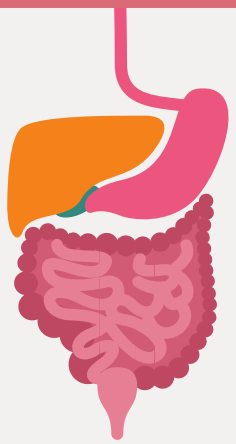
hepatotoxic drugs



= Important!

Objectives:

- Define the role of liver in drug detoxification
- Discuss the types (patterns) of hepatotoxicity
- Classify hepatotoxins
- Explain how a drug can inflict hepatotoxicity
- State the pathological consequences of hepatic injury
- Contrast the various clinical presentation of hepatotoxicity
- Enlist the possible treatment

Done by:

Editing file

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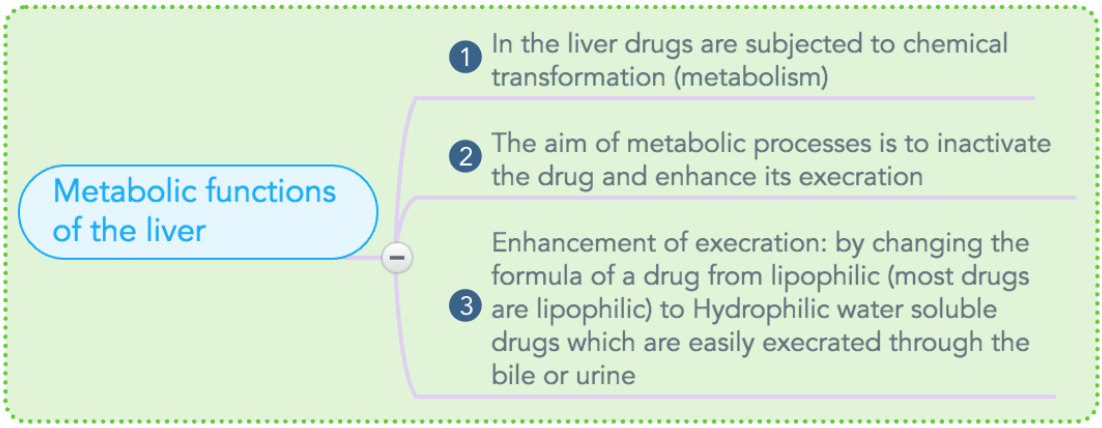
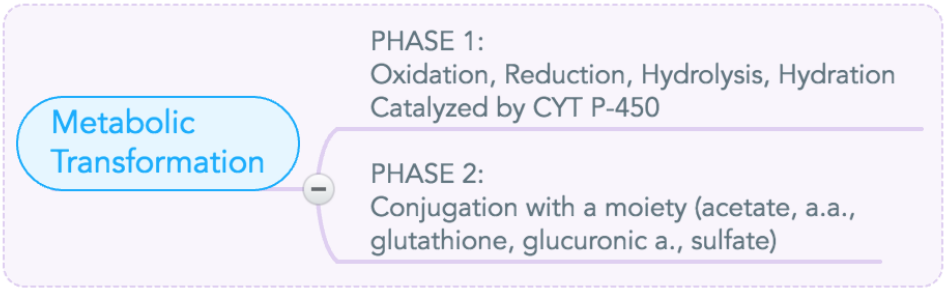
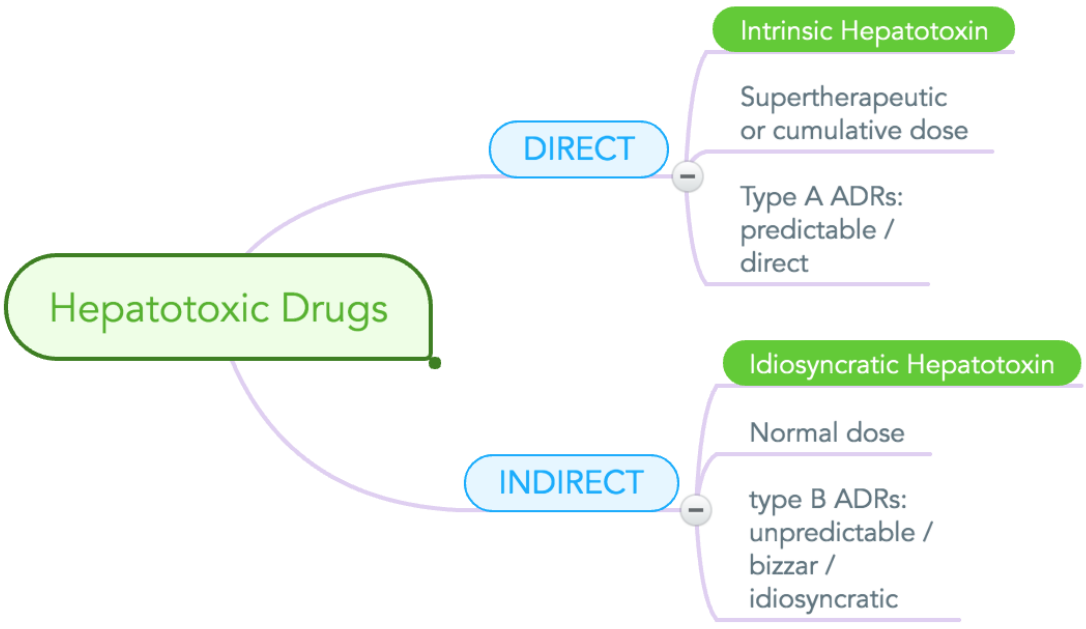
Drugs names | Doctors notes | Important | Extra

