroviral drugs  | Stavudine        | 8              | Box warning   | Yes                    | 12.83 |
| Hormone modifiers     | Danazol          | 8              | Box warning   | Yes                    | 12.82 |
| Antiparkinson agents  | Tolcapone        | 8              | Box warning   | Yes                    | 12.25 |
| Antivirals            | Tipranavir       | 8              | Box warning   | No                     | 12.04 |

### Table 5

Reporting odds ratio estimate for hepatotoxic drugs associated with mitochondrial mechanisms of toxicity compared to non-mitochondrial mechanisms.

| DILI group                                                                 | Odds ratio | 95% CI          | P-value       |
|---------------------------------------------------------------------------|------------|-----------------|---------------|
| Drugs associated with mitochondrial mechanisms of toxicity                | 1.43       | 1.42–1.45       | <0.0001       |

### Table 6

Association of age and gender with hepatotoxic drugs with mitochondrial toxicity mechanisms as compared with non-mitochondrial mechanisms, using a univariate logistic regression model.

| Independent variable | Odds ratio | 95% CI | P-value |
|----------------------|------------|-------|---------|
| Age                  |            |       |         |
| <65 years            | Reference  |       |         |
| >65 years            | 2.2        | 2.12–2.26 | <0.0001 |
| Gender               |            |       |         |
| Male                 | Reference  |       |         |
| Female               | 0.63       | 0.61–0.64 | <0.0001 |
injury reports as it is a straightforward and frequently used measure for the analysis of FAERS data. The review published by Will et al. indicated that the most commonly used prescriptions and over-the-counter medications for geriatric patients had published reports of various toxicities linked to mitochondrial dysfunction. Our study reported that reports for DILI involving mitochondrial mechanisms of toxicity had a 1.43 (95% CI 1.42–1.45; \( P < 0.0001 \)) times higher odds compared to drugs associated with non-mitochondrial mechanisms of toxicity. The ROR scores with the highest risk of liver injury based on mitochondrial or non-mitochondrial mechanisms were highest for drugs from the antineoplastic, antiviral, analgesic, antibiotic, and antimycobacterial classes. This finding agreed with the published literature. Sonawane et al. indicated that antineoplastic, analgesic, and antibiotics were among the top 10 drugs that reported severe adverse events in the FAERS database from 2006 to 2014. Additionally, our study observed that over 88% of adverse reports were expedited, while the rest of the reports were either direct or periodic in both drug categories. This observation also agreed with the published literature. Sonawane et al. also reported that expedited reports were the most common and over 72% of all serious adverse events with available data on the report type.

Antidiabetic, antiretroviral, anti-inflammatory, anti-Parkinson, vasoactive, neuroprotective, antihyperlipidemic drug classes were primarily associated with mitochondrial toxicity mechanisms. In recent years, an impaired mitochondrial function has been documented as one of the critical factors in inflammation, sarcopenia, metabolic (obesity, type two diabetes, non-alcoholic fatty liver disease), and neurodegenerative diseases (Parkinson’s, Alzheimer’s, Huntington’s diseases). Patients with reduced mitochondrial function occurring as a manifestation of their underlying disease state may be more vulnerable to drugs that cause toxicity via mitochondrial mechanisms. Alternatively, anti-adrenergic, leukotriene pathway modulators, alcohol antagonists, CNS stimulants, and platelet inhibitor drug classes were the drugs that were primarily associated with non-mitochondrial toxicity mechanisms.

Figure 3 Sum of all ROR of “most-DILI-concern” drugs associated with mitochondrial and non-mitochondrial mechanisms of toxicity per therapeutic class. Drugs from the antineoplastic, antiviral, analgesic, antibiotic, and antimycobacterial classes were the top 5 drug classes associated with higher ROR scores. Drugs from the antidiabetic, antiretroviral, anti-inflammatory, anti-Parkinson, vasoactive, neuroprotective, and antihyperlipidemic drug classes were primarily associated with mitochondrial mechanisms. Alternatively, leukotriene pathway modulators, alcohol antagonists, CNS stimulants, and platelet inhibitor drug classes were the drugs with non-mitochondrial mechanisms having higher RORs.

Figure 4 Categorization based on liver injury drug label for “most-DILI concern” drugs based on their association with mitochondrial and non-mitochondrial mechanisms of toxicity. There was not any notable trend between two groups based on drug label.
The hallmark of mitochondrial aging includes a decreased mitochondrial number, reduced mitochondrial function, and individual mitochondrial mechanisms of toxicity. There was not any notable trend between two groups based on severity class.

