Truths and Myths Surrounding Drug Induced Liver Injury: Prescription, OTC and Holistic Therapies

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Importance of Drug-Induced Liver Injury (DILI)

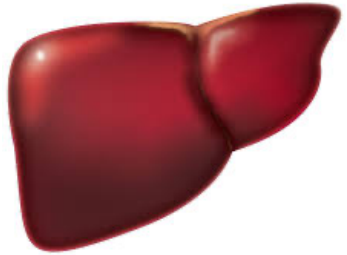
- The liver is responsible for concentrating, metabolizing and eliminating most drugs and toxins
- Target organ for serious adverse effects of drugs
- DILI responsible for ~3-10% of acute liver injury in the US
- Single, major cause of acute liver failure
- Common cause for withdrawal or restriction of use of an approved medication
  - Troglitazone, bromfenac, trovafloxacin, bosentan, telithromycin, lumiracoxib, ximelagatran, tolvaptan
- Common cause for a medication to be abandoned during drug development

Drugs Which Are Hepatically Metabolized Are More Hepatotoxic

Compounds	Proportion of Compounds Causing				
	ALT > 3 ULN (n=61)	Jaundice (n=93)	Liver Failure (n=49)	Liver Transplant (n=15)	Fatal DILI (n=39)
Extensive hepatic metabolism	34%	43%	28%	9%	23%
Without extensive hepatic metabolism	10%	34%	9%	1%	4%
P-value	0.007	0.2	0.001	0.45	0.0003

Lammert C, et al. *Hepatology*. 2009.

