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ORIGINAL ARTICLE

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)]

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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($P < 0.0001$), suggesting that age may play a role in susceptibility to DILI *via* mitochondrial mechanisms of toxicity. Univariate logistic regression analysis showed 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 less than 65 years of age. Compared to males, female patients were 37% less likely (odds ratio: 0.63, 95% CI 0.61−0.64) to be subjects of liver injury reports for drugs associated with mitochondrial toxicity mechanisms. Given the higher proportion of severe liver injury reports among drugs associated with mitochondrial mechanisms of toxicity, it is essential to understand if a drug causes mitochondrial toxicity during preclinical drug development when drug design alternatives, more clinically relevant animal models, and better clinical biomarkers may provide a better translation of drug-induced mitochondrial toxicity risk assessment from animals to humans. 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.

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[1−4]. The clinical profile of DILI is challenging to diagnose as it can mimic almost any type of liver disease[5,6] and mild, asymptomatic transaminase elevations may mimic those caused by diet[7]. Prediction of liver injury remains a challenge for the pharmaceutical industry, regulators, and clinicians[5]. DILI symptoms range from non-specific mild elevations in liver enzymes (aminotransferases) to severe liver illnesses such as cirrhosis or acute hepatitis[5,6] and there is no specific biomarker that links drug exposure as the contributing cause of liver injury[8].

There are two types of DILI: intrinsic (*i.e.*, dose-dependent) and idiosyncratic (*i.e.*, dose-independent)[6]. 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[9]. 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[9]. Idiosyncratic DILI is highly dependent on environmental and host factors that alter the susceptibility of individual patient responses to the drug. Hamilton et al.[10] 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[10]. Environmental risk factors include lifestyle, viral co-infection, co-prescriptions, diet, and alcohol consumption[10]. Finally, drug-specific risk factors include the relationship of applied dose (exposure) and chemical structure with reactive metabolite formation, mitochondrial dysfunction, and lipophilicity[10−12]. 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[8].

In recent years, drug-induced mitochondrial toxicity has been shown to play an essential role in intrinsic and idiosyncratic DILI. Many medications from different drug classes, such as antidiabetic, antilipidemic, antiviral, antibiotic, anti-inflammatory, and antipsychotic agents have toxicities mediated by mitochondrial mechanisms, which may contribute to DILI[13]. Mitochondrial toxicants affect mitochondrial homeostasis by numerous mechanisms such as oxidative stress, inhibition or uncoupling of respiratory complexes of electron transport chain, impairment of mitochondrial replication or promoting mitochondrial DNA damage[14]. Drug-induced mitochondrial toxicity is difficult to be detected in standard preclinical animal testing models and requires specific studies to examine disruptions in liver energy status[15]. Only recently, there has been the development of clinical biomarkers specific for mitochondrial dysfunction in disease[16] and DILI[17] beyond changes in blood lactate. With these inadequacies, a drug candidate can enter human clinical trials only to fail for evidence of mitochondrial toxicity[18,19]. Examples of non-mitochondrial toxicity mechanisms that drive DILI are generation of reactive metabolites, activation of cell death pathways, activation of innate or adaptive immune response pathways, or disruption of cellular homeostasis[20]. This study evaluates the frequency of reports of hepatotoxicity injury in drugs that cause DILI with mitochondrial and non-mitochondrial mechanisms.

Patient demographics influence risk or susceptibility for DILI. Boelsterli and Lim[21] indicated that older age and female gender were important susceptibility factors for DILI; however, the reasons were still unknown. There are no clinical studies that link the sensitivity of the female gender to DILI caused by mitochondrial dysfunction. Amacher et al.[22] indicated that women are more susceptible to DILI than men. Several hypotheses were proposed to explain gender differences in susceptibility, including pharmacokinetic or pharmacodynamic differences, interactions of sex hormones with signaling molecules, and a difference in immune system responses[22]. Similarly, it is believed that older adults are more susceptible to DILI caused by mitochondrial dysfunction. The review published by Will et al.[13] indicated that the most commonly used prescription and over-the-counter medications for geriatric patients, such as antilipidemic, pain, and heartburn medications, had published reports of toxicities linked to mitochondrial dysfunction[13]. As the United States' elderly population is growing rapidly, identifying and addressing risk factors of DILI, where mitochondrial dysfunction may play a substantial role in

adverse events, will be beneficial to this vulnerable patient population. 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 characteristic 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 patient'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[23–25]. Additionally, the development of clinically relevant animal models or study designs may provide drug-induced mitochondrial toxicity risk translation from animals to humans[24].

