

# Medicines in liver disease

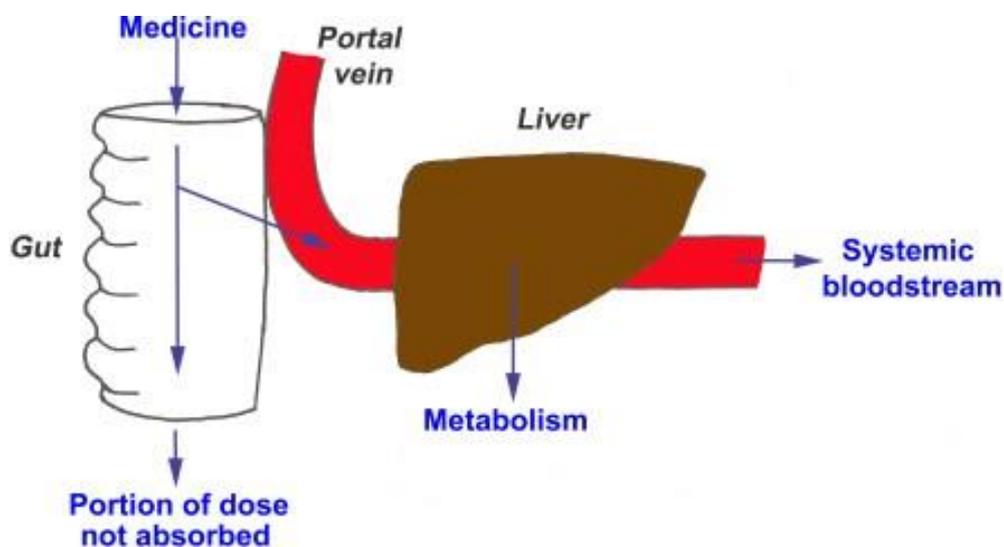
## Introduction

The liver is the main site of drug metabolism in the body, but not the only one. However, it is the principal location for [cytochrome p450 metabolism](#). The liver's main job in metabolism is to alter molecules so that they become more water soluble – this enables elimination by the kidney.

Most drugs are pharmacologically inactivated by metabolism, but other drugs (**pro-drugs** such as cyclophosphamide) need to be metabolised to become active. Several drugs have pharmacological activity both before and after metabolism by the liver,

due to the production of active metabolites.

The metabolic role of the liver is particularly important for drugs administered orally. Blood from the gut passes through the liver first before entering the systemic circulation, and this gives an opportunity for the organ to remove a high proportion of a dose. This '**first-pass metabolism**' significantly reduces the bioavailability of many oral drugs (e.g. opioids), and in some cases is so efficient that administration by the oral route is not possible (e.g. buprenorphine).



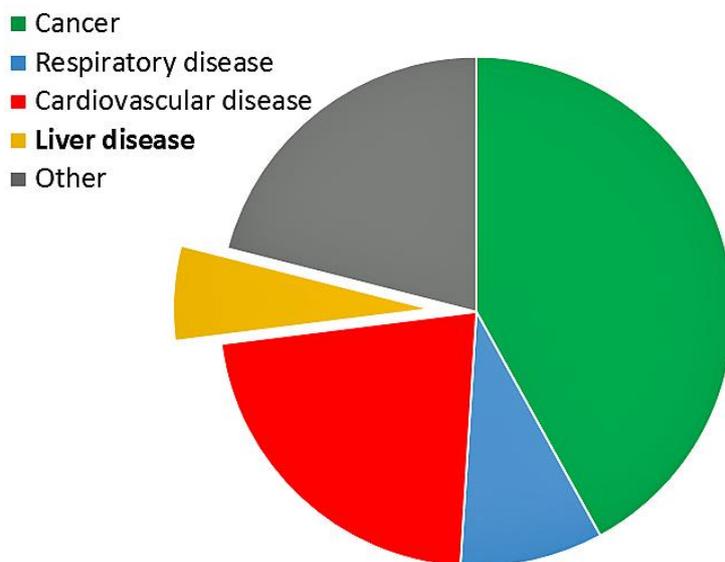
*Courtesy of Simon Wills*

In addition to this major metabolic role, the liver does actually **excrete** some drugs from the body as well, via bile (e.g. rifampicin, leflunomide). Many of these drugs are excreted in the bile conjugated to bile salts. The flora of the bowel can digest these conjugates, releasing free drug into the gut, which then enables it to be re-absorbed. This is called **entero-hepatic recycling** and is an important mechanism by which blood levels of some drugs are maintained (e.g. oestrogens).