Acetaminophen, aspirin, niacin, many antineoplastic agents



Isoniazid, troglitazone, amoxicillin/clavulanic acid, minocycline, diclofenac

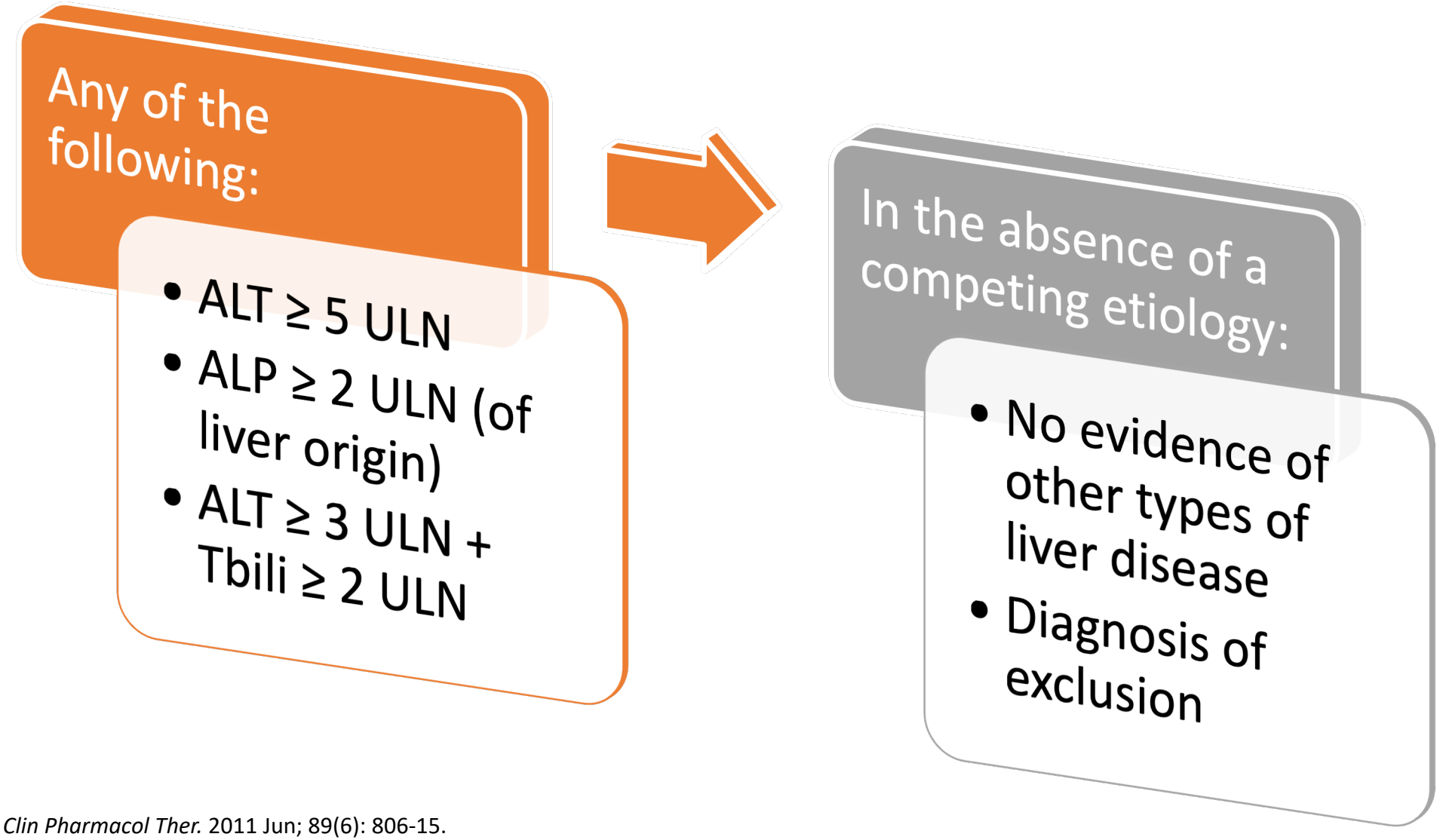
Direct Hepatotoxicity

- Intrinsically hepatotoxic agent
- Injury is frequent (1-100%)
- Dose-related
- Reproducible in animal models
- “Expected”

Idiosyncratic

- Not inherently hepatotoxic
- Rare (1:1000-1:1,000,000)
- Not dose related
- Not reproducible in animals
- “Unexpected”

Clinical Chemistry Criteria for DILI



Aithal GP et al., *Clin Pharmacol Ther.* 2011 Jun; 89(6): 806-15.

Pattern of Liver Injury

	Hepatocellular	Cholestatic	Mixed
ALT	≥ 2x	Normal	≥ 2x
ALP	Normal	≥ 2x	≥ 2x
ALT:ALP “R"	High, ≥ 5	Low, ≤ 2	2-5
Examples	APAP (Acetoaminophen) Allopurinol Amiodarone HAART NSAID Diclofenac Isoniazid	Anabolic steroid Chlorpromazine Clopidogrel Erythromycin Contraception	Amitryptyline Enalapril Carbamazepine Sulfonamide Phenytoin
	➡ acute liver failure	➡ vanishing bile duct syndrome	

Causality in Drug Induced Liver Injury

- DILI is a diagnosis of exclusion
- Compatible history
- Negative tests for hepatitis A, B, C and E
- Absence of alcoholism, shock, autoimmunity
- Imaging studies of liver and biliary tree
- Known cause and compatible signature
- No specific tests to prove causality

Top 10 Therapeutic Classes and Individual Agents Causing DILI in the USA (N=899)

