

Medicines in liver disease

After completing this tutorial, you will be able to:

- Recognise the main types of liver disease and dysfunction.
- Describe how to assess a patient's liver dysfunction, including the commonest liver function tests.
- Make decisions about appropriate choice and dose of medicines in patients with liver dysfunction.

Why this subject matters...

It is likely you will see patients with **liver disease** in your practice (e.g. cirrhosis due to alcoholism). You will also encounter patients with **liver dysfunction**, who may not have liver disease but the function of their liver is affected in some way (e.g. secondary to sepsis).

In this tutorial we will cover the normal functioning of the liver, how this can change when a patient has liver dysfunction, and how you can tell. Above all, we will provide pointers on how to use medicines safely and effectively in this patient group.

Role of the liver

The liver is an important organ for many functions of the body. It is where a wide variety of compounds are synthesised, including bile, clotting factors, hormones, cholesterol and triglycerides, albumin, glycogen to store glucose, and many more. It also has important metabolic functions, breaking down hormones such as insulin and oestrogen, as well as many waste products such as ammonia and bilirubin to allow their excretion.

Many of these actions determine the absorption, distribution, metabolism and excretion of medicines. As a result, changes in liver function can have significant implications for how we use drugs. Some of these are reviewed briefly below.

1. Absorption

Lipophilic drugs often need bile salts for absorption from the gut (e.g. fat-soluble vitamins), so any impairment in bile excretion may reduce drug absorption. This may happen in patients with cholestasis, for example.

2. Distribution

Many drugs are bound to plasma proteins produced by the liver such as albumin. These proteins are important for transporting drug molecules around the body in blood. The portion of a drug dose bound to plasma proteins is not free to bind to receptors and exert a pharmacological effect and cannot be eliminated from the body.

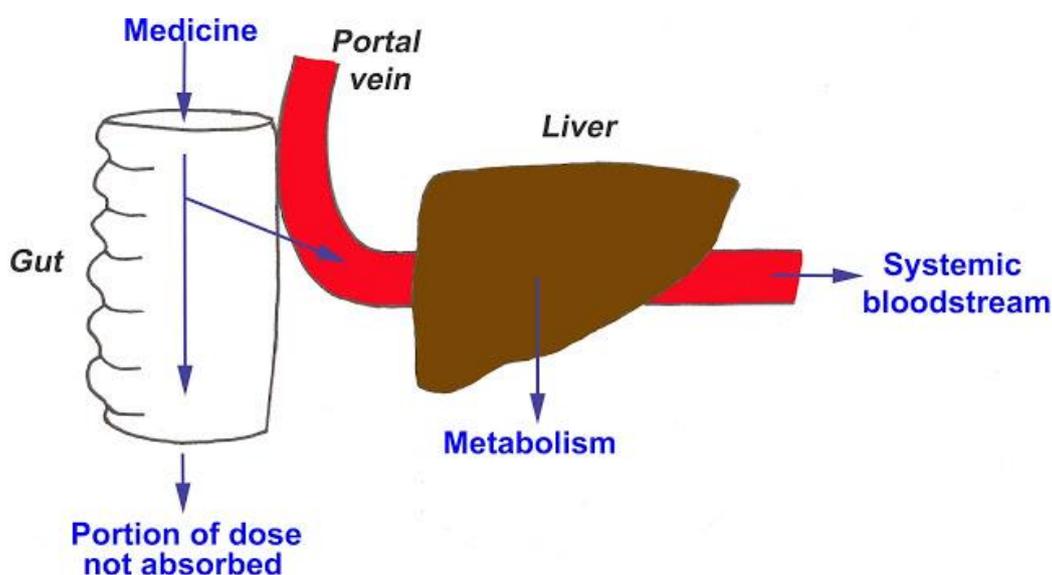
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If the liver's ability to make proteins (its 'synthetic function') is impaired, there will be reduced amounts in the systemic circulation. This may lead to an increase in the pharmacologically active unbound or 'free' fraction of drug in the blood. In this situation, highly protein bound medicines may appear more potent in liver dysfunction causing increased side effects: so you may consider reducing the dose or using a different drug. Sometimes, highly protein bound drugs can be displaced from albumin in patients with high bilirubin levels which also gives higher levels of free drug.

3. Metabolism

The liver is the main site of drug metabolism in the body, and the principal location for cytochrome p450 and other metabolic enzymes. Liver metabolism often alters molecules so that they become more water soluble, enabling elimination by the kidney.