The liver also produces the majority of the **plasma proteins** (e.g. albumin). These are important for transporting drug molecules around the body. The portion of a drug dose bound to plasma proteins cannot bind to receptors to exert a pharmacological effect and cannot be eliminated from the body. This is a major mechanism by which blood levels of highly plasma protein bound drugs are sustained.

## Liver disease

Liver disease is an important cause of illness. In the UK it is the only major cause of death to be on the increase, with a 20% rise in cases over the past decade. Liver disease is now the fifth biggest cause of premature death behind cancer, heart disease, stroke, and respiratory disease.



[Mortality statistics](#) show that for a city with a population of 350,000, then 450 people under 75 will die each year prematurely of cancer, 250 people from heart disease and stroke, 100 people from respiratory disease, and 50 people from liver disease.

Terminology associated with liver disease can be confusing. These are some of the common terms you may hear:

1. **Hepatocellular injury.** Damage to the main cells of the liver (hepatocytes). Hepatitis (inflammation of the liver) is a type of hepatocellular injury.
2. **Cholestasis.** Disruption or stagnation of the bile flow through the bile ducts. Can occur within the liver (intrahepatic) or in the major bile ducts outside the liver (extrahepatic).
3. **Cirrhosis.** Destruction of the liver cells. Damage is chronic and irreversible. The remaining functioning liver cells may be sufficient to maintain normal liver homeostasis (compensated liver disease), or may be insufficient to fulfil this role (decompensated liver disease). Decompensated disease is commonly manifested by ascites, jaundice and encephalopathy.
4. **Liver failure.** Severe hepatic dysfunction manifested by symptoms such as encephalopathy and coagulopathy. May be acute and reversible, or may indicate end-stage cirrhosis.
5. **Liver impairment.** This term is used to describe deterioration in liver function, which may range from mild to severe.

Many cases of liver disease are preventable, and attributable to alcohol, obesity, and viruses. About two-thirds of all [alcohol-related deaths](#) in the UK are attributed to its causing liver disease. The [British Liver Trust](#) reviews these causes of liver disease and gives advice on prevention.

## Liver function

There is no one specific test that gives a good measure of liver dysfunction. Assessments are made according to the whole clinical picture, which includes:

1. Signs and symptoms (e.g. jaundice, encephalopathy, varices).
2. Blood tests – such as liver function tests (see below), clotting screen, virological markers (e.g. hepatitis B or C).
3. Biopsy and imaging techniques.

### Liver Function Tests (LFTs)

Not all elements of LFTs are specific to the liver, and they do not in themselves provide a diagnosis, although they can help to confirm or exclude liver disease. Symptomatology and other test results should always be considered together with LFTs.

LFTs can be useful for monitoring disease progression and response to therapy. But LFTs alone are not necessarily a good indicator of severity of liver disease or extent of liver dysfunction.



*Viral disease Hepatitis A manifested here as jaundice  
Courtesy of CDC/ Dr. Thomas F. Sellers; Emory University*

A *significant change* in any particular enzyme is difficult to quantify, but greater than double the upper limit of normal (or baseline) is a useful guide. A particular enzyme should not, however, be considered in isolation. The 'battery' of liver function tests should be considered as a whole in order to identify the 'picture' generated.



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Note that drugs which induce cytochrome p450 enzymes may elevate some LFT values.

