Inherited disorders

After completing this tutorial, you will be able to:

- Describe the role of the pharmacy team in managing patients with porphyria, phenylketonuria, glucose-6-phosphate dehydrogenase deficiency and cystic fibrosis.
- Know where to look for information if asked a clinical question about a medicine for a patient with one of these inherited disorders.

There are many types of inherited medical condition, but in this tutorial we have chosen four examples where patients may particularly need help from a pharmacist to optimise their medicines. Each inherited disorder features a faulty or absent protein, such as an enzyme.

You may like to complete the topic on Pharmacogenomics alongside this one.

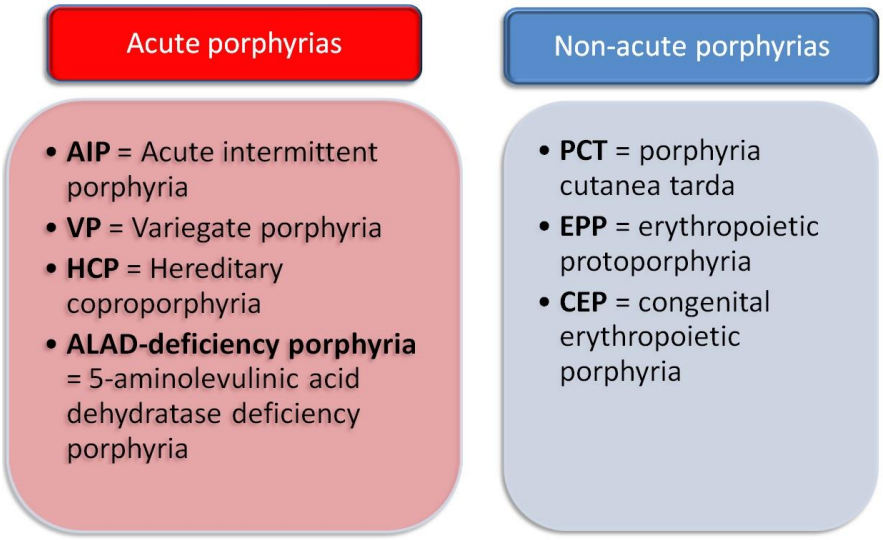
1. Porphyria

This learning was prepared in partnership with BIPNET, the British and Irish Porphyria Network, and the UK Porphyria Medicines Information Service, Cardiff.

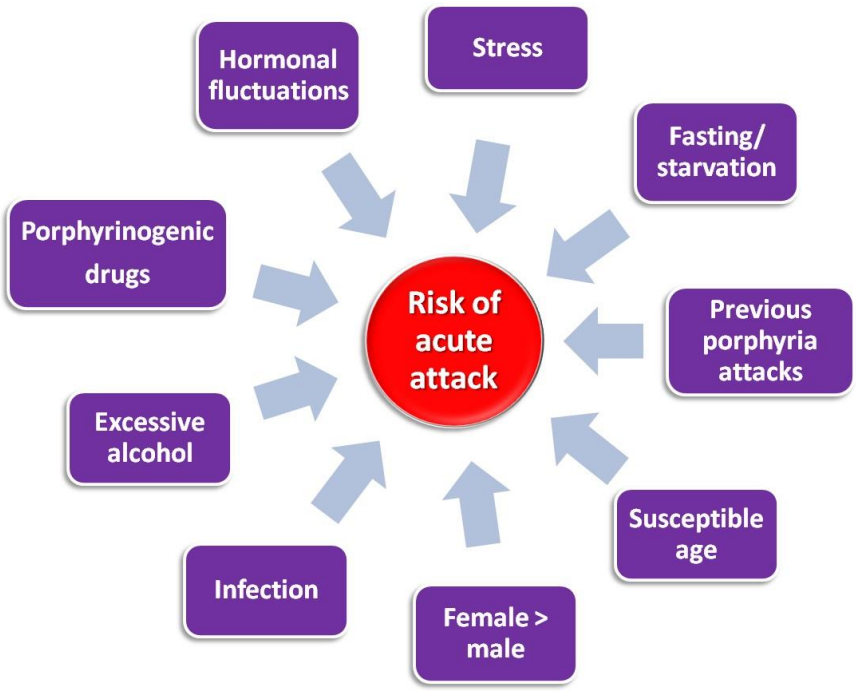
Porphyrias are a group of inherited metabolic disorders of the haem biosynthesis pathway, caused by a fault with one of the enzymes involved. Haem is a molecule created by human metabolism and is used to build larger molecules such as haemoglobin, myoglobin, and cytochrome. Porphyrias lead to accumulation of neurotoxic and/or phototoxic haem precursors, and so these conditions are characterised by acute neurological and visceral symptoms ('neurovisceral crises') and/or skin lesions.