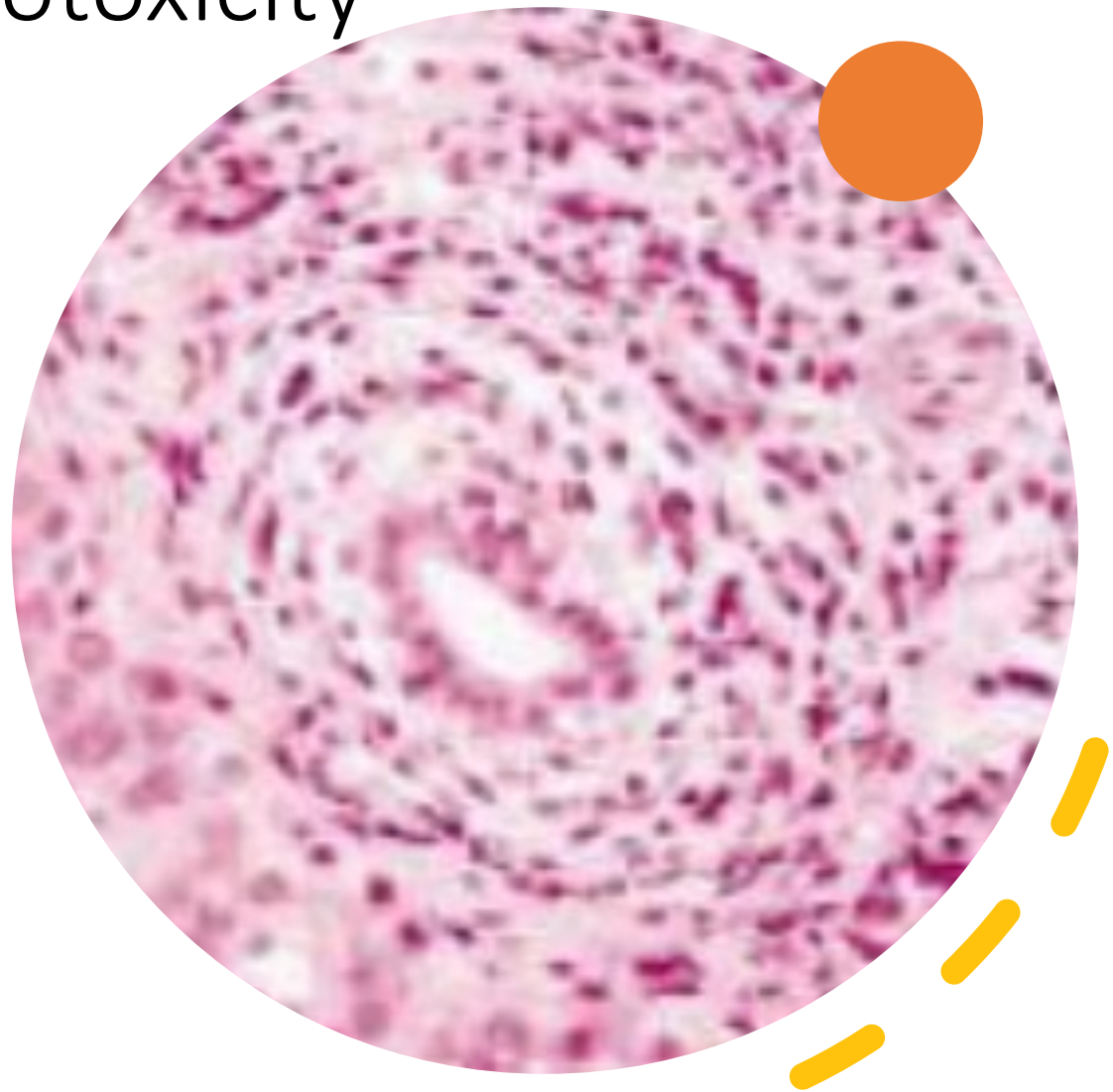
	Therapeutic Class	n
1	Antimicrobials	408
2	Herbal and dietary	145
3	CVS agent	88
4	CNS agents	82
5	Anti-neoplastics	49
6	Analgesics	33
7	Immunomodulatory	27
8	Endocrine	20
9	Rheumatologic	13
10	Gastrointestinal	12

	Individual Agent	n
1	Amox-Clavulanate	91
2	INH	48
3	Nitrofurantoin	42
4	TMP/SMX	31
5	Minocycline	28
6	Cefazolin	20
7	Azithromycin	18
8	Ciprofloxacin	16
9	Levofloxacin	13
10	Diclofenac	12