The individual elements of LFTs are discussed briefly below:

1. **Bilirubin.** This is a product of haemoglobin breakdown and is normally excreted in the bile. It is particularly raised in cholestasis, but can also be raised in hepatocellular disease.
2. **Alkaline Phosphatase (ALP).** Is raised in cholestasis since it is secreted into bile ducts. It is slightly raised in hepatocellular disease. Reference values vary markedly between hospitals according to assay technique so make sure you know your own local ones!
3. **Transaminases.** These are markers of hepatocellular injury. Alanine aminotransferase (also known as alanine transaminase – ALT) is more specific to the liver than aspartate aminotransferase (also known as aspartate transaminase – AST). Note in the US, ALT is known as SGPT (serum glutamic pyruvate transaminase) and AST is known as SGOT (serum glutamic oxaloacetic transaminase).
4. **Gamma Glutamyl Transferase (GGT).** Levels rise in almost all kinds of liver disease and are therefore of little value in differentiating between them. Levels may also rise in patients taking enzyme-inducing drugs and in alcohol dependency.
5. **Albumin.** This is synthesised in the liver but has a long half-life (20 days). Although not a very specific indicator, a low albumin in association with deranged LFTs may suggest chronic liver disease.
6. **Prothrombin Time.** Clotting factors are made in the liver, and an elevation of PT by more than 3 seconds is significant. It is a useful indicator of the synthetic ability of the liver and can increase in both acute and chronic liver disease. Changes can occur rapidly due to the relatively short half-life of clotting factors.

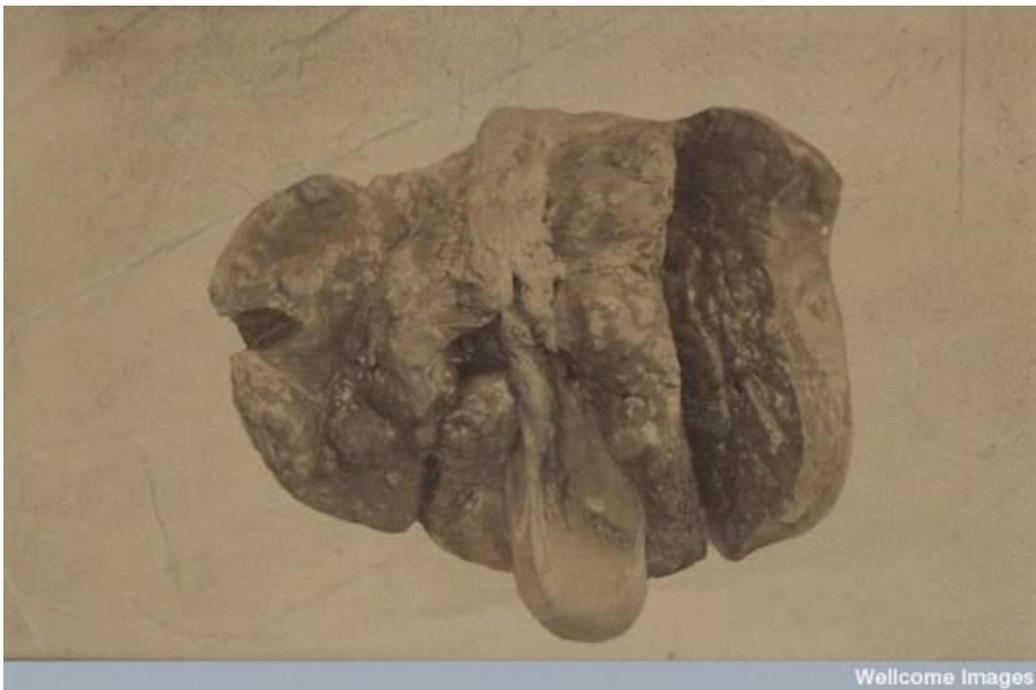
Note that some patients will have a combined cholestatic/hepatocellular picture.

Make sure you are familiar with the local LFT reference ranges that are appropriate for the age of your patient. Usual paediatric ranges may be different to those used for adults.