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. Additionally, 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 devices to the FAERS database. The FAERS database has a vital role in post-market drug surveillance in terms of detection and characterization of drug and device-related adverse events.

We extracted adverse event reports from the FAERS 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[26]. Adverse drug event reports considered periodic were submitted from manufacturers, included in the label, and sent to the FDA quarterly or annually[26]. 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 Regulatory Activities) terms for DILI[27]. Although DILI has complex clinical symptoms, there has been documentation for the utilization of the FAERS database to investigate emerging DILI adverse events for newly marketed drugs[8].

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 descriptions from the FDA-approved drug labeling regulatory documents as well as evaluating causality evidence in the literature[28]. This database was created by the FDA to help clinicians, toxicologists, and researchers access information on DILI annotation of various drugs[28,29]. NCTR-LTKB serves as a centralized source to study the mechanism of DILI and the development or validation of emerging biomarkers and predictive models[29]. 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 connecting a drug to liver injury[28]. 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[28–30]. Therefore, both mitochondrial and non-mitochondrial mechanisms of toxicity groups are associated with severe hepatic injury.

The study drugs represented various drug classes such as analgesic, anti-inflammatory, antidepressant, antibiotic, antidiabetic, and antineoplastic agents. Most of these drugs had been withdrawn, have boxed warnings, or have warnings and precautions 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; liver necrosis, level 7; acute liver failure, and level 8; hepatotoxicity[28]. Examples of withdrawn drugs include bromfenac, chlorzoxazone, troglitazone, and trovafloxacin, which have been assigned a severity level of 8, suggesting evidence of fatal hepatotoxicity. Drugs such as bosentan, danazol, ketoconazole, nefazodone, 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* (*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 mitochondrial fatty acid oxidation or mitochondrial DNA damage, etc.)[31–42] 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.)[43,44]. 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 evidence. 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 information 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[45]. 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[45]. 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 interest[45] (ROR for acetaminophen = [8509 × 27,852,908)/(51,732 × 383,540) = 11.94]. Within the timeframe, a ROR higher than one for a drug indicates a higher proportion of severe liver injury reports for a drug of interest than all the other drug reports in the database. In this case, acetaminophen was associated with proportionally more reports for serious liver adverse events than other drugs in the database.

2.3. Association of age, gender, and other factors in two groups of DILI (mitochondrial and non-mitochondrial mechanisms of toxicity)

Mitochondrial function declines with aging[13]; 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[46]. 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

Table 2 Example reporting odds ratio estimate for an individual drug: acetaminophen (FAERS Reports).

Drug	Hepatotoxicity	All other adverse events	Total
Acetaminophen	8509	51,732	60,241
All other drugs of any type	383,540	27,852,908	28,236,448
Total	392,049	27,904,640	28,296,689

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, and 64.9% of mitochondrial mechanisms of toxicity drugs had warning and precautions label as compared to 79.1% 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 ± 20.8 compared to 70.2 ± 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	30,859 (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 (19.8%)
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 ± SD	68.6 ± 20.8	70.2 ± 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 ± SD	56.1 ± 18.33	48 ± 19.53

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.