« باذلًا وسعي في استنقاذها من الهلاك والمرض، والألم والقلق »

Mind Map







If you really don't have time, slides **5, 8, 9** & **10** are the most important to know.

To understand better

Functions of liver

1-Regulation, synthesis & secretion

utilization of glucose, lipids & proteins + bile for digesting fats.

2-Storage

Glucose (as glycogen), fat soluble vitamins (A, D, E & K) & minerals .

3-Purification, transformation & clearance

of endogenous (steroid hormones, cholesterol, FA, & proteins..) & **exogenous** (**drugs**, toxins, herbs…etc) chemicals.

Liver Subjects drugs to chemical transformation (METABOLISM)

↓

to become inactive & easily excreted. Since most drugs are lipophilic

↓

they are changed into hydrophilic water soluble products

↓

suitable for elimination through the bile or urine

↓

This metabolic transformation occur in 2 PHASES

Phase I reactions (modification)

- Oxidation, Reduction, Hydrolysis, Hydration
  Catalyzed by **CYT P-450**
- Produce active metabolites
  polar, transient, usually highly reactive
  far more toxic than parent substrates
  may result in liver injury
  Drug-Induced Liver Injury (**DILI**)

Phase II reactions (conjugation)

- With moiety (acetate, a.a., glutathione, glucuronic acid , sulfate)
  - attachment of small polar endogenous molecule such as glucuronic acid, sulfate, or glycine to form water-soluble compounds.
  - *The addition of large anionic groups detoxifies reactive electrophiles and produces more polar metabolites that cannot diffuse across membranes, and may, therefore, be actively transported.
- Products of increased solubility
  - If of high molecular weight ➔ excreted in bile.
  - If of low molecular weight ➔ to blood ➔ excreted in urine.

To understand better

Human body identifies almost all drugs as foreign substances i.e. **Xenobiotic** → The body has to **get rid of them mainly by the liver** → **Metabolic clearing house**

Hepatotoxicity

Hepatotoxic drugs are the Leading cause of ADRs (adverse drug reactions)

Why the liver is the major site of ADRs ?

- It is the first organ to come in contact with the drug after absorption from the GIT.
- Being the metabolic clearing house of the body ➔ it expresses the highest levels of drug metabolizing enzymes that converts some drugs (PROTOXINS) into **intermediate (TOXINS)** (result from phase I) before being conjugated (phase II) for elimination
- Drug (Pro-toxin) ➔ Toxin ➔ Injury
- **Paracetamol** ➔ ***CYT P450*** ➔ **NABQI** centrilobular liver necrosis. ***(NAPBQI)*** *: N-acetyl-p-benzoquinone imine.* → paracetamol causes liver toxicity in large doses.
- Injury / damage of the liver Caused by exposure to a drug Inflict varying impairment in liver functions Manifests clinically a long range hepatitis ➔ failure

  (Inflammation ➔ Apoptosis ➔ Necrosis)

Can any drug cause liver-related ADRs?