## Medicines and the liver

The effects of liver disease on drug handling are determined by the nature and severity of the impairment. However, these are examples of what may occur:

- **Hepatocellular damage** can reduce the metabolising capacity of the liver. When metabolism is slowed, drugs may accumulate.
- If the levels of **plasma proteins** fall, due to reduced synthesis by the liver, drugs that are normally highly protein bound will have a greater proportion of free drug in circulation. This may result in increased potency and the half-life may be affected.
- If there is **cholestasis**, excretion via the bile is impaired.
- **Cirrhosis** may result in blood from the gastrointestinal tract bypassing the liver, so that first-pass metabolism is reduced. For drugs that are normally subject to a high rate of first-pass metabolism, this increases bioavailability and therefore the potency of a given dose.



*Cirrhosis of the liver*

*Courtesy of St Bartholomew's Hospital Archives and Wellcome images*

- **Hepatic encephalopathy** may occur when nitrogenous compounds absorbed from the gut accumulate and render the brain more susceptible to the CNS depressant effects of drugs.

## Prescribing in Liver Disease

The following tips may be helpful:

- **Avoid hepatotoxic drugs** where possible. Patients with existing hepatic disease are not more prone to hepatotoxicity (unless it is dose-related), but they do have diminished reserve hepatic function and may suffer disproportionately if hepatotoxicity does occur. The advent of drug hepatotoxicity on top of existing liver disease will also confuse the diagnostic picture.
- Continue to **monitor LFTs** regularly while liver dysfunction persists.
- For drugs cleared or metabolised by the liver, be alert to signs of **drug side effects**: know what they are and monitor for them. Monitor drug levels where appropriate.
- **Non-systemic treatments** should be chosen where possible. Renally-excreted drugs are also preferred as long as renal function is normal. Monitor for any changes in renal function regularly.
- Drugs that increase the **risk of bleeding** should be avoided or used with extreme caution, depending on the severity of liver disease.



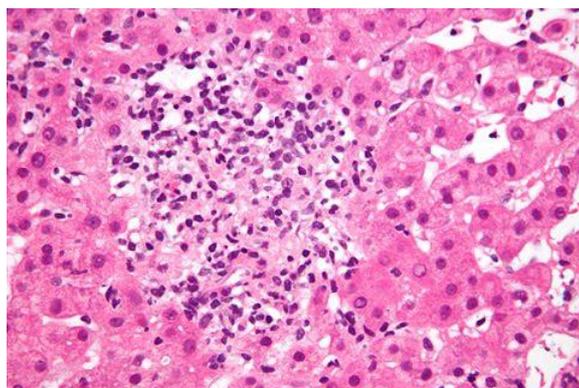
- Drugs that are highly dependent on the liver for deactivation or clearance are likely to need **dose reduction** in moderate to severe liver disease.
- **Avoid sedating drugs** in patients at risk of developing encephalopathy. Many of these drugs have long half-lives and are liver metabolised, so their duration and intensity of action may be prolonged in liver disease. The brain also becomes more sensitive to sedating effects in liver disease. A sedative drug may precipitate or mask encephalopathy.
- The doses of **highly protein bound drugs** may need reducing in patients with low albumin levels due to chronic liver disease.
- Keep drug **prescribing to a minimum** – use the smallest effective doses at greatest interval, and titrate according to clinical response.

## Hepatotoxic medicines

Some drugs are hepatotoxic in a dose-dependent way (e.g. paracetamol, alcohol) but for the majority, hepatotoxicity is an idiosyncratic reaction. If the reaction is immune-mediated it usually takes some weeks to develop and sometimes involves other signs of hypersensitivity such as fever, rash and eosinophilia.