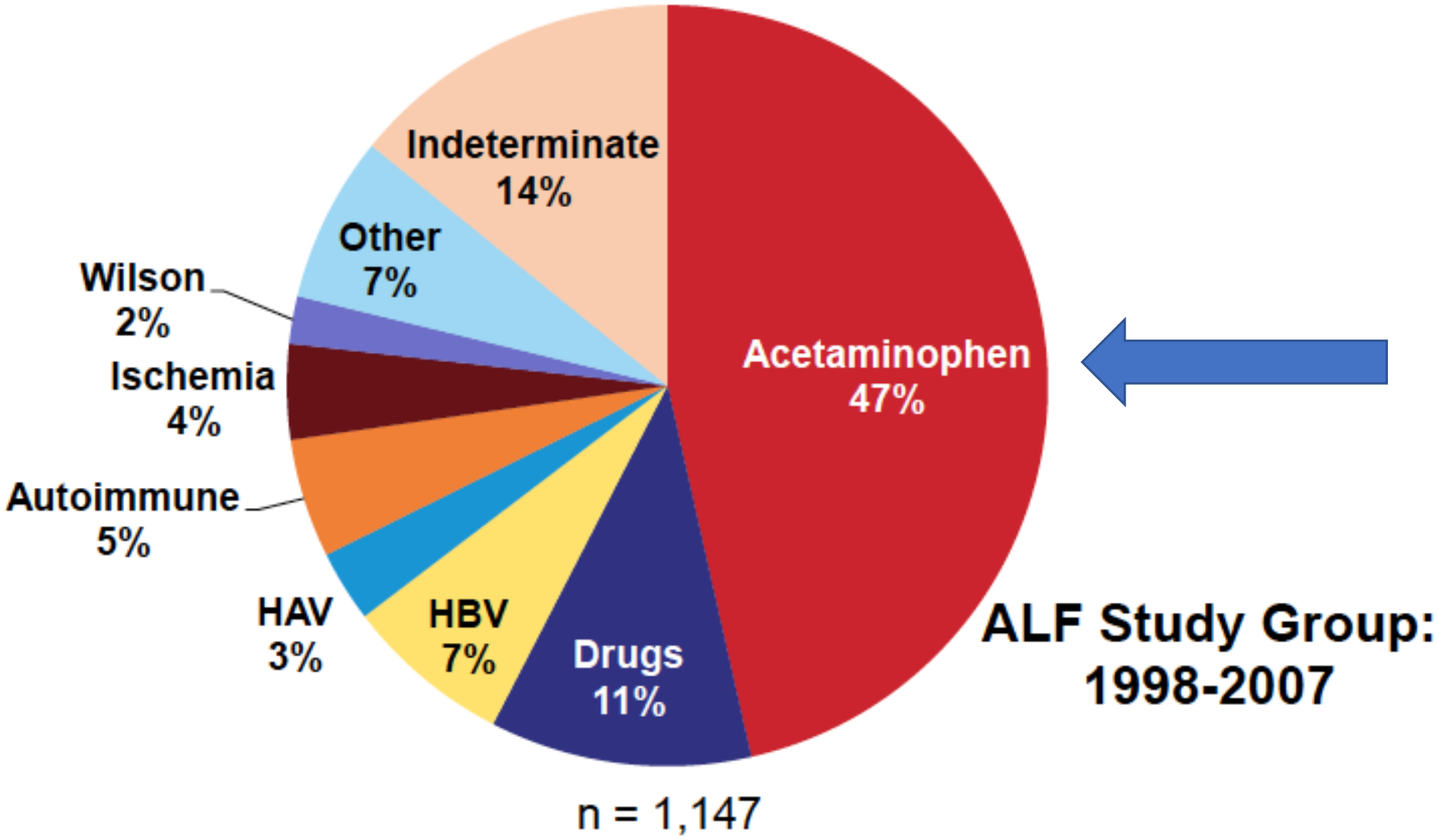
Chalasani N, et al. for the US DILIN. *Gastroenterology*. 2015.

Amoxicillin/Clavulanate Hepatotoxicity

- Amoxicillin/clavulanic acid is one of the most prescribed antibiotics for URI
- Mild, reversible elevation of ALT is noted in 2-3% of those treated
- Serious hepatotoxicity occurs with an incidence of 1:56-78,000 prescriptions written
- Hypersensitivity features including rash and eosinophilia are seen in 40-60%
- Associated with HLA haplotypes: DRB1*07:01-DQB1*03:03; DRB1*15:01-DQB1*06:02



Etiology of Acute Liver Failure



Acetaminophen

- Available in the US as OTC since 1960
- One of most used meds in US: >25 billion doses sold/year
- Recommended oral dose is
  - Adults: 660-1000 mg every 4-6 hours, not exceeding 3 g/day
  - Children: <75 mg/kg/day
- Frequent component in OTC combinations with decongestants and antihistamines and in combo prescription pain medications
  - Patients unknowingly ingest acetaminophen through multiple products

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Acetaminophen. [Updated 2016 Jan 28]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548162/

Acetaminophen and DILI

- Chronic therapy of 4 g/day led to transient elevations in AST/ALT (>3x ULN) after 3-7 days in 39% of individuals.
- Acetaminophen overdose intentional or unintentional) can lead to acute, serious hepatocellular injury.
  - Generally starts 24-72 hours after ingestion with marked elevations in ALT and AST
  - After 48-96 hours, clinical symptoms such as jaundice, confusion, hepatic failure appear
  - Renal insufficiency also common
  - AST/ALT fall promptly, and recovery is rapid if injury not too severe

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Acetaminophen. [Updated 2016 Jan 28]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548162/