Not all drugs do …
Drugs that can cause ADRs in the liver (hepatotoxicity are called **HEPATOTOXIN**)

Toxicity potential of the drug

- Chemical composition of the drug itself
- Nature of its reactive metabolite → its state after phase I
- Conjugation reactions linked to it & their availability
- Mitochondrial effects of the drug
- Drug formulation (Long-acting drugs)

Nature of a Hepatotoxin (Hepatotoxic Drug)

intrinsic hepatotoxin

Direct hepatotoxicity.

Inflicted by:

Super-therapeutic[1] or **cumulative**[2].

belong to type **A** ADRS **: predictable / direct.**

type **A** ADRS: drug side effect which is **predictable**.
E.g.: **warfarin** may cause bleeding in large dose →
Related to **pharmacological effect**.

idiosyncratic hepatotoxin

Indirect hepatotoxicity.

Inflicted by:

Normal dose.

belong to type **B** ADRS: **bizzar / unpredictable / idiosyncratic**

type **B** ADRS: **unpredictable** side effect, may happened because of hypersensitivity.
e.g. chlorpromazine, it SMTM causes cholestatic jaundice.
Don't related to pharmacological actions.

[1] Super-therapeutic dose: the toxicity is related to overdose.

[2] Cumulative dose: the toxicity is related to repeated doses of the drug.

1- DIRECT hepatotoxicity

- **Type A: Dose-dependent** hepatotoxicity.
- Caused by intrinsic hepatotoxin.

Cumulative Dose/effect = for long time	**Amiodarone.** (antiarrhythmic) **Oral contraceptives**
Increased Dose	**Acetaminophen. (paracetamol)** **Salicylates** **(all 3 are NSAIDs)** **Statins** (Hyperlipidemia)
BOTH	**Methotrexate** (anticancer) **Alcohol**

ماراح نسألكم مين اللي يسوي الهيباتوتوكسستي بال cumulative or incresed dose or both

2- INDIRECT hepatotoxicity

- **Type B: Dose-independent** hepatotoxicity.
- Caused by idiosyncratic hepatotoxin. (bizzar)

a- Hypersensitivity or immuno-allergic reactions

A drug or its metabolite binds to hepatic membranes or proteins ➔ act as hapten to induce a variety of immune reactions

Inflammatory cholestasis (bile stagnation)	Viral hepatitis-like pattern
Chlorpromazine (antipsychotic) **Chlorpropamide**. Oral hypoglycemic for DM **Erythromycin**.	**Isoniazid.** TB **Phenytoin.** antiepileptic **Methyldopa.** Parkinson

b- Metabolic-idiosyncratic reactions

The metabolite of the offending drug **interferes with hepatic metabolism** as that of bilirubin or protein synthesis…etc

Interfere with bilirubin metabolism	Interfere with protein synthesis
Erythromycin **Rifampicin**	**Corticosteroids** **Tetracycline**

N.B. Not all drugs fall neatly into one of these categories, and overlapping mechanisms may occur with some drugs. e.g. Erythromycin

How can a drug induce hepatotoxicity?

المعلومات هذي خاصة بمواد ثانية، مو مادتنا ☺

- Drug or its reactive metabolites can form covalent bonds with target molecules or alter the target molecule by non-covalent interactions or both.

Covalent interactions:	Non-covalent interactions
A type of chemical bond involving the sharing of electrons between atoms in a molecule (**stronger**). ○ It is adduct formation between the metabolite of the drug & cellular macromolecules ○ **If covalent binding to protein ➔ immunogenic reaction.** ○ **If binding to DNA ➔ carcinogenesis.**	**Weaker** than the covalent. ○ **Lipid peroxidation ➔ generation of cytotoxic oxygen radicals.** ○ **Impairment of mitochondrial respiration.** ○ **Depletion of GSH reactions ➔ oxidative stress.** ○ **Modification of sulfhydryl groups ➔ impair Ca^{2+}homostasis.** ○ **Protein synthesis inhibition**

Do hepatotoxins cause liver disease in all person?

- Most hepatotoxins cause liver disease only in certain persons

depending on:

Environmental host factors	Host genetic makeup
○ **Race** ○ **Age** ○ **Sex** ○ **Nutritional status** ○ **Drugs** ○ **Concomitant habits** ○ **Diseases**	○ **Metabolizing Enzymes** ○ **Detoxifying System** ○ **Drug Transport**

Hepatotoxic drugs (drug- induced liver "hepatic" injury ➔ **DIHI**)

Is DIHI common?

