Hepatic toxicity, drug failures, comorbidities and regulatory body positions

Hepatic toxicity and drug failure

"DILI is estimated to have an annual incidence of 10 to 15 per 10,000 to 100,000 persons exposed to prescription medications. This makes it costly in terms of not only its toll on humans, but also healthcare expenditures. This prevalence is expected **to increase with the widespread use of dietary supplements**. Of the 2,000 cases of acute liver failure (ALF) that occur in the U.S. each year, medications account for >50%, with 37% of cases attributable to APAP and 13% attributable to idiosyncratic adverse drug reactions." See more at: https://www.uspharmacist.com/article/druginduced-liver-injury-an-overview#sthash.v9KiN5K7.dpuf

Name of medicine (brand name)	Year action taken	Primary safety concerns
Naftidrofuryl oxalate injection (Praxilene)	1995	Cardiotoxicity
Pemoline (Volital)	1997	Liver toxicity
Troglitazone (Romazin)	1997	Liver toxicity
Fenfluramine (Ponderax)	1997	Heart valve disease
Dexfenfluramine (Adifax)	1997	Heart valve disease
Sertindole (Serdolect)*	1998	Disorders of heart rhythm
Tolcapone (Tasmar)†	1998	Liver toxicity
Mibefradil (Posicor)	1998	Drug interactions
Trovafloxacin (Trovan)‡	1999	Liver toxicity
Grepafloxacin (Raxar)	1999	Disorders of heart rhythm
Pulmonary surfactant (Alec)	2000	Increased mortality
Cisapride (Prepulsid)	2000	Disorders of heart rhythm
Droperidol (Droleptan)	2001	Disorders of heart rhythm
Cerivastatin (Lipobay)	2001	Muscle toxicity
Levacetylmethadol (Orlaam)	2001	Cardiac arrhythmias
Kava kava	2003	Liver toxicity
Rofecoxib (Vioxx)	2004	Myocardial infarction/stroke
Valdecoxib (Bextra)	2005	Serious skin reactions

* Sertindole has since been reintroduced under very restricted conditions.

‡ Tasmar, Trovan and Orlaam were licensed through the centralised procedure with the European Commission as the Licensing Authority.

‡ Trovafloxacin was never marketed in the UK.

source of image: UK MHRA

"A drug-drug interaction (DDI) may be defined as the modification of a patient's clinical response to the administered drug by co-administration of another drug…. DDIs are an important and avoidable cause of serious adverse events and can result in early termination of development or withdrawal of drugs from the market.

As polypharmacy is commonplace in many patient populations, the risk of dangerous DDIs is high. For example, in the general population, **DDIs have been considered responsible for 20%-30% of all adverse drug reactions and account for about 10% of visits to emergency departments**.

In hospitalized patients, they represent 3%-5% of medication errors and have been estimated to be the cause of death in 4% of cancer patients, to whom drugs are frequently administered at or close to the maximum tolerated dose. Both transporter- and enzyme-mediated DDIs can significantly alter drug pharmacokinetics and have therefore the potential to affect the therapeutic efficacy or toxicity of drugs."

Palatini et al, World J Gastroenterol 2016 January 21; 22(3): 1260-1278

Diseases and their comorbidities

	Cardiac muscle involvement	Skeletal muscle involvement
COPD	yes	yes
Osteoporosis	yes	yes
Heart disease (s)	-	yes
CVDs	yes	yes
PADs	yes	No
Obesity*	yes	yes
NAFLD	yes	No
NASH	yes	No
Diabetes*	yes	yes
Immune disorders	yes	No
Inflammation*	yes	yes
Glucose metabolism	yes	No
Lipid metabolism*	yes	yes
Metabolic disorders*	yes	No
Asthma	No (more CVD)	No
Pulmonary fibrosis	yes	No
Dermatitis	yes (more lifestyle based)	No
Psoriasis*	yes	No
Epilepsy	yes	yes (linked to Arthritis)
Parkinsons*	yes	yes
Restless legs syndrome	yes (secondary type - hypertensive)	Inconclusive
RA	yes	yes
Axial spondyloarthritis	yes	yes
Psoriatic arthritis	yes	yes
Crohns disease	yes	yes
Lupus	yes	yes (secondary to vasculature)
Juv. Idio. arthritis	yes	yes (secondary to cardiac)
CDK	yes	yes
Sarcopenia	yes	-
Cancer (cachexia)**	yes	yes
NSCLC	yes	yes
PDAC	yes	yes
HCC	yes	yes
Prostate	yes	yes
Renal	yes	yes
Multiple Myeloma	yes	yes
Bladder	yes	yes
Tongue	yes	yes
Lung	yes	yes
Rhabdomyosarcoma	yes	yes
Esophegeal	yes	yes
HNSCC	yes	yes
Colorectal	yes	yes