First pass metabolism

If the liver isn't working effectively, the levels of hepatically metabolised drugs **may be increased**. However, some medicines are inactive when taken and need to be metabolised to active compounds in order to work. Pro-drugs of this kind include cyclophosphamide. Liver dysfunction may **decrease activity of these medicines** because they don't get activated to the same extent.

The metabolic role of the liver is 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 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).

4. Excretion

The liver excretes some medicines into the gut via bile (e.g. rifampicin, leflunomide). Impairment of bile production and excretion may therefore affect drug clearance. 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 **enterohepatic recycling** and is an important mechanism by which blood levels of some drugs are maintained (e.g. oestrogens).

Describing liver dysfunction



Liver disease is a major cause of morbidity and mortality and is rated as one of the top 5 commonest causes of premature death in the UK. However, not all liver problems are related to an underlying liver disease. Many patients have liver dysfunction which may be secondary to drug therapy, infections or sepsis, gallstones or trauma.

It is important to differentiate between **liver disease** and **liver dysfunction** to understand how significant it might be when considering how it affects drug handling. For example, a transient rise in transaminases (ALT or AST) in someone newly started on a statin is an established side effect and doesn't reflect any change in the liver's ability to metabolise other drugs.

Conversely, a rise in ALT in someone with autoimmune hepatitis is likely to indicate worsening liver disease.

Common terminology used to describe liver disease/ dysfunction is explained below. Fitting your patient into one (or more) of these categories can help you think about how their medicines might be affected:

Hepatocellular injury

This describes damage to the hepatocytes which are the main cells responsible for most liver functions. It is subdivided by severity:

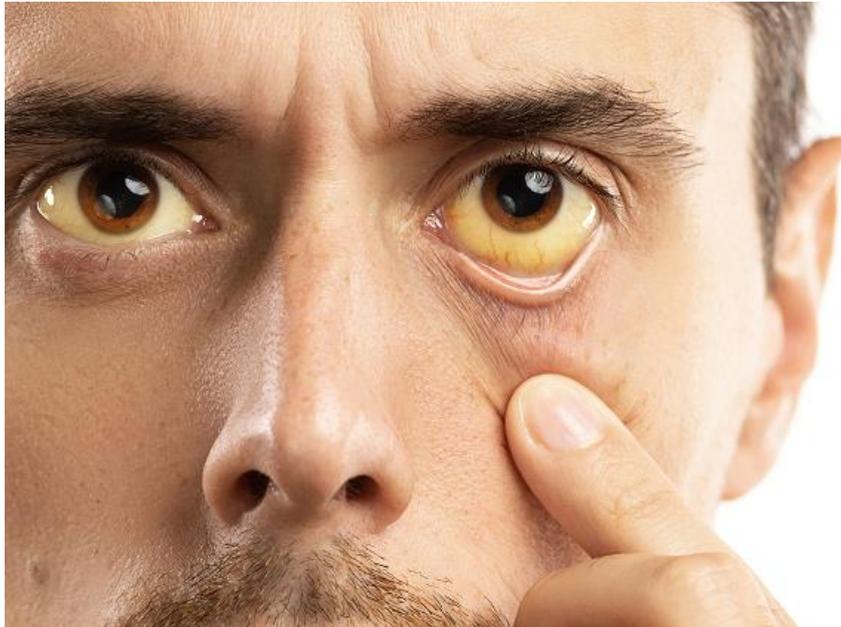
- ◆ **Hepatitis.** Inflammation of the hepatocytes.
- ◆ **Fibrosis.** Early scar tissue is formed around the hepatocytes if the inflammation continues. Fibrosis is reversible if the cause is removed or treated.
- ◆ **Cirrhosis.** This is where scar tissue has built up and permanently damaged the architecture of the liver. It is not reversible. Cirrhosis can be subdivided into:
 - ◇ *Compensated cirrhosis* – where there is sufficient hepatocyte function remaining for the majority of the liver's roles to continue satisfactorily.
 - ◇ *Decompensated cirrhosis* – there is insufficient hepatocyte function remaining and the patient develops signs of endstage liver disease or liver failure (e.g. encephalopathy and ascites).

Cholestasis

This means the patient has impaired bile flow. It can be **intrahepatic** if it originates within the liver (e.g. caused by erythromycin), or **extrahepatic** (e.g. as a result of gallstones or biliary atresia).