- **Incidence of DIHI:**
  Drugs produce about **10%** of all cases of hepatitis in **young adults** and **40%** of cases in patients **older than 50 years**.

Hepatotoxins

Are certain persons or population more susceptible?

- **Upon exposure to hepatotoxins people are categorized as:**

1- Tolerators	3- Susceptibles
No injury	Develop overt symptoms depending on existing predisposing factors.
2- Adaptors	**4- In threat**
Mild transient injury but adapt	DILI accelerates beyond initial target due to loss of synthetic & clearance function of hepatocyte with recruitment of inflammatory cells, provoke apoptosis & necrotic signals. Liver transplant الحالة هنا خطيرة جدًا! ممكن نحتاج لل

Presenting manifestations

- **Individual drugs tends to have characteristic signature composed of:**

1- Latency period

2- Clinical pattern

3- Pathological finding

1- Latency period

- Short (hrs/days)
- Intermediate (1-8ws)
- Long (1-12ms)

In **direct dose dependent** hepatotoxicity:

Latent period is **short** as it occurs after a threshold of toxicity is reached

→ **Acetaminophen** (**toxic dose**)

In **Direct cumulative** (taken for long time) or In **Indirect Immunoallergic Idiosyncratic** Hepatotoxicity:

Latency period is **Intermediate** but may continue to **evoke even after drug withdrawal** → **Amiodarone** (**cumulative**)/ **phenytoin**, **isoniazid** (**idiosyncratic**)

In **indirect metabolic idiosyncratic** hepatotoxicity

latency period → usually **long** → unpredictable → most problematic → tetracycline, oral contraceptives.

2- Clinical pattern

- The clinical presentation could be of variable intensity, ranging from **asymptomatic** ↑ of liver enzymes → **fulminant hepatic failure** (e.g. paracetamol)

Some drugs just **induce**: المريض ما تظهر عليه أعراض؛ فلو جاء سؤال فيه أعراض كثيرة أكيد هذي الدرقز ماراح تكون السبب

Asymptomatic increase in the enzymes (↑ Amintransferase)

Phenytoin **Statins** **Sulfonamides** **Sulfonylureas**

Other drugs induce → **symptomatic manifestations**

1- If injury targets **hepatocyte** → apoptosis or necrosis → Hepatitis **(cytotoxic) develops**:

- Rapid onset of **malaise**, **severe anorexia** and jaundice.
- ⬆ **Alanine aminotransferase** (**ALT**).

2- If injury targets **biliary system** (canalicular or ductal)
Cholestasis develop:

- **Jaundice** + severe **puritus** predominate
- ⬆ **Alkaline phosphatase** (**ALP**) + hyperbilirubinaemia

4- If injury targets **both hepatocyte & biliary system** → **Mixed type** → ⬆ ALT & ALP

Some Patterns of symptomatic drug-induced liver disease

Very very imp.!

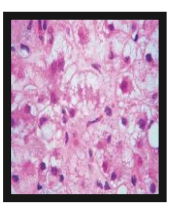
هذا الجدول مهم جدًا، أسئلة الامتحان بتجي معتمدة عليه، بيعطيك الأعراض اللي صارت له (نفس المذكورة هنا) والإنزايمز اللي مرتفعة، مهم مرة تعرفون إن ارتفاع ALT سببه hepatocellular و ALP سببه cholestatic وبعدها بيسألكم أي دواء سبب هذي الأعراض؟ (من الأدوية المذكورة في هالجدول).. عشان تتدربون، افتحوا سلايد ١١ بعد ما تخلصون مذاكرة.

Hepatic injury	Hepatocellular	Cholestatic	Mix
Clinical manifestations	- Flu-like, **malaise** - m. aches **weakness** - Loss of appetite - GIT symptoms - Diarrhea - Jaundice - **urine discolored**	- **Yellowish discoloration of skin** - **Dark urine** - Rash - **Pruritus** - Stool may be light	
ALT (Alanine aminotransferase)	**≥ 3 fold rise**	**Normal** or slight ↑	**≥ 3 fold rise**
ALP (Alkaline phosphatase)	**Normal**	**≥ 2 fold rise**	**≥ 2 fold rise**
Example	ANIA = آنيا - **Acetaminophen** - **NSAIDs** - **Isoniazid** - **Amiodarone**	ChERO - **Chlorpropamide** (DM) - **Erythromycin** - **Rifamycin** - **Oral contraceptives**	PASCa (pasta) - **Phenytoin** - **ACE Inhibitors** - **Sulfonamides** - **Carbamazepine**