**liver damage also a comorbidity, or higher frequency of adverse drug event*

*** Cachexia has been recognized for a long time as an adverse effect of cancer. Considering that one in four people will die of cancer, and that cachexia affects most patients with advanced disease, it is very common. The prevalence of cancer anorexia-cachexia depends greatly on the type of cancer, but 50% to 85% of subjects with gastrointestinal, pancreatic, lung, and colorectal cancer have weight loss when they are diagnosed and before they begin treatment. In the United States alone, it has been estimated that over 1.3 million people have cancer anorexia-cachexia. Cancer anorexia-cachexia is directly responsible for 20% of all cancer deaths, contributing to more than 7.4 million deaths worldwide each year.*

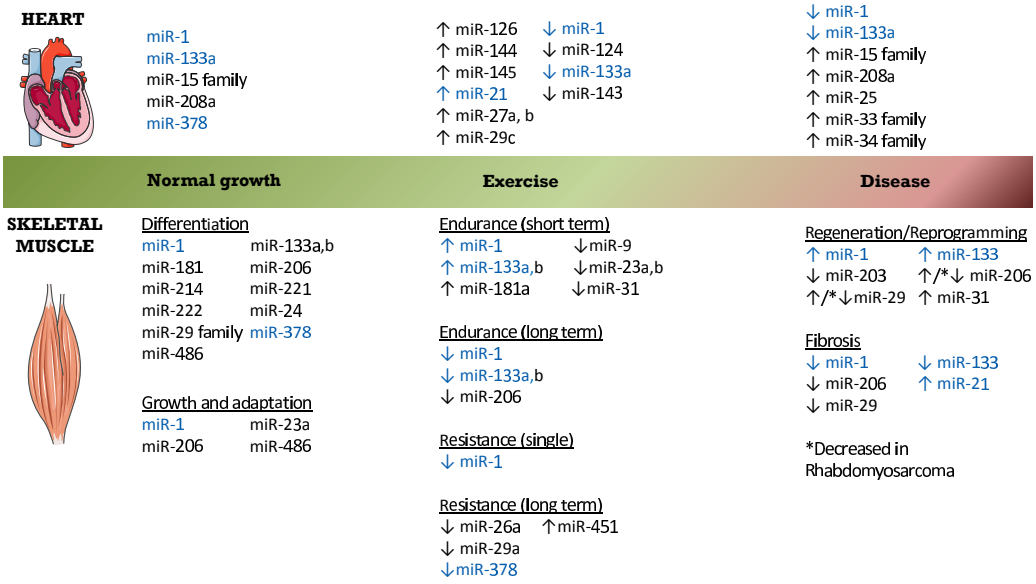

image source: Winbanks et al, Proc. Austra. Physio. Soc. 2014, 45;1-13

MicroRNA measurement considered by EMA as a promising 'Marker candidate' for DILI

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 September 2016
EMA/423870/2016
Executive Director

Letter of support for drug-induced liver injury (DILI) biomarker

Summary

The Drug-Induced Liver Injury (DILI) work package 3 (WP3) of the SAFE-T consortium specifically aimed to address the current lack of sensitive and specific clinical tests to diagnose, predict and monitor drug-induced injury to the liver, which is a major hurdle in drug development.

*"The parameters total HMGB1, total and caspase-cleaved keratin 18**, miR-122** and GLDH **have the potential to be used as clinical safety biomarkers that sponsors may choose to incorporate in clinical trials** with compounds having suspected intrinsic liver toxicity in order to potentially improve the early (within 24 hours) prediction of the occurrence of liver injury."*

"The following parameters have potential as clinical DILI biomarkers that sponsors may choose to incorporate into their clinical trials to assess whether they provide additional information beyond the diagnostic value of ALT and TBIL. Currently available data indicate that the potential for diagnostic value is related to the following mechanism of pathophysiology/pathogenesis of DILI:

*a) CK18, **miR-122**, total HMGB1, GLDH, and SDH for hepatocyte necrosis b) ccCK-18 for apoptosis c) hyperacetylated HMGB1 and MCSFR1 for immune activation. The presented results are considered exploratory in nature. For the time being, **the proposed markers have to be considered marker candidates (albeit promising)** for the potential contexts of use."*