What type of porphyria?

It is important to understand the type of porphyria your patient has been diagnosed with, and in particular whether it is **acute porphyria** or **non-acute porphyria**.



In practice, acute intermittent porphyria (AIP), variegate porphyria (VP) and hereditary coproporphyria (HCP) are the conditions that pharmacists may see presenting acutely. Many factors can precipitate an acute attack by increasing the body's need for haem, and they act **cumulatively** as shown in the diagram below. In patients with porphyria the haem is produced, but precursors in the pathway may accumulate and cause symptoms. In addition, several patient factors can predispose individuals to developing an attack.



Four types of acute porphyrias affect the nervous system (AIP, VP, HCP, ADP). Two of these can also affect the skin (VP,HCP). Symptoms for acute porphyrias develop over hours or days and last for days or weeks.

[Last updated: 19 December 2024]

Early symptoms of an acute attack can include tachycardia, acute severe abdominal pain, nausea and vomiting, constipation, peripheral motor neuropathy, and paraesthesia. This may progress to severe cardiovascular, neurological and psychiatric symptoms, and a progressive, irreversible neuropathy. Ultimately, this can be fatal if untreated.

Three types of cutaneous porphyrias affect only the skin and cause chronic, or long lasting, symptoms (PCT, EPP, CEP). People with cutaneous porphyria may develop skin symptoms—such as blistering or pain—after their skin is exposed to sunlight.

Acute porphyria and medicines

Medicines can contribute towards triggering an acute attack of porphyria in a patient with AIP, VP, HCP or ADP. There are a number of ways by which they can do this, including:

- **Induction of the haem pathway**. Some medicines increase the activity of haem pathway enzymes or induce cytochrome p450 synthesis.
- **Female sex hormones**. The mechanism is unclear, but these are known to be highly porphyrinogenic.
- **Adverse drug reactions**. A side effect may cause sufficient physiological disturbance to trigger an acute attack (e.g. drug-induced vomiting, leading to reduced calorific intake).

Deciding whether a medicine is safe

If you are asked about choosing a 'safe' medicine for a patient with porphyria, you must start by identifying the type of porphyria they have. **It's only patients with acute porphyrias that must avoid the medicines that trigger acute attacks.** If you're not able to speak to the patient directly about their precise diagnosis then you may be able to ask a relative or carer: *Does the patient suffer from acute porphyria and have they ever had an acute attack?*

Note that patients can still have a diagnosis of acute porphyria, even if they have never suffered from an acute attack.