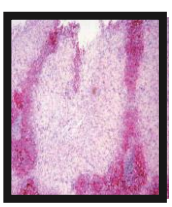
3- Pathological finding

You can skip this ☺

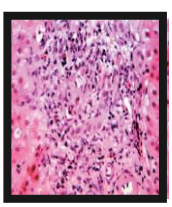
- **No universal histopathological pattern** of DIHI exist.
- **The commonest are:**
  - Hepatocellular necrosis.
  - Cholestasis.
  - Steatosis.
- More than one type of injury may occur in the same patient.
  Any one agent may produce different types of injury in different patients.



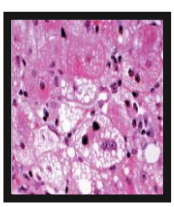
Ballooning & Degeneration of hepatocytes



Centrilobular & midzonal necrosis



Cholistatic injury with damages bile duct



Fatty accumulation

Lines of treatment

Important for SAQs

Immediate withdrawal → of any suspected drug.

No specific treatment → Largely Symptomatic & Supportive

Symptomatic	Supportive
1. **Severe allergic reaction** is observed → Corticosteroids 2. **Pruritus** → enhance bile acid secretion → Colestyramine 3. **Cholestatic liver injury** → ursodeoxycholic acid (Ursodiol) بيجي سيناريو وعنده cholestatic Injury، ايش العلاج؟ أول شيء أشيل من بالي الدواء المسبب، ثانيًا نستخدم ursodeoxycholic acid 4. Coagulopathy or encephalopathy develop → treat accordingly	✓ High carbohydrate ✓ Moderate protein diet ✓ Adequate in calories.

Specific antidotes:

1. Acetaminophen toxicity → N-Acetylcyteine
2. Valproate toxicity → L-Carnitine

Emergency Liver Transplantation → during induced fulminant hepatic failure

Extra summary

For your own knowledge

DISEASE	CAUSE
Tumors	
Angiosarcoma	Vinyl chloride, arsenic, thorium dioxide (radioactive contrast material)
Cholangiocarcinoma	Thorium dioxide
Hepatocellular carcinoma	Vinyl chloride, aflatoxin (produced by *Aspergillus* mold)
Liver cell adenoma	Oral contraceptive pills
Other Liver Diseases	
Acute hepatitis	Isoniazid (caused by toxic metabolite), halothane, acetaminophen, methyldopa
Cholestasis	Oral contraceptive pills (OCPs; estrogen interferes with intrahepatic bile secretion), anabolic steroids (same mechanism as OCPs)
Fatty change	Amiodarone (resembles alcoholic hepatitis; Mallory bodies and progression to cirrhosis), methotrexate
Fibrosis	Methotrexate, retinoic acid, amiodarone

Cases- From doctor's slides

A long standing rheumatoid arthritic patient developed TB 2 months ago. Today she was received in the ER complaining of yellowish discoloration, severe anorexia, vomiting, and flue like manifestations since two days. She is very weak and looks toxic. Her drug history reveals that she has been 4 months ago on cyclosporine to control the arthritic exacerbations. A month ago, she was put on isoniazid when she developed TB and multivitamins because she is weak. Currently she is given domperidone for the emesis. Lab results reveals severe elevation in ALT but no elevation on ALP.

Q1: Which one of the following drugs is the likely cause of her symptoms?

A. Cyclosporine
B. Multivitamins
C. Isoniazid
D. Domperidone

Q2: Which type of Hepatotoxin is considered?

Q3: What is the likely hepatotoxic pattern inflicted by the drug?

A hypercholesterolemic patient was received in the ER complaining of yellowish discoloration of the skin, change in the color of the urine & stools, and severe itching. He has been receiving statins for the long time for the hypercholestrolemia. 3 months ago he was diagnosed as being diabetic and hypertensive and since then he is receiving chlorpropamide for the diabetes and nadolol for the hypertension. The last couple of days he has a flue for which he was given acetaminophen for muscle aches and nasal drops for his nasal stuffiness. Lab investigation shows severe elevation of ALP and no significant elevation in ALT

Q1: Which one of the following drugs is the likely cause of his symptoms?