Assessing liver function

There is no single specific test that gives a measure of liver function, and assessment is based upon the whole clinical picture. This includes a combination of signs and symptoms, liver function tests, histopathology and imaging. Signs and symptoms include jaundice, pruritus, varices and spider naevi. Patients with more advanced liver impairment may have multiple symptoms and are more likely to have ascites, varices, and encephalopathy.



Symptoms of jaundice include yellowing of skin and whites of the eyes, dark urine and pruritus

Liver function tests (LFTs)

Not all LFTs are specific to the liver and they should be interpreted alongside other markers of liver dysfunction and the overall clinical picture.

- **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.
- **Alkaline phosphatase (ALP)** – This is raised in cholestasis, since it is secreted into bile ducts, and slightly raised in hepatocellular disease. Other causes, such as bone diseases, can also increase ALP.
- **Transaminases (ALT / AST)** – These are markers of hepatocellular injury. Transaminases can also be raised in cardiac disease.
- **Albumin** – This is synthesised in the liver and 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/ dysfunction.
- **Prothrombin time** – As the liver makes clotting factors, an increased prothrombin time suggests the synthetic ability of the liver has been affected. Clotting factors have short half-lives, so changes in prothrombin time can happen quickly and can be seen in both acute and chronic liver disease.

Local LFT reference ranges may differ between hospitals and paediatric ranges may be different to those used for adults.

Interpreting liver function tests (LFTs)

When a change in a particular LFT becomes important is difficult to quantify, but any level greater than twice the upper limited of normal (ULN) could warrant further investigation. However, it is important to review this in line with the clinical picture – consider the patient as a whole, rather than looking at LFTs in isolation. Not all deranged LFTs indicate liver dysfunction.

Child-Pugh score

The Child-Pugh score, or its associated Child-Pugh grade, is used as a means to indicate the severity of the condition for patients with cirrhosis of the liver. It is occasionally used to suggest dose adjustments by manufacturers of medicines, but is more useful as a measure of a patient's degree of liver disease. Further information on the Child-Pugh score can be found on the [Specialist Pharmacy Service website](#).



Adverse effects and the liver

As well as understanding how liver dysfunction can affect the way the body handles medicines, it is also important to consider how medicines can affect the liver. This depends on the type of liver disease, the degree of hepatic dysfunction, and the patient's signs and symptoms. So it needs to be considered for each individual patient.

Some medicines have an adverse effect profile that can cause problems for patients with liver disease. Quite apart from this, there are also medicines that may damage the liver itself, and this is called hepatotoxicity.

Adverse effect profile

Consider the potential for medicines to cause adverse reactions such as those described below when choosing or monitoring a medicine in a patient with liver dysfunction. You can read more about this subject via the [SPS website](#), but example side effects that may be of concern include:



◆ Changes to LFTs

Some drugs can cause mild, transient, insignificant rises in LFTs but this may not be an absolute contraindication in patients with liver dysfunction. The risks and benefits of using the medicine need to be considered, although be careful because interpretation of LFTs and monitoring of the course of a patient's liver disease may become more complicated.

◆ Pruritus

Patients with cholestatic liver disease often experience severe itch. Avoid drugs with a high incidence of urticaria or itching.

◆ Fatigue

Patients with cholestasis and cirrhosis often suffer from tiredness. Encephalopathy can be made worse by medicines that cause sedation. Avoid drugs which cause drowsiness.

◆ Clotting abnormalities

Patients with liver dysfunction may have impaired clotting. Drugs with a bleeding risk (e.g. anticoagulants, NSAIDs, antiplatelets) should only be used where the benefit outweighs the risk.

◆ Changes to electrolytes

Ascites is a build-up of fluid in the abdomen caused by significant liver disease. It can be made worse by increasing sodium levels. Avoid drugs which can increase sodium (e.g. NSAIDs inhibit sodium and water excretion) and consider the sodium content of drugs (e.g. effervescent tablets, IV

preparations). Encephalopathy can be precipitated by electrolyte disturbances. Drugs which can cause electrolyte disturbances should only be used where the benefits outweigh the risks, and with appropriate monitoring.

◆ **Constipation**

Encephalopathy can be precipitated by constipation, so avoid drug-induced constipation.

◆ **Gastrointestinal irritation**

Patients with oesophageal varices due to liver disease may be at increased risk of bleeding from drugs that irritate the GI tract (e.g. NSAIDs, bisphosphonates).