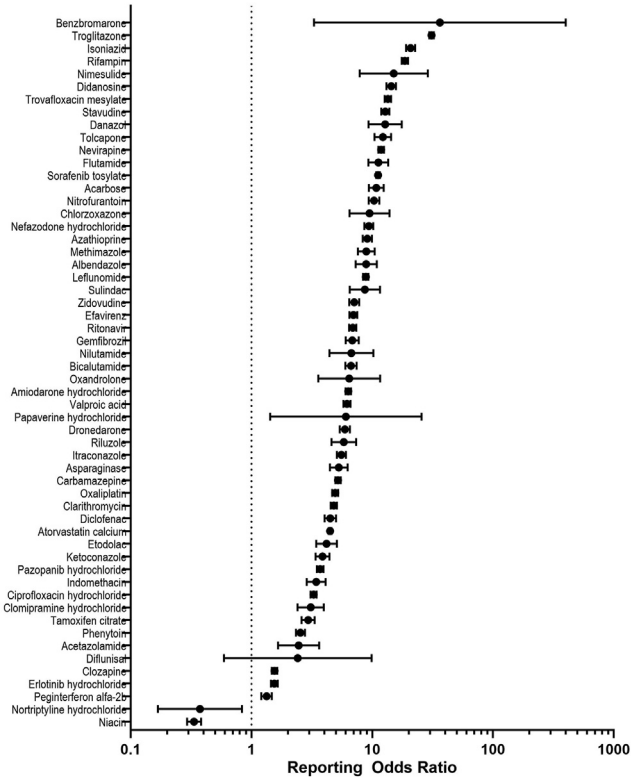

Figure 1 Reporting odds ratios (RORs) for hepatotoxic drugs associated with mitochondrial mechanisms of toxicity. Benzbromarone, troglitazone, isoniazid, rifampin, and nimesulide had the highest ROR values in this group.

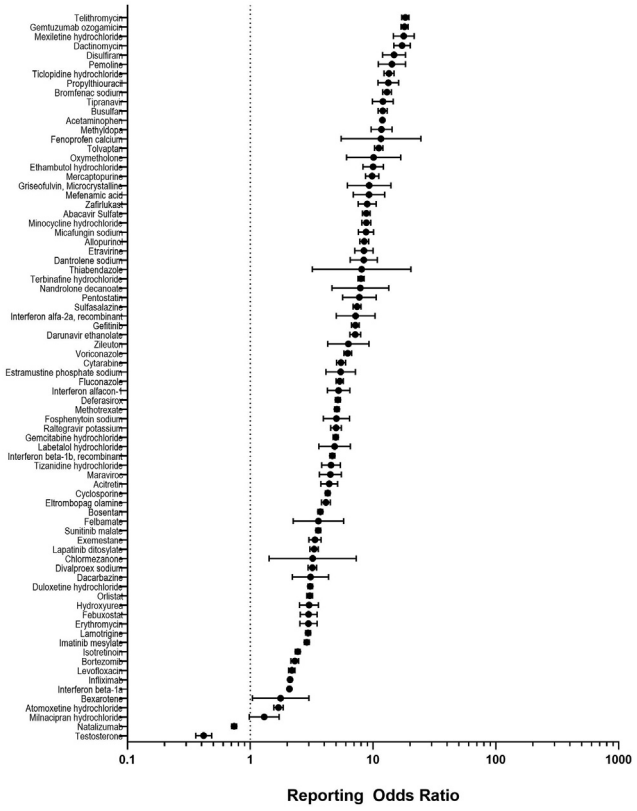

Figure 2 Reporting odds ratios (RORs) for hepatotoxic drugs associated with non-mitochondrial mechanisms of toxicity. Telithromycin, gemtuzumab ozogamicin, mexiletine, dactomycin, and disulfiram had the highest ROR values in the group.

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,

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	Trovafloxacin mesylate	8	Withdrawn	Yes	13.48
Antithyroid agents	Propylthiouracil	8	Box warning	No	13.33
NSAID	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

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[5]. 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[5]. 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[13]. Mitochondrial dysfunction is one of the reasons known to cause muscle toxicity by HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitor (cerivastatin), cardiovascular toxicity by anthracyclines (daunorubicin, doxorubicin, idarubicin), and DILI by an antidepressant (nefazodone), antibiotics [isoniazid, ketoconazole (oral)], and anxiolytic (panadiplon) drugs[19,47−50].