A. Nadolol
B. Chlorpropamide
C. Acetaminophen
D. Statins

Q2: Which type of Hepatotoxin is considered?

Q3: What is the likely hepatotoxic pattern inflicted by the drug?

Cases- From doctor's slides

Hepatocellular

A long standing rheumatoid arthritic patient developed TB 2 months ago. Today she was received in the ER complaining of yellowish discoloration, *severe anorexia*, *vomiting, and flue like manifestations since two days. She is very weak and looks toxic.* Her drug history reveals that she has been 4 months ago on *cyclosporine* to control the arthritic exacerbations. A month ago, she was put on *isoniazid* when she developed TB and *multivitamins* because she is weak. Currently she is given *domperidone* for the emesis. Lab results reveals *severe elevation in ALT but no elevation on ALP.*

Q1: Which one of the following drugs is the likely cause of her symptoms?

A. Cyclosporine
B. Multivitamins
C. Isoniazid
D. Domperidone

Q2: Which type of Hepatotoxin is considered?

Hypersensitivity or immuno-allergic reactions (indirect)

Q3: What is the likely hepatotoxic pattern inflicted by the drug?

Viral hepatitis-like pattern.

Cholestatic

A hypercholesterolemic patient was received in the ER complaining of yellowish discoloration of the skin, change in the color of the urine & stools, and severe itching. He has been receiving *statins* for the long time for the hypercholestrolemia. 3 months ago he was diagnosed as being diabetic and hypertensive and since then he is receiving *chlorpropamide* for the diabetes and *nadolol* for the hypertension. The last couple of days he has a flue for which he was given *acetaminophen* for muscle aches and nasal drops for his nasal stuffiness. Lab investigation shows severe elevation of *ALP and no significant elevation in ALT*

Q1: Which one of the following drugs is the likely cause of his symptoms?

A. Nadolol
B. Chlorpropamide
C. Acetaminophen
D. Statins

☺ حاطين لكم acetaminophen ، لا تتخدعون
عشان كذا لازم تعرفون الأعراض والإنزايمز زين!

Q2: Which type of Hepatotoxin is considered?

Hypersensitivity or immuno-allergic reactions (indirect)

Q3: What is the likely hepatotoxic pattern inflicted by the drug?

Inflammatory cholestasis

Summary of Types Of Hepatotoxins

	Intrinsic Hepatotoxin	Idiosyncratic Hepatotoxin
Cause	Direct Hepatotoxicity	Indirect Hepatotoxicity
Type	**TYPE A Adrs:** • Predictable / Direct • Dose-dependent Hepatotoxicity	**TYPE B Adrs:** • Unpredictable / Bizzar / Idiosyncratic • Dose-independent Hepatotoxicity
Dose	Supertherapeutic Or Cumulative Dose Of The Drug	Normal Dose Of The Drug
Drugs	**Direct increased dose dependent hepatotoxicity** • Acetaminophen • Salicylates • Statins(Hyperlipidemia)	**Hypersensitivity or immunoallergic reactions** A drug or its metabolite binds to hepatic membranes or proteins ➔act as hapten to induce a variety of immune reactions Inflammatory cholestasis: Chlorpromazine. Chlorpropamide. Erythromycin. Viral hepatitis-like pattern: Isoniazid. Phenytoin. Methyldopa.
	Direct cumulative hepatotoxicity • Amiodarone • Oral contraceptives	**Metabolic Idiosyncratic Hepatotoxicity** The metabolite of the offending drug interferes with hepatic metabolism as that of bilirubin or protein synthesis….etc Interfere with bilirubin metabolism: Erythromycin, Rifampicin Interfere with protein synthesis: Corticosteroids, Tetracycline
	Mixed • Methotrexate • Alcohol	

Some PATTERNS of SYMPTOMATIC drug-induced liver disease "very important !"

Hepatic injury	Hepatocellular	Cholestatic	Mixed
	Flu-like, malaise, m. aches weakness, loss of appetite, GIT symptoms, diarrhea, jaundice, urine discolored,	Yellowish discoloration of skin, dark urine, rash, pruritus, stool may be light	
ALT	≥ 3 fold rise	Normal or slight	≥ 3 fold rise
ALP	Normal	≥ 2 fold rise	≥ 2 fold rise
Examples	○ Acetaminophen ○ NSAIDs ○ Isoniazid ○ Amiodarone	○ Chlorpropamide ○ Erythromycin ○ Rifamycin ○ Oral contraceptives	○ Phenytoin ○ Carbamazepine ○ Sulfonamides ○ ACE Inhibitors

Summary of "What are the presenting manifestations?"