◆ **Nephrotoxicity**

Certain types of liver disease increase the risk of developing renal impairment. Use potentially nephrotoxic drugs with caution, and avoid if possible – especially in patients with 'hepatorenal syndrome' (impaired kidney function in patients with severe liver disease in the absence of any other identifiable cause of renal pathology).

Hepatotoxicity

There are two types of hepatotoxicity:

- (1) **Intrinsic** is predictable, reproducible, and dose-dependent (e.g. when caused by paracetamol overdose or alcohol). It is the less common type.
- (2) **Idiosyncratic** hepatotoxicity is unpredictable and independent of dose. It is more common and may involve signs of hypersensitivity such as fever, rash and eosinophilia.

The decision to use a drug with a hepatotoxicity risk depends on various factors, including:

- The reported frequency and severity of hepatotoxicity.
- Clinical urgency of treating the condition concerned.
- The other options available as treatment.
- Reversibility of liver damage upon withdrawal of the drug.

In general, patients with pre-existing liver disease are thought to be at no greater risk of drug-induced liver damage than the general population. There are a few exceptions to this rule (e.g. methotrexate, rifampicin). However, patients with pre-existing liver disease may have less hepatic reserve if hepatotoxicity occurs; therefore avoid drugs that have a high incidence of causing liver damage if at all possible.

Liver transplant patients

After a transplant, patients with normal liver function are the same as any other patient when considering the effect of medicines on liver function. However, remember that transplant rejection medicines interact with many other drugs so don't start any new medicine without checking for a potential interaction first.

Making decisions about medicines

There's been a lot to learn in this tutorial, so this page is a summary to help you when choosing a medicine for a patient with liver dysfunction. It's the commonest problem you'll face. If you need to revert to first principles then, as we saw on the first page of this tutorial, you need to look at the way the drug is handled by the body:

Absorption

◆ Is the drug lipophilic? Lipophilic drugs often need bile salts for absorption, so patients with cholestasis may experience a reduction in drug absorption.



Distribution

◆ Is the drug highly plasma protein bound? For drugs that are highly protein bound, the risk of side effects might be increased in patients with low albumin levels. This is because there is less protein for the drug to bind to, leading to higher levels of free drug. Sometimes, highly protein bound drugs can be displaced from albumin in patients with high bilirubin levels which also gives higher levels of free drug.

◆ Is the drug water soluble? Larger doses of water soluble drugs may be needed in patients with ascites as the drug distributes into the ascitic fluid resulting in lower blood concentrations.

Metabolism

◆ Is the drug metabolised (or activated) by the liver? In liver dysfunction, cytochrome p450 and other enzyme levels may be reduced. This means that some drugs might accumulate as they are not metabolised readily, or inactive pro-drugs are not changed into their active forms.

◆ Note that oral medicines subject to high first-pass metabolism may be metabolised less if there is portal hypertension, which may divert blood supply away from the liver. This may make a medicine more bioavailable.

Elimination

◆ Is the drug excreted in bile? If the patient has cholestasis, biliary excretion may be impaired. This may particularly become an issue if the drug is excreted in an active form.

◆ Does the drug undergo enterohepatic recirculation? If the patient has cholestasis then reabsorption via this route may be reduced, resulting in lower levels.

But it's not just pharmacokinetics. On the previous pages, we also look at **side effects** that are of particular concern in patients with liver dysfunction. There are many of these, but three to always keep in mind are:

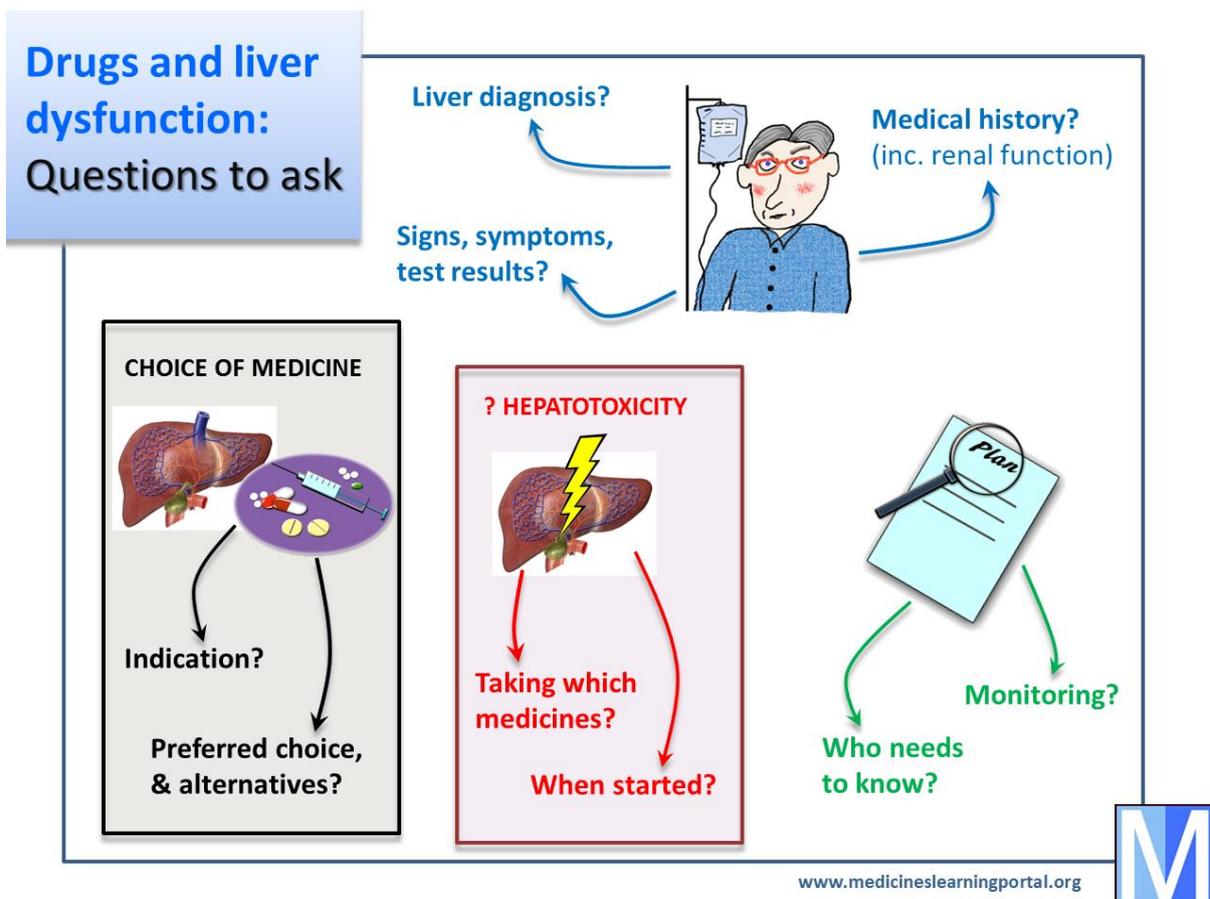


- ◆ Avoid **hepatotoxic drugs** where possible. Patients with existing hepatic disease have diminished reserve hepatic function and may suffer disproportionately if hepatotoxicity does occur. The advent of drug-induced hepatotoxicity on top of existing liver disease will also confuse the diagnostic picture.
- ◆ Drugs that **increase the risk of bleeding** should be avoided or used with extreme caution, depending on the severity of liver disease.
- ◆ Avoid **sedating drugs** in patients at risk of encephalopathy. Many of these have long half-lives and are hepatically metabolised, so their duration and intensity of action may be prolonged in liver dysfunction. The brain also becomes more sensitive to sedating effects in liver disease. A sedative drug may precipitate or mask encephalopathy.

Finally here are some practical clinical tips to assist you when making decisions about choice of drug and dose in liver dysfunction:

- ◆ Drugs that are highly dependent on the liver for deactivation or clearance may need **dose reduction** in moderate to severe liver disease. Be alert to drug side effects: know what they are and monitor for them. Monitor drug levels where appropriate.
- ◆ Continue to **check LFTs regularly** while liver dysfunction persists. A significant improvement or deterioration may require a review of drug choice or dose.
- ◆ Keep drug **prescribing to a minimum** – use the smallest effective doses at greatest interval, and titrate according to clinical response.
- ◆ In some circumstances **non-systemic treatments or non-pharmacological options** can be a helpful way to minimise drug handling by the liver.
- ◆ **Renally excreted drugs** are also preferred as long as renal function is normal. Monitor for any changes in renal function regularly.
- ◆ Look carefully at the **side effect profile** of the medicine you want to use and compare it to the patient's existing signs and symptoms, and their liver diagnosis.