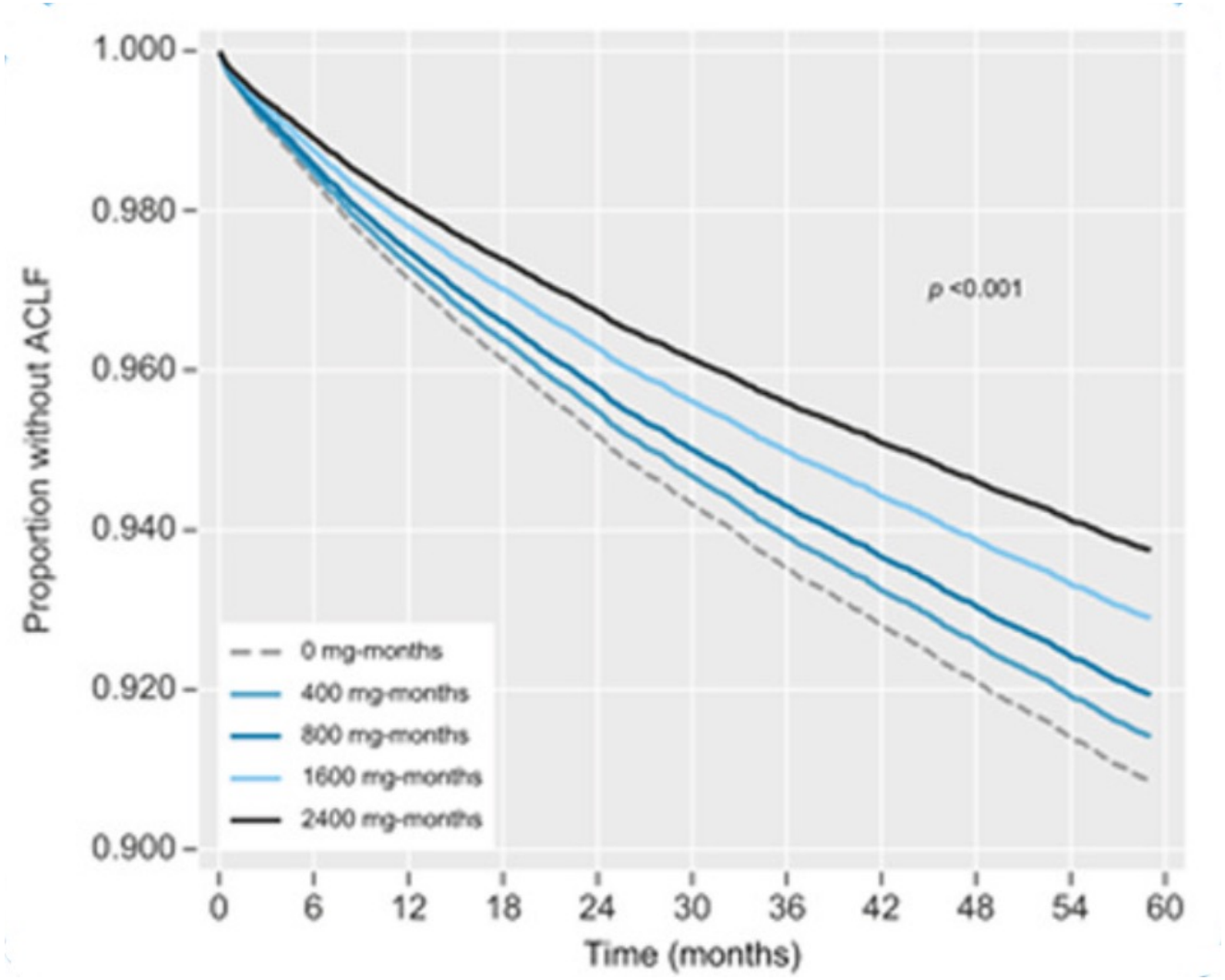
HMG-CoA Reductase Inhibitors (Statins): Bad for the Liver? No!

- ALT >3xULN is seen in 1-%, class effect, dose-dependent, typically transient
- Clinically significant liver injury extremely rare 0.001%!
- Individuals with underlying liver disease are NOT at increased risk for statin hepatotoxicity
- Variable presentation, both hepatocellular and cholestatic. Rarely, autoimmune like, with long latency
- Liver chemistry tests SHOULD NOT be routinely obtained in the absence of symptoms of liver dysfunction (FDA 2012)

Russo M, for the US DILIN. *Hepatology*. 2014; 60: 679-686; Newman B, ATVB 2019

Role of Statins in Acute-on-Chronic Liver Disease (ACLF)

- Of 84,963 US veterans with cirrhosis, 8,558 (10.1%) were hospitalized with ACLF.
- Binary statin exposure was associated with a 38% reduced hazard of developing ACLF.
- Increasing dose exposure was associated with a progressively reduced hazard of ACLF.