Drug	Individual drugs **tend to have** ➔ CHARACTERISTIC SIGNATURE		
duration	**short (hrs/dys)**	**intermediate (1-8ws)**	**long (1-12ms)**
latency period	Direct dose-dependent Hepatotoxicity ➔ Latency period ➔ SHORT as it occurs after a threshold of toxicity is reached ➔ *acetaminophen* (toxic dose)		
	In Direct cumulative or In Indirect Immunoallergic Idiosyncratic Hepatotoxicity ➔ Latency period ➔ INTERMEDIATE ➔ but may continue to evoke even after drug		
CLINICAL PATTERNS	Some drugs just induce ➔ ASYMPTOMATIC Manifestations ➔ ↑ In aminotransferases Ex. Phenytoin, Statins, Sulfonamides, Sulfonylureas		
	Other drugs induce ➔ SYMPTOMATIC MANIFESTATIONS 1- If injury targets hepatocytes ➔ apoptosis or necrosis ➔ HEPATITIS (cytotoxic) develops ➔ rapid onset of malaise, severe anorexia and jaundice + ↑ in alanine aminotransferases (ALT) 2-If injury targets biliary system (canalicular or ductal) ➔ CHOLESTASIS develop ➔ jaundice ± severe pruritis predominate ➔ ↑ in alkaline phosphatase (ALP) ± hyperbilirubinaemia 3- If injury targets both hepatocytes & biliary system ➔ MIXED TYPE		
lines of treatment	Immediate withdrawal ➔ of any suspected drug		
	No specific treatment ➔ largely symptomatic & supportive Symptomatic: If a severe allergic reaction is observed ➔ Corticosteroids If pruritus ➔ enhance bile acid excretion ➔ Cholestyramine If cholestatic liver injury ➔ Ursodeoxycholic acid (Ursodiol) If coagulopathy or encephalopathy develop Supportive; High carbohydrate, moderate protein diet adequate in calories		
	Specific antidotes N-acetylcysteine ➔ acetaminophen toxicity L-carnitine ➔ valproate toxicity		
	Emergency liver transplantation ➔ for drug induced fulminant hepatic failure		

MCQs

1- The first organ that come intact with the drugs is:
A- Salivary gland
B- Esophagus
C- Liver

2- The toxic byproduct produced during the xenobiotic metabolism of the analgesic paracetamol is:
A- N-acetyl-p-benzoquinone imine
B- glucuronic acid
C- Cytochromes P450

3- Hepatitis is an injury in:
A- Biliary system
B- Hepatocyte
C- Both A & B

4- ALT (alanine aminotransferase) will be normal or slightly incresed in case of:
A- Cholestatic
B- Hepatocellular
C- Mixed type

5- Which of the following antitubercular drugs is not hepatotoxic:
A- Isoniazid
B- Rifampicin
C- Ethambutol

6- A 63-year-old man presents to the emergency depart- ment with altered mental status after ingesting an entire bottle of acetaminophen. The patient's heart rate is 120 beats/minute, blood pressure is 100/58 mm Hg, and respiration rate is 28/minute. His aspartate aminotransferase and alanine aminotransferase are 4,128 IU and 3,978 IU, respectively. What is the most appropriate treatment for this patient?
A- Ammonium chloride
B- L-Carnitine
C- N-Acetylcysteine
D- Noaloxone

7- A56-year-oldmanwhoisanalcoholicpresentstothe emergency department with altered mental status. Blood tests reveal normal creatinine but hyperammo- nemia. He is admitted to the hospital for treatment. He has several comorbidities that are being managed well as an outpatient. His wife brings a list of his home medications, which includes bimatoprost, sim- vastatin, alprostadil, aspirin, and lisinopril. Which of the following should be held (not given to him) dur- ing his hospital stay?
A- Alprostadil
B- Simvastatin
C- Bimatoprost
D- Lisinopril

Answers: 1-C 2-A 3-B 4-A 5-D 6- C 7-B

Thank you for checking our team!

Pharmacology 435

@ pharmacology435

Sources:

1. 435's slides.
2. Wikipedia.