We identified statistically significant differences ($P < 0.0001$) in drug severity classification, label section for liver injury, and report type between these two mechanisms for DILI. For drugs withdrawn for liver injury, there were a higher number of hepatotoxicity reports (10.5%) associated with mitochondrial than non-mitochondrial mechanisms (1.2%). Dykens and Will (2007) noted that 38 marketed drugs withdrew from the market between 1994 and 2006. Among these, for cerivastatin, nefazodone, troglitazone, and tolcapone, there was substantial evidence of mitochondrial-induced organ toxicity. Therefore, our observations agreed with reports in the medical literature of drug-induced mitochondrial dysfunction playing an important role in drug withdrawal. Furthermore, Boelsterli and Lim in 2007, suggested that several drugs, such as amiodarone, dantrolene, diclofenac, isoniazid, lamivudine, leflunomide, mefenamic acid, nimesulide, perhexiline, simvastatin, stavudine, sulindac, tolcapone, troglitazone, trovafloxacin, and valproic acid, are associated with idiosyncratic DILI with a clear link to mitochondrial toxicity. Many of these drugs reported a relatively higher ROR in our study.

Our study reported an older mean patient age [56.1 ± 18.33 (SD)] associated with reports for drugs that cause DILI via mitochondrial mechanisms compared to mean age [48 ± 19.53 (SD)] associated with reports for drugs that cause injury via non-mitochondrial mechanisms ($P < 0.0001$). This was further substantiated in a univariate logistic regression analysis where reports of liver injury were 2.2 (odds ratio: 2.26, 95% CI 2.12–2.26) times more likely to be associated with older patient age, as compared with reports involving patient ages under 65 years. This finding is consistent with physiological information indicating age as a risk factor for both mitochondrial DNA abnormality and increased oxidative stress-related injury. There is evidence that mitochondrial function declines with age, including the role of mitochondrial DNA mutation, increased production of reactive oxygen species, and the dysfunction in oxidative phosphorylation pathways. The hallmark of mitochondrial aging includes a decreased mitochondrial number, reduced mitochondrial function, and individual electron transport chain activities. Mitochondrial function deteriorates progressively with age. Therefore, older age populations may be more vulnerable to hepatotoxic drugs associated with mitochondrial mechanisms of toxicity.

Our study indicated that female patients were 37% less likely to report liver injury adverse events for drugs associated with mitochondrial mechanisms of toxicity compared to males. There are conflicting reports associating male gender as a susceptibility factor for DILI and a clear link for this association is absent in the literature. Several articles allude to the potential involvement of a reactive metabolite, and differences in pharmacokinetics, pharmacodynamics, sex hormones, and immune system response between males and females. Therefore, drug-induced mitochondrial toxicity does not reveal itself in animal models due to the young age, lack of genetic divergence, health status, and lack of concomitant drug exposure. Therefore, drug-induced mitochondrial toxicity is often idiosyncratic, meaning it is not predictable until a large population is exposed. Based on this study, we provide evidence of a higher proportion of reports of severe liver injury adverse events among drugs associated with mitochondrial mechanisms of toxicity as compared with non-mitochondrial mechanisms of toxicity. Furthermore, we found that reports of liver injury were 2.2 (odds ratio: 2.2, 95% CI 2.12–2.26) times more likely to be associated with older patient age, as compared with reports involving patients ages under 65 years. This finding aligns with the theory that age is a susceptibility factor in liver injury via the mitochondrial mechanisms of toxicity.

6. Limitation

The FAERS database describes adverse event reports but does not include information about the number of patients treated with a drug. Therefore, incidence rates, prevalence rates, and causal relationships between drugs and adverse events cannot be determined for drugs according to mitochondrial or non-mitochondrial mechanisms of toxicity. For example, the population incidence of DILI may be higher for drugs associated with non-mitochondrial mechanisms than mitochondrial mechanisms of toxicity. Nevertheless, researchers and health authorities have used the FAERS database for adverse event signal identification, developing ideas, and hypothesis generation despite this limitation. The hypothesis and ideas generated using this database could serve as a foundation for more robust study designs, and for in vitro or in vivo studies investigating the causal relationship of a drug with liver injury. The FAERS database provides a suitable source to evaluate the volume and characteristics of adverse event reports for marketed medications. Furthermore, factors such as age, gender, weight, drug severity class, and label section of FAERS reports can provide valuable insights to health authorities during the post-market surveillance of marketed medications.