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

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.[8] 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[8]. 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[8]. 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[8,51,52]. Our study utilized reporting odds ratios to characterize the frequency of liver

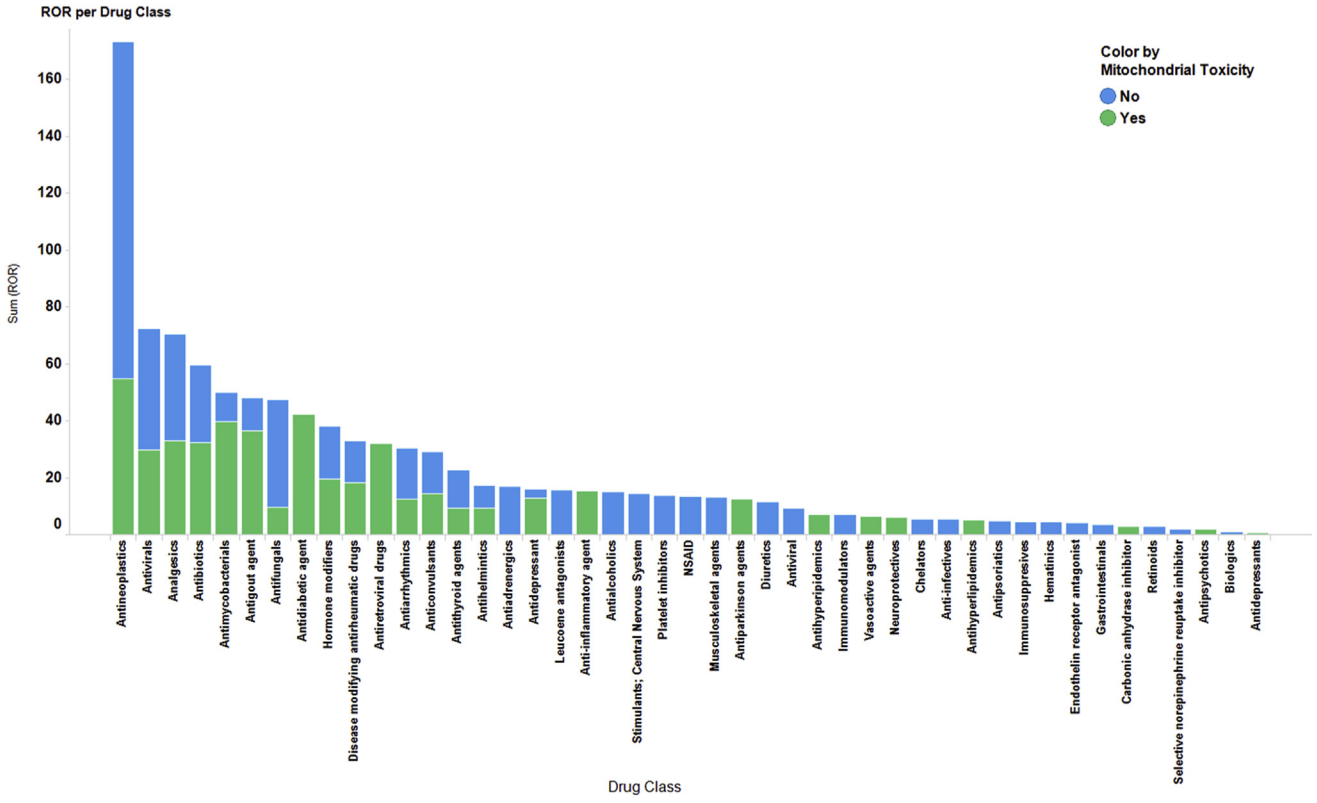

Figure 3 Sum of all ROR of "most-DILI-concern" drugs associated with mitochondrial and non-mitochondrial mechanisms of toxicity per therapeutic class. Drugs from the antineoplastic, antiviral, analgesic, antibiotic, and antimycobacterial classes were the top 5 drugs classes associated with higher ROR 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.

injury reports as it is a straightforward and frequently used measure for the analysis of FAERS data[45,53–57].