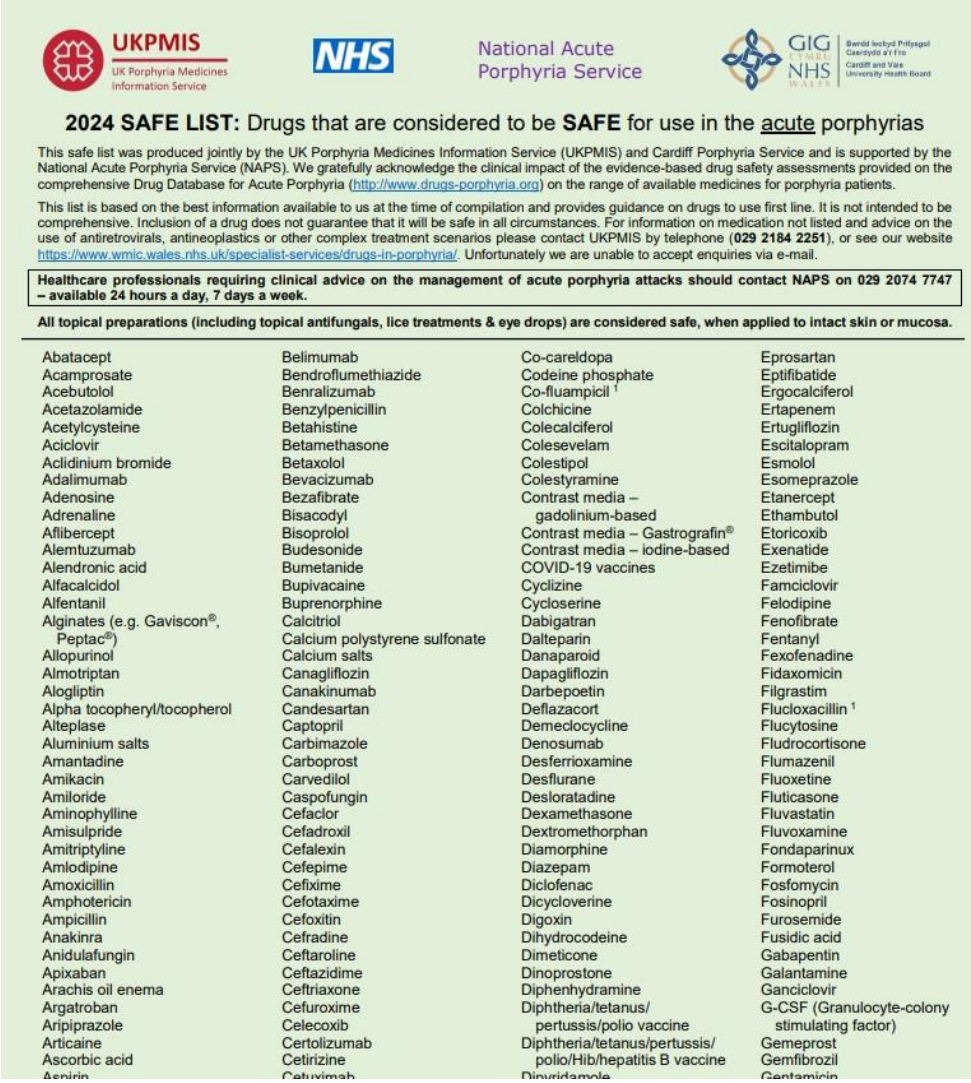
At present there is no consensus view about the safety of many widely-used drugs; largely because of difficulty in reconciling evidence from disparate sources. However, you have two core sources of information to help you. The BNF contains a list of medicines that are rated as ***unsafe*** in acute porphyria. There is also a list of medicines rated as ***safe***, produced by the UK Porphyria Medicines Information Service. You should always check ***both*** lists.

If you cannot find out if a medicine is safe, or you are uncertain, then you can contact the following services for advice:

- **UK Porphyria MI Service** (UKPMIS) Tel. 029 2184 2251 (Monday to Friday 9am to 5pm; Saturdays 9am to 12.45pm)
- **National Acute Porphyria Service** (NAPS) Tel. 029 2074 7747 (available 24/7)

Where there is no safe alternative, drug treatment for serious or life-threatening conditions should not be withheld from patients with acute porphyria.

When advising on the safety of medicines in acute porphyria, you should point out that any risk from a medicine is **cumulative** with other precipitants of an acute attack such as infection etc.



UKPMIS
UK Porphyria Medicines Information Service

NHS
National Acute Porphyria Service

GIG CYMRU NHS WALES

2024 SAFE LIST: Drugs that are considered to be **SAFE** for use in the acute porphyrias

This safe list was produced jointly by the UK Porphyria Medicines Information Service (UKPMIS) and Cardiff Porphyria Service and is supported by the National Acute Porphyria Service (NAPS). We gratefully acknowledge the clinical impact of the evidence-based drug safety assessments provided on the comprehensive Drug Database for Acute Porphyria (http://www.drugs-porphyria.org) on the range of available medicines for porphyria patients.

This list is based on the best information available to us at the time of compilation and provides guidance on drugs to use first line. It is not intended to be comprehensive. Inclusion of a drug does not guarantee that it will be safe in all circumstances. For information on medication not listed and advice on the use of antiretrovirals, antineoplastics or other complex treatment scenarios please contact UKPMIS by telephone (**029 2184 2251**), or see our website https://www.wmic.wales.nhs.uk/specialist-services/drugs-in-porphyria/. Unfortunately we are unable to accept enquiries via e-mail.

Healthcare professionals requiring clinical advice on the management of acute porphyria attacks should contact NAPS on 029 2074 7747 – available 24 hours a day, 7 days a week.

All topical preparations (including topical antifungals, lice treatments & eye drops) are considered safe, when applied to intact skin or mucosa.