Mahmod, *Journal of Hepatology* 2022

Herbal and Dietary Supplements

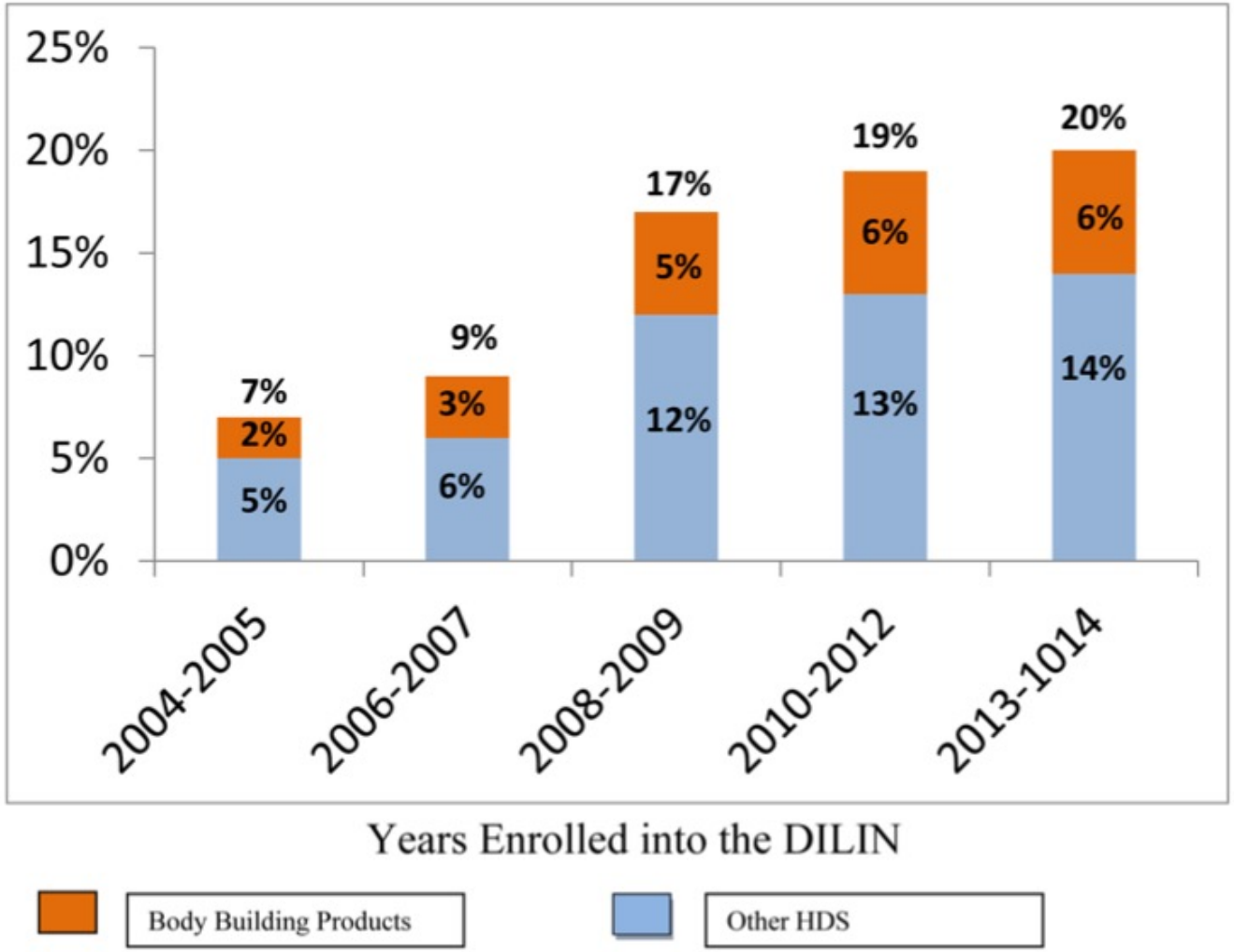
HDS

Herbal and Dietary Supplements

- Not regulated as drugs or subjected to rigorous assessment of efficacy and safety by US.
- Past: Single botanical entities (ginseng, saw palmetto, turmeric) with long history on market
- Current: 68% are now multi-ingredient products containing botanicals, vitamins, minerals and other nutrients.
- Widely used for obesity, fatigue and complications of aging.
- Chemical analyses show product labels are often inaccurate and many contain unlisted substances and not the listed ones.
- Implicated in ~20% of US DILI cases.

Navarro V et al., *Hepatology* 2017; 65(1): 363-73. Navarro V et al., *Hepatol Commun* 2019; 3(6): 792-794.

Proportion of DILI Cases Due to Herbal and Dietary Supplements (HDS)



Navarro V et al., *Hepatology* 2017 January; 65(1): 363-373.