Suggested questions



The Patient

- Do they have a liver diagnosis? *If yes, this will help you with details of extent of likely dysfunction, duration, prognosis etc. If no, be careful about advising about medicines until a diagnosis and/or cause has been made.*
- What are the signs, symptoms and test results? *Look at all LFTs, clotting screen, and symptoms. Are these stable, or changing? Trends are really important.*
- Ask about the patient's medical history. *As pharmacy staff, we often think that medicines both cause and fix all problems, but there can be other causes of the signs and symptoms of liver dysfunction. For example, broken bones may increase ALP levels, CPR may affect the liver. It's important to know about renal function too as this could markedly affect the safe choice and dose of medicines.*

Choice of medicine in liver dysfunction

- What is the indication? *You need this information in order to advise about potential alternatives.*
- What is your preferred choice? *If the patient didn't have liver dysfunction, what drug would you want to use? This can help narrow down vague or sprawling questions.*
- Have alternatives been considered? *Otherwise you may advise using a medicine that has already been tried unsuccessfully, or suggest using a medicine that is not appropriate for other reasons.*

Drug-induced hepatotoxicity

- You've already asked about signs and symptoms and the diagnosis (see above), and this is important in helping to determine whether liver dysfunction is drug-related because some medicines cause characteristic presentations. You should also ask:
- What medicines are being taken? *Even if there is one suspect agent already, ask about what else is being taken, or any medicines that have been stopped recently.*
- When were any suspect drugs started? *This may help you narrow down the most likely cause from a group of medicines.*

Going Forward

- Who else needs to know about the advice you give? *For example, you might need to know who can amend the patient's therapy if necessary, counsel the patient, or document your advice in the patient's notes.*
- If any monitoring is required, who will do this? *Do they know what to do if the liver function changes, and where to go for advice?*

Information sources

As you have seen through this tutorial, there isn't just one type of liver dysfunction, so there unfortunately isn't a one-stop reference source with all the answers. You'll often need to use more than one resource to build an answer, and you may need to revert to first principles. However, there are some key resources that may be helpful.



General resources

- ◆ **This tutorial** provides guidance that will help you solve clinical problems from first principles. (You might also find the [Adverse Reactions](#) tutorial useful.)
- ◆ [Drugs and the Liver](#) by Penny North-Lewis (Pharmaceutical Press, 2008) has good coverage of how to approach questions, and chapters on specific topics such as choosing analgesics and antiemetics in patients with liver dysfunction.
- ◆ The adverse effects and pharmacokinetics sections of SPCs are particularly useful. There is sometimes information in the posology, contraindications and cautions sections too. However, bear in mind that in clinical trials, patients with liver disease are often excluded so a manufacturer's contraindication in liver disease may be due to a lack of information rather than observed harm. A **manufacturer's medical information department** may have extra information to that in their SPCs.
- ◆ Your Pharmacy or MI may have access to **other general sources** that can sometimes help such as Martindale, Micromedex, AHFS Drug Information, or Lexicomp.

Choice of medicine in liver dysfunction

The general resources above may help you, sometimes starting from first principles. Otherwise, you might:

- ◆ Check if any **expert bodies** have issued general guidance for treating the condition your patient is suffering from. They will often cover treatment for special groups such as patients with liver disease.

- ◆ Consider a **Embase** and **Medline** search. In addition to looking for published papers about 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 suitable alternatives you hadn't considered.
- ◆ See if you have a **liver or gastroenterology expert** available locally who you can ask for advice. A specialist pharmacist or doctor will probably be familiar with your clinical situation, and may even know your patient.

Drug-induced hepatotoxicity

◆ **LiverTox** has information on the diagnosis, frequency, patterns, and management of liver injury attributable to medicines, herbals, and dietary supplements. It is a really useful American site hosted by the National Institutes of Health and supported by the National Library of Medicine.

- ◆ The European Association for the Study of the Liver has published a clinical practice guideline for drug-induced liver disease. It identifies the drugs commonly responsible, including herbals, and discusses presentation and management.

General internet searches

Be careful about conducting a general internet search on this subject. If you do, you may like to look at our brief guide to [evaluating websites about medicines](#).

Presenting your answer

Once you've asked sufficient questions, gathered the information required and assessed it, you'll need to provide an **answer**. As a reminder, we offer some [general guidance on answering clinical problems](#). You might like to refresh your memory if you've not looked at this recently.

Next steps in learning...



CPPE has links to useful learning resources via its [Liver gateway page](#), including an introduction to liver disease and a quiz. There is a drug-induced liver injury case study, designed to help you recognise abnormal liver function test results and to take appropriate action when abnormal results are due to a medicine.

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.