Abatacept
Acamprosate
Acebutolol
Acetazolamide
Acetylcysteine
Aciclovir
Aclidinium bromide
Adalimumab
Adenosine
Adrenaline
Aflibercept
Alemtuzumab
Alendronic acid
Alfacalcidol
Alfentanil
Alginates (e.g. Gaviscon®, Peptac®)
Allopurinol
Almotriptan
Alogliptin
Alpha tocopheryl/tocopherol
Alteplase
Aluminium salts
Amantadine
Amikacin
Amiloride
Aminophylline
Amisulpride
Amitriptyline
Amlodipine
Amoxicillin
Amphotericin
Ampicillin
Anakinra
Anidulafungin
Apixaban
Arachis oil enema
Argatroban
Aripiprazole
Articaine
Ascorbic acid
Aspirin

Belimumab
Bendroflumethiazide
Benralizumab
Benzylpenicillin
Betahistine
Betamethasone
Betaxolol
Bevacizumab
Bezafibrate
Bisacodyl
Bisoprolol
Budesonide
Bumetanide
Bupivacaine
Buprenorphine
Calcitriol
Calcium polystyrene sulfonate
Calcium salts
Canagliflozin
Canakinumab
Candesartan
Captopril
Carbimazole
Carboprost
Carvedilol
Caspofungin
Cefaclor
Cefadroxil
Cefalexin
Cefepime
Cefixime
Cefotaxime
Cefoxitin
Cefradine
Ceftaroline
Ceftazidime
Ceftriaxone
Cefuroxime
Celecoxib
Certolizumab
Cetirizine
Cetuximab

Co-careldopa
Codeine phosphate
Co-fluampicil [1]
Colchicine
Colecalciferol
Colesevelam
Colestipol
Colestyramine
Contrast media – gadolinium-based
Contrast media – Gastrografin®
Contrast media – iodine-based
COVID-19 vaccines
Cyclizine
Cycloserine
Dabigatran
Dalteparin
Danaparoid
Dapagliflozin
Darbepoetin
Deflazacort
Demeclocycline
Denosumab
Desferrioxamine
Desflurane
Desloratadine
Dexamethasone
Dextromethorphan
Diamorphine
Diazepam
Diclofenac
Dicycloverine
Digoxin
Dihydrocodeine
Dimeticone
Dinoprostone
Diphenhydramine
Diphtheria/tetanus/pertussis/polio vaccine
Diphtheria/tetanus/pertussis/polio/Hib/hepatitis B vaccine
Dipyridamole

Eprosartan
Eptifibatide
Ergocalciferol
Ertapenem
Ertugliflozin
Escitalopram
Esmolol
Esomeprazole
Etanercept
Ethambutol
Etoricoxib
Exenatide
Ezetimibe
Famciclovir
Felodipine
Fenofibrate
Fentanyl
Fexofenadine
Fidaxomicin
Filgrastim
Flucloxacillin [1]
Flucytosine
Fludrocortisone
Flumazenil
Fluoxetine
Fluticasone
Fluvastatin
Fluvoxamine
Fondaparinux
Formoterol
Fosfomycin
Fosinopril
Furosemide
Fusidic acid
Gabapentin
Galantamine
Ganciclovir
G-CSF (Granulocyte-colony stimulating factor)
Gemeprost
Gemfibrozil
Gentamicin

The UKPMIS safe list

The Welsh Medicines Advice Service have produced a series of articles on prescribing in patients with porphyria;

Prescribing restrictions in non-acute cutaneous porphyria (available in Welsh)
Travel – a guide for people with acute porphyria (available in Welsh)
Are topical medicines safe in people with porphyria?
How should haem arginate (human hemin) be administered in the management of acute porphyrias?
Acne treatment in those with acute porphyria (available in Welsh)
Safety of dental medicines in acute porphyria
Making safe medicine choices during general anaesthesia and surgery in acute porphyria