Hydroxycut: “America’s #1 Selling Weight Loss Brand”

- History
  - 2004: Hydroxycut products containing ephedra (from plant genus Ma Huang) were withdrawn from US due to cardiovascular risks
  - 2009: More Hydroxycut products removed due to hepatotoxicity (hepatocellular pattern)
- Now
  - Contain vitamins, probiotics and “extracts”

Ephedra

FDA Prohibits Sales of Dietary Supplements Containing Ephedra

On February 9, 2004, the Food and Drug Administration (FDA) issued a final rule prohibiting the sale of dietary supplements containing ephedrine alkaloids (ephedra) because such supplements present an unreasonable risk of illness or injury. The rule will become effective in 60 days. In addition, FDA reiterates its advice that consumers stop using ephedra products immediately.

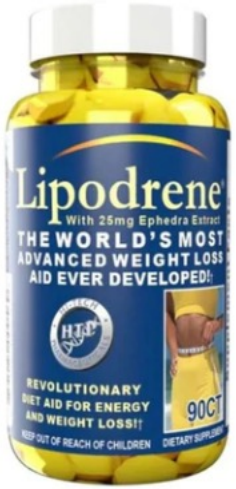
But Are Ephedra Based Products Really Gone? NO!

1. Don't listen to the FDA regarding anything health or nutrition.
2. Eat healthy and exercise 30 minutes a day (an hour or two if you are a bad ass).
3. Supplement with a diet pill for absolute maximum weight loss.

There you go, three short sentences, and you can break the fit – fat cycle forever.

The short story is that **ephedra is still legal to be sold as a supplement, but ephedrine alkaloids are not.**

So Hi-Tech Pharmaceuticals is removing the banned alkaloids from the ma huang plant, then legally selling it in fat burner supplements.



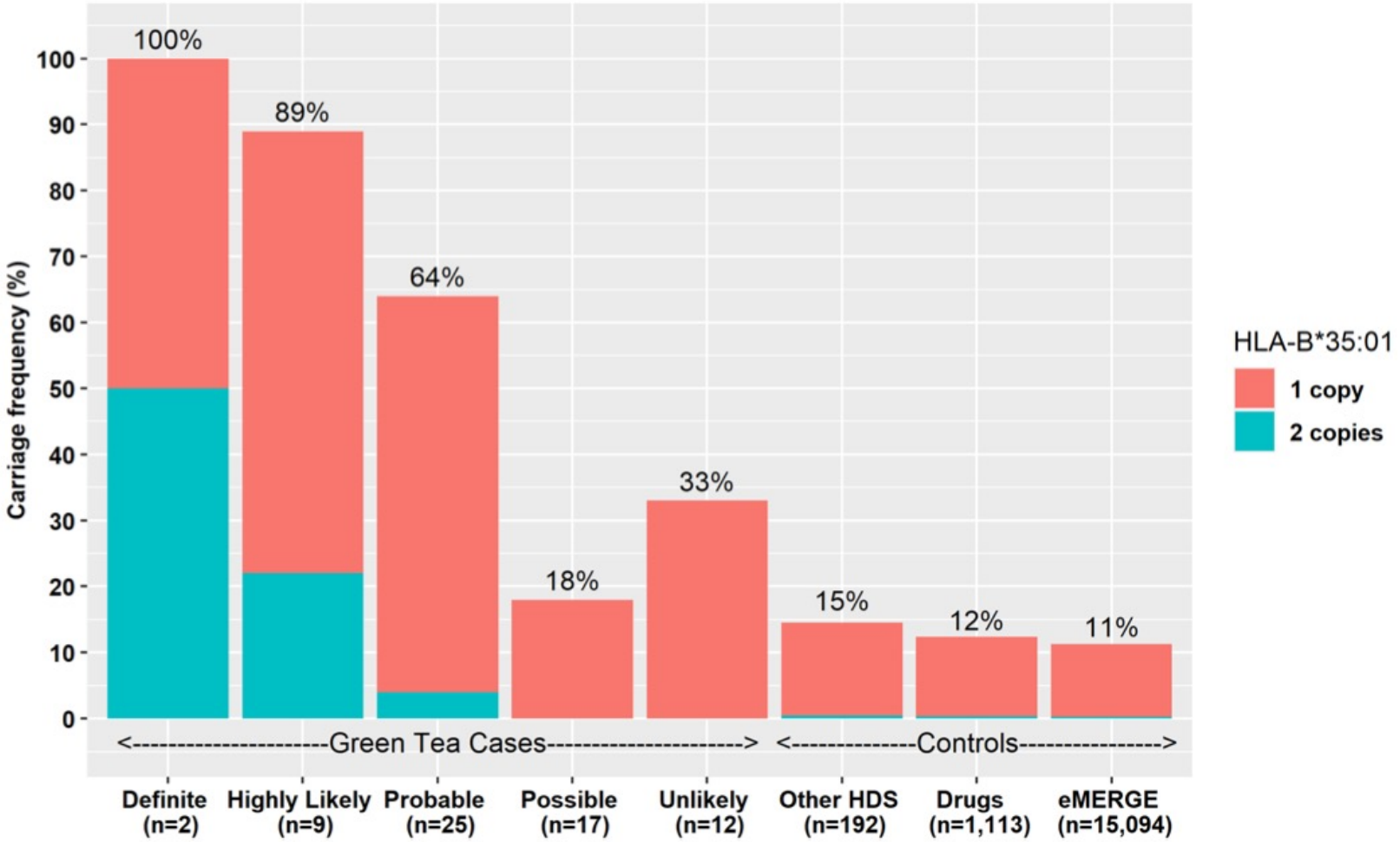
www.ephedraoutlet.com; blog.priceplow.com

