A comparison of drugs that cause injury via mitochondrial or other mechanisms

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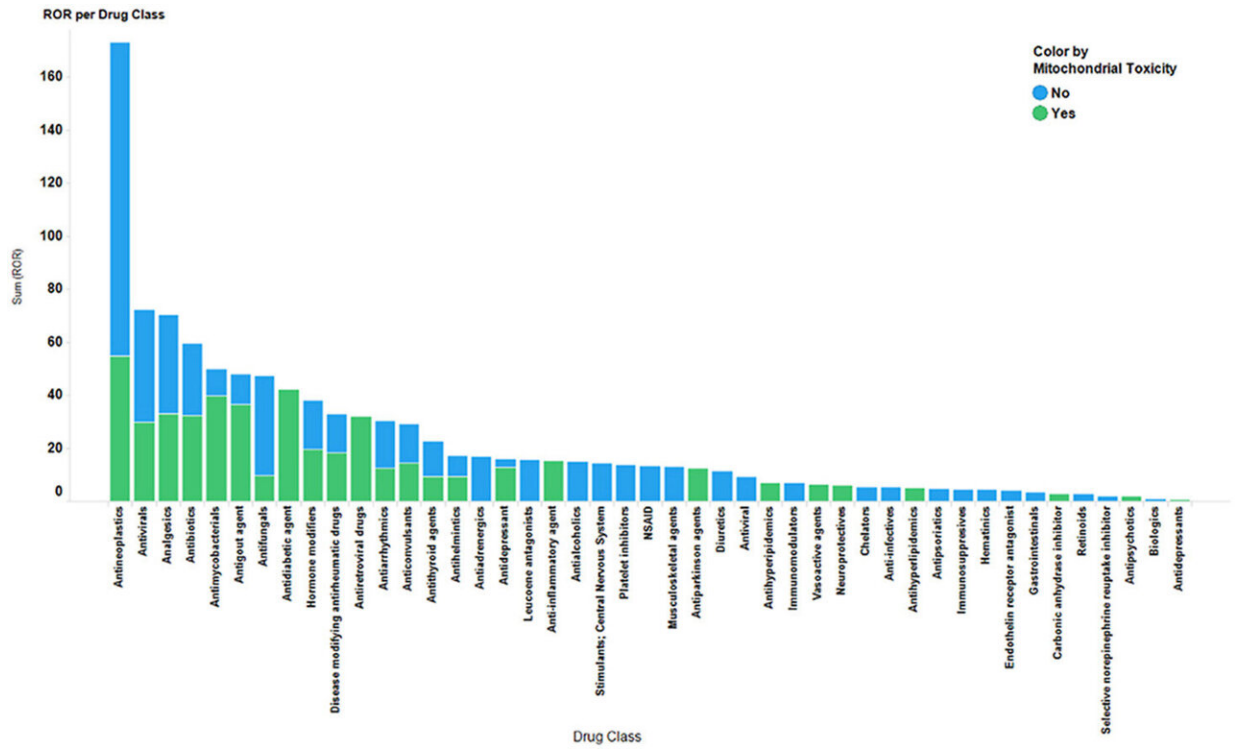

Graphical abstract. In this study, we investigated liver injury reports submitted to the FAERS database and compared the frequency of reports between drugs that can cause hepatotoxicity via mitochondrial mechanisms and those without mitochondrial mechanisms of toxicity. Credit: DOI: 10.1016/j.apsb.2021.05.028

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. In this study the authors 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

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)] (P

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. The authors 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.

More information: Payal Rana et al, Hepatotoxicity reports in the FDA adverse event reporting system database: A comparison of drugs that cause injury via mitochondrial or other mechanisms, *Acta Pharmaceutica Sinica B* (2021). DOI: 10.1016/j.apsb.2021.05.028