The FAERS database is a spontaneous reporting system with limitations when used for drug safety research, including the potential for under or over-reporting events, duplicate reports, influence of media, and uncertainty of reported events. For example, troglitazone received significant media attention due to a class-action lawsuit which called attention to its DILI risk. Therefore, troglitazone may have a higher number of hepatotoxicity reports than some drugs that did not receive media attention. Moreover, the FAERS database could be associated with the
“Weber effect”, where adverse event reports are higher in initial marketing stages following a gradual decline.

Mitochondria have a diverse role in the pathophysiology of DILI. In current literature, most of the mitochondrial-induced toxicity is derived from *in vitro* studies. *In vitro* assays using immortalized cell lines or primary human hepatocytes have their limitations as they generally lack competent metabolic function, xenobiotic biotransformation capacity, appropriate drug receptors and transporters, and cellular architecture. Therefore, it is unclear how mitochondrial *in vitro* mechanisms truly translate to liver injury outcomes in humans; there appear to be strong associations as outlined here.

Characterizing DILI drugs based on mitochondrial dysfunction *versus* other mechanisms may have limitations. For acetaminophen, mitochondrial dysfunction plays an essential role in liver injury. This was demonstrated in primary human hepatocytes and preclinical models. Mechanistically, acetaminophen produces a reactive metabolite leading to disruption of cellular homeostasis. However, acetaminophen as a parent drug does not directly affect the mitochondrial respiratory chain or cause direct toxicity to mitochondria. Therefore, we included acetaminophen in non-mitochondrial DILI drugs while considering that mitochondrial dysfunction plays an important role in acetaminophen-induced liver injury. Moreover, given the limitations of the data source we were unable to discern intrinsic from idiosyncratic DILI.

Patients with an underlying condition such as obesity may be more vulnerable to drugs that cause toxicity via mitochondrial mechanisms; thus, we attempted to include patient weight in our study. However, about 79%–81% of the reports missed the bodyweight information; therefore, the effect of patient weight was not examined. The study may also have several unmeasured confounding factors as patient comorbidities, pre-existing liver disease, and concomitant drug use is not captured in FAERS reports. Additionally, the findings regarding age and gender are unadjusted; therefore, it should be used merely for hypothesis generation. Moreover, gender bias may be due to disease demographics. Some of the DILI drugs with mitochondrial toxicity mechanisms are prescribed for diseases with a higher male predisposition. For example, benz bromarone is prescribed for gout, which has six times higher occurrence in males. Similarly, isoniazid and rifampin are prescribed for the treatment of tuberculosis, which has two times higher occurrence in males. ROR depends on the reporting rates of liver injury adverse events and all other adverse events reports in compared drug classes. DILI drugs associated with non-mitochondrial mechanisms of toxicity have a significantly higher number of non-hepatic adverse events reports. Therefore, we are not sure if larger ROR values are due to the higher reporting of hepatotoxicity in the drugs with mitochondrial mechanisms of toxicity, or higher reporting of non-hepatic adverse events reported for the drugs with non-mitochondrial mechanisms of toxicity.

For this analysis, we utilized ROR, which is a disproportionality measurement of spontaneous reports and not a method to measure drug-related risks quantitatively. Regulatory actions in response to safety concerns related to age and gender using the FAERS database must be determined via individual cases to determine causality. Despite these database limitations, we were able to show that drugs that cause hepatotoxicity via mitochondrial mechanisms were associated with a higher proportion of adverse event reports than drugs having non-mitochondrial mechanisms of toxicity. Additionally, age may play a role in susceptibility to DILI via mitochondrial mechanisms of toxicity. Our findings from this study align with mitochondrial mechanisms of toxicity being an important cause of DILI, and this should be further investigated in real-world studies with robust designs.

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Author contributions

Payal Rana was responsible for hypothesis generation, predictive analysis, manuscript outline, and generation of figures & tables. Payal Rana, Dr. Stephen Kogut and Dr. Michael Aleo were accountable for creating the primary manuscript. Dr. Xuerong Wen was responsible for guiding statistical analysis on univariate and multivariable logistic regression models. All authors reviewed, edited, and refined the final manuscript and have given approval to the final version.

Conflicts of interest

The authors declare that there was no conflict of interest.

Appendix A. Declaring information

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