Green Tea: Good or Bad for Your Liver?

- Drinking green tea
  - No association with liver injury ; regular use is associated with lower ALT and AST
- Green tea extract (GTE) (*Camellia sinensis*)
  - Ingredient in many weight loss agents (e.g., Hydroxycut, Dexatrim, Slimquick)
  - Potential for GTE to cause hepatotoxicity but very rare
  - Present with acute hepatitis-like syndrome and hepatocellular pattern
  - Close association of liver injury from GTE with HLA allele B*35:01 (immunologic etiology).
  - HLA association, lack of dose dependency and recurrence of injury on reexposure: Idiosyncratic toxicity.
  - Area of active research

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Green Tea. [Updated 2020 Nov 20]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547925

Hepatotoxicity of Green Tea Extract Linked to HLA-B*35:01



Hoofnagle JH et al., *Hepatology*. 2021 June ; 73(6): 2484–2493. doi:10.1002/hep.31538.

Milk Thistle (Silybum Marianum): Good or Bad for Your Liver?

- Herb native to Mediterranean region used for centuries to treat liver conditions.
- Extracts of milk thistle seeds contain silymarin.

- Helpful to Liver? *Probably Not.*
  - Cell culture and animal model data silymarin was shown to prevent or ameliorate acute liver injury.
    - Controlled trials in hepatitis C and in NAFLD found no benefit.
- Hurtful to Liver? *Probably Not.*
  - Widespread use in patients with and without liver disease.
  - No implication in causing serum enzyme elevations or acute liver injury.

Wikipedia image.

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Milk Thistle. [Updated 2020 Jan 21]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548817/

Herbals & Acute Hepatitis

- Ramachandran R and Kakar S, *J Clin Pathol* 2009; 62:481-492.

Herbal products with known hepatotoxicity

Herbal product10 11	Intended use	Biopsy findings
Chaparral leaf (creosote bush, *Larrea tridentata*),12 teas and capsules	Antimicrobial, anti-aging, skin conditions	Acute hepatitis, cholestasis, hepatocellular necrosis
Germander (*Teucrium* genus),13 14 teas and tablets	Antiseptic, antipyretic, abdominal ailments, obesity	Acute hepatitis, centrizonal necrosis, rarely chronic liver disease with cirrhosis
Pennyroyal (*Mentha pulegium*, *Hedeoma pulegioides*),15 "squaw mint" oil	Emmenagogue, abortifacient, anti-flea agent for pets	Centrizonal necrosis
Glue thistle (*Atractylis gummifera*),16 found in Mediterranean region and North Africa	Emetic, diuretic, antipyretic	Centrizonal necrosis, panacinar necrosis
Jin bu huan (*Lycopodium serratum*),17 marketed as anodyne tablets in 1990s	Sleeping aid, analgesic	Acute hepatitis, chronic hepatitis, microvesicular steatosis
Kava (*Piper methysticum*)2 18	Stress relief, anti-anxiety, sleeping aid, premenstrual syndrome	Acute hepatitis, fulminant hepatitis
Mistletoe (*Phoradendron* and *Viscum geni*)19	Digestive aid, heart tonic, sedative	Acute hepatitis

Drug-Induced Liver Injury Summary

- Most drug-induced liver injury is idiosyncratic and unpredictable
- A wide spectrum of clinical and histological manifestations may result from DILI
- Underlying liver disease may predispose to injury from some, but not all drugs. Predisposing risk factors.
- A high index of suspicion is needed to diagnose drug-induced liver injury. Timeline of exposure
- Known potential for hepatotoxicity of the implicated drug
    - Best resource is NIDDK: **LiverTox website**
    - Up to date information on prescription, OTC and herbal/dietary supplements
        - https://www.ncbi.nlm.nih.gov/books/NBK547852/