The review published by Will et al.[13] 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, analgesics, antibiotics, and antimycobacterial classes. This finding agreed with the published literature. Sonawane et al.[26] indicated that antineoplastic, analgesics, 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.[26] 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)[13,58–60]. 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, antiadrenergic, leukotriene pathway modulators, alcohol antagonist, CNS stimulants, and platelet inhibitors were drug classes that were primarily associated with non-mitochondrial toxicity mechanisms.

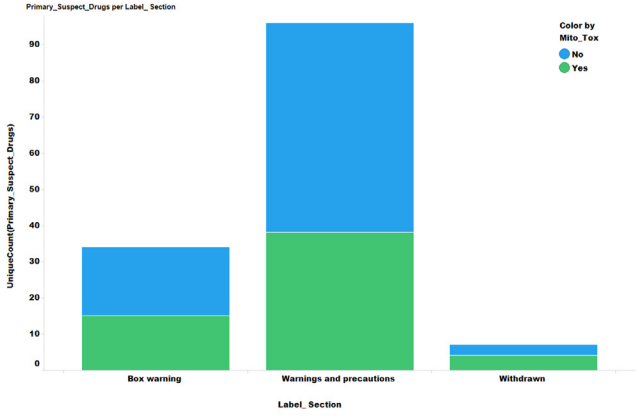

Figure 4 Categorization based on liver injury drug label for "most-DILI concern" drugs based on their association with mitochondrial and non-mitochondrial mechanisms of toxicity. There was not any notable trend between two groups based on drug label.

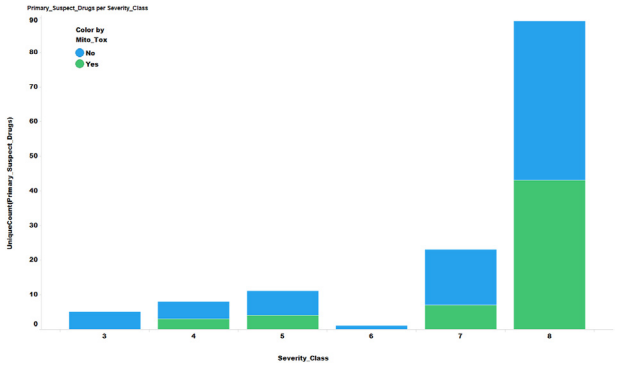

Figure 5 Categorization based on liver injury severity class for "most-DILI concern" drugs based on their association with mitochondrial and non-mitochondrial mechanisms of toxicity. There was not any notable trend between two groups based on severity class.

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[48]. 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[21], 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: 2.2, 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[59]. 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[58]. The hallmark of mitochondrial aging includes a decreased mitochondrial number, reduced mitochondrial function, and individual electron transport chain activities[13]. 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[21,61]. 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[21,22].

5. Conclusions

Mitochondria play an important part in DILI, including idiosyncratic liver injury. There have been various proposed mechanisms for mitochondrial involvement in DILI[59]. There is a gap in the literature describing the differences in clinical outcomes for patients who experienced DILI from mitochondrial mechanisms of toxicity as compared with non-mitochondrial mechanisms of toxicity drugs. There are limitations in detecting drugs that have mitochondrial liability in the drug development phase of the discovery. For the most part, 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[13]. Therefore, drug-induced mitochondrial toxicity is often idiosyncratic, meaning it is not predictable until a large population is exposed[21,60]. 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 safety 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[8,62]. 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[8].

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, benzbromarone is prescribed for gout, which has six times higher occurrence in males[63]. Similarly, isoniazid and rifampin are prescribed for the treatment of tuberculosis, which has two times higher occurrence in males[64].

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. Supporting information

Supporting data to this article can be found online at https://doi.org/10.1016/j.apsb.2021.05.028.

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