Drugs can mimic every known kind of liver disease, but the most important acute reactions are:

1. **Hepatocellular disease** – any form of liver injury which causes destruction of liver cells (e.g. hepatitis). Sometimes called necro-inflammatory or cytotoxic. Drugs causing this type of injury include methotrexate and diclofenac.
2. **Cholestasis** – in this form of injury, the cells in the main body of the liver (the parenchyma) are not damaged, but bile flow is impeded. This causes jaundice. Drugs responsible for this type of reaction include phenothiazines and sex steroids.
3. **Mixed presentation** – drugs commonly cause both of the above forms together.
4. **Subclinical** – seen as minor liver enzyme elevation. It may subside with continued exposure to the drug or, more rarely, progress to liver impairment (e.g. many anticonvulsants).



*Drug-induced hepatitis*  
Courtesy of Wikimedia Commons

It has been estimated that up to 5% of jaundice in hospital is caused by drugs, and that 40% of hepatitis in patients over 50 years of age is caused by drugs.

Drugs can also cause chronic liver disease. Examples include primary biliary cirrhosis caused by chlorpromazine, and hepatoma caused by anabolic steroids.

Most drugs with hepatotoxic potential can usually cause more than one type of liver damage.

## Suggested questions

They may not apply to every situation you come across, but here are some questions you should be thinking about in practice.



### The Medicine

If drug-induced **hepatotoxicity** is suspected:

- Is the patient currently taking the drug in question, if so what dose and frequency?
- What other drugs are being taken or have been taken recently?

If requesting advice on **dosage or suitability** of a drug in hepatic dysfunction:

- What is the indication for the drug?
- Have alternatives been considered?
- What agent would normally be used if the patient did not have liver dysfunction?

### The Patient

- Clinical condition of the patient, age, and presumed diagnosis.
- Results of LFTs (including clotting screen), biopsies and other diagnostic liver tests.
- Are the LFTs stable or changing?
- What is the patient's renal function?

### Going Forward

- Who is in a position to change therapy if necessary and who will be monitoring the patient?
- How might any advice given change if the patient's liver function deteriorates further?

## Information sources

For clinical problems about prescribing in liver disease, there isn't a one-stop reference source with all the answers; you'll often need to search through several resources to try to build your answer. You might also need to consult some of the other Clinical Topics such as [Adverse Reactions](#) and [Interactions](#).

Having said that, [Drugs and the Liver](#) by Penny North-Lewis (Pharmaceutical Press, 2008) has some really helpful chapters on choosing drug therapy in patients with liver disease including analgesics and antiemetics.

The [SPCs](#) can be helpful in this respect too, and there may be guidance on dose in liver disease in the Posology section (4.2), but the nature of clinical trials is such that patients with more severe liver disease are often excluded, and so information may be lacking. In this case look in section 5.2 of an SPC (Pharmacokinetic Properties) which should explain whether the liver plays an important part in drug clearance. The **manufacturer's Medical Information department** may have some extra information to that in their SPCs.



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Literature searches in **Embase** and **Medline** may help. In addition to looking for published papers about prescribing of your drug in liver disease, think 'big picture' and find out how the disease is treated in patients without liver disease – you may find some alternatives you hadn't considered.

Establish whether any **expert bodies** have issued general guidance for the condition your patient is suffering from. They will often cover treatment of a condition in otherwise healthy patients, and then provide treatment advice for special groups such as patients with liver disease. Alternatively specialist hepatology groups such as [British Association for the Study of the Liver](#) (BASL) or the [European Association for the Study of the Liver](#) (EASL) may have some information.

Don't forget your local experts. Do you have a local **gastroenterology** or **liver pharmacist**? Or can you contact a local specialist doctor for advice?

Finally, general resources such as **Martindale**, **Micromedex**, and **AHFS Drug Information** can be helpful if you have them available locally.



## Next steps in learning...



CPPE has an e-learning programme called [Liver Disease](#) which is designed to provide you with a better understanding of the factors you need to consider when advising on medicines for patients with impaired liver function.



The WHO-sponsored [World Hepatitis Day](#) website has a helpful overview of the five basic types of viral hepatitis: A, B, C, D and E.

The Royal College of General Practitioners has free e-learning on [Hepatitis B and C](#). The emphasis is on the epidemiology, testing, and risks associated with these conditions rather than drug management. You need to register with the site to access the learning.