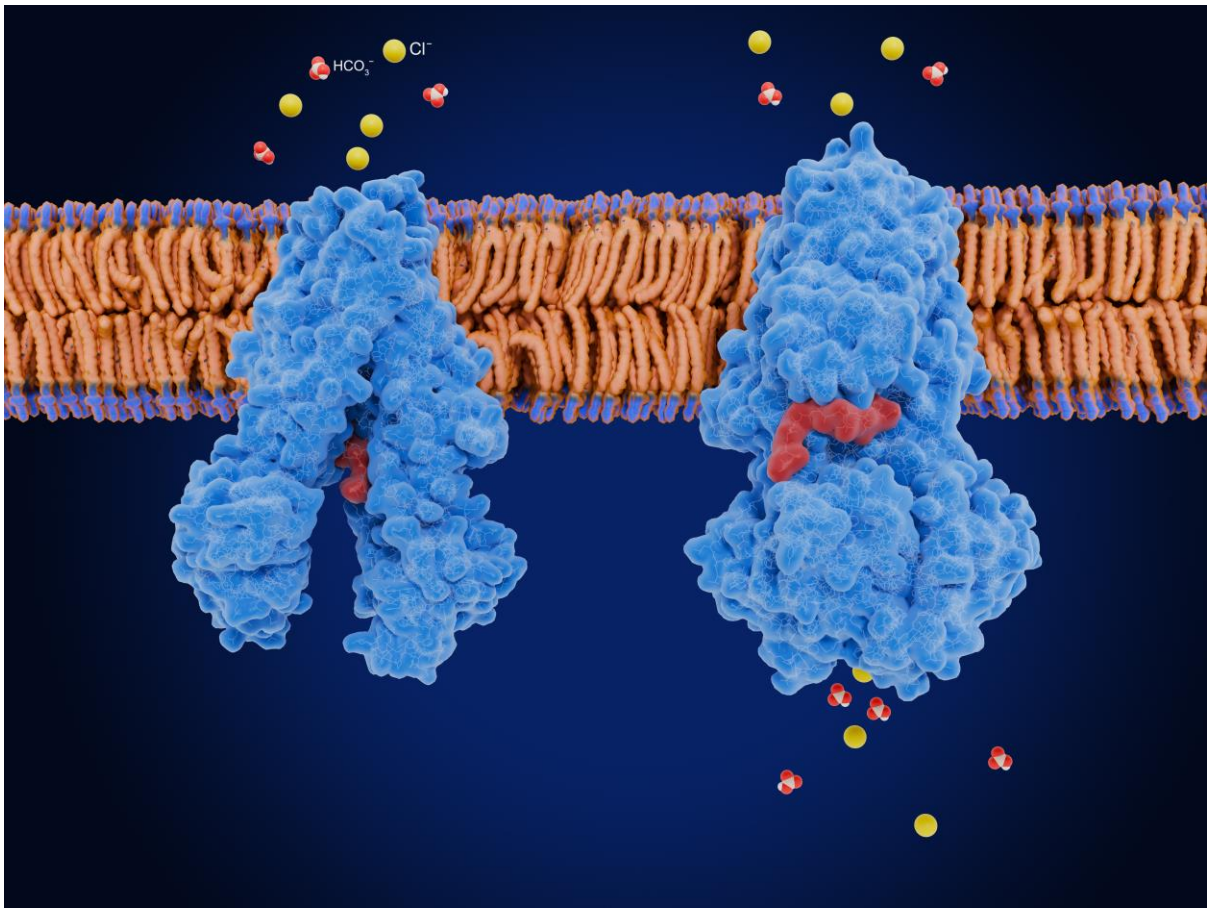
[Last updated: 19 December 2024]

2. Cystic fibrosis

CFTR protein

Cystic fibrosis (CF) is a disorder usually diagnosed at birth in the UK through newborn screening programmes. Variants in **the cystic fibrosis transmembrane conductance regulator (CFTR)** gene result in faulty production of the CFTR protein. This protein regulates the movement of **chloride**, **bicarbonate** and **water** across membranes. If it is not functioning correctly, secretions in certain parts of the body, such as the lungs, pancreas and gut, become very thick and are difficult to clear.

The CFTR protein is shaped like **a channel with a gate**. The gate needs to be present at the cell surface and open for chloride to flow through it. Around 85% of patients with CF in Europe can make the CFTR protein but it does not fold into shape correctly and so cannot move to the cell surface. The most common variant causing this is F508del. Other patients have gene variants which result in the gate of the channel not opening, or mean the channel is completely absent.



A computed generated image of the CFTR protein. On the left-hand side the channel is closed and chloride and bicarbonate cannot pass. On the right-hand side the channel is open and the ions can move across the cell membrane.

[Last updated: 19 December 2024]

CFTR modulators

The introduction of CFTR modulators has significantly improved the quality of life and health outcomes for many patients with CF.

There are 4 CFTR modulators currently approved for use in the NHS;

- Kaftrio (ivacaftor, tezacaftor, elexacaftor – sometimes referred to as 'triple therapy')
- Orkambi (ivacaftor, lumacaftor)
- Symkevi (ivacaftor, tezacaftor)
- Kalydeco (ivacaftor)

Ivacaftor is called a '**potentiator**' which means it holds the gate of the CFTR channel open so chloride can flow through the cell membrane. Tezacaftor, elexacaftor and lumacaftor are called '**correctors'**. They act by helping the CFTR protein form the correct shape, get to the cell surface and stay there longer. Correctors and potentiators are used in combination to optimise their efficacy.

In practice, in the UK, most eligible adults and children over 2 years are given triple therapy (ivacaftor, tezacaftor, elexacaftor) in the morning with single agent ivacaftor given in the evening. Patients are required to have specific gene mutations to qualify as outlined by NHS England.

Chronic complications

Despite the introduction of the CFTR modulators and other advances in physiotherapy and medicine, some patients will still suffer from chronic complications. For example, CFTR modulators will not work in patients who have a gene variant which means they produce no CFTR protein.

[Last updated: 19 December 2024]

Mucus accumulates in the lungs which become infected by bacteria (most commonly Pseudomonas aeruginosa). Recurrent, intermittent infections occur and can become chronic, which may accelerate a decline in respiratory function. **Preventing chronic chest infection** is therefore a key element in increasing survival. Airways clearance techniques such as physiotherapy help to reverse the build-up of mucus, and medicines such as inhaled dornase alfa or hypertonic saline reduce the viscosity of lung secretions. Infections may be managed with inhaled antibiotics such as tobramycin or colistimethate sodium, or a variety of oral medication depending on the bacteria present in sputum samples.

Damage to the **pancreas** results in its **digestive enzymes not reaching the bowel in sufficient quantity**, and this can give rise to malnutrition. This dietary deficiency can affect growth. Patients with CF often take pancreatic enzyme supplements orally (pancreatin) and sometimes the doses may be higher compared to that used in other indications (e.g. 40 capsules daily of the 25 000 unit strength). In addition, they may need nutritional supplements to boost their calorific intake and to ensure they receive adequate fat-soluble vitamins. Some patients suffer from liver impairment, and patients with CF can develop diabetes type 3c because of ongoing damage to the pancreas which may need to be treated pharmacologically.

Medicines optimisation

Patients with CF may handle medicines differently, but it's difficult to make generalisations as the effects of cystic fibrosis vary widely between patients. All cystic fibrosis specialist centres in the UK have pharmacist team members, who can provide advice on medication, while lung transplant centres manage these specialist medicines, including interpreting therapeutic drug monitoring.

The absorption of medicines may be reduced because of the effects that CF has on the gut.

[Last updated: 19 December 2024]

Many patients with CF are children and the special care required with medicines in this age group is discussed in our children's tutorial.

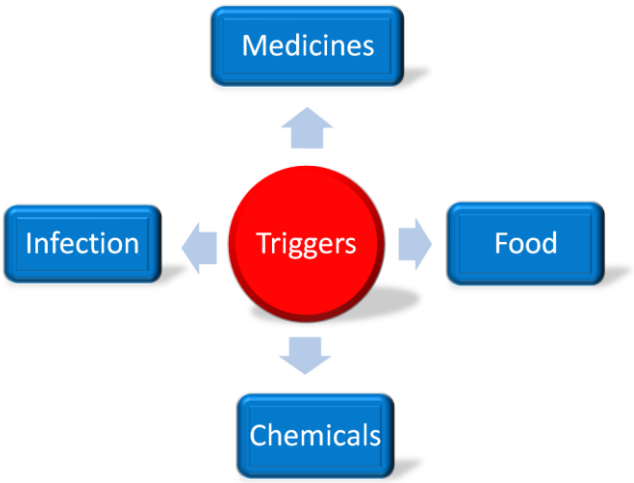
As above, some patients with cystic fibrosis have CF-related liver disease, and the principles discussed in our liver tutorial are useful for considering the impact of any liver dysfunction.

Patients with CF may need medicines that are not commonly used in other patient groups, and so pharmacists have a particular role to ensure that prescribed regimens are safe and correct. The medicines concerned may be unlicensed, given via an unlicensed route, or be taken at larger than expected doses. Pharmacists also counsel patients on the benefits and risks of taking their medicines including their CFTR modulators, and the importance of adherence even if symptoms improve and patients feel relatively well.

Read the most recent UK Cystic Fibrosis Registry summary to see how health outcomes have changed from 2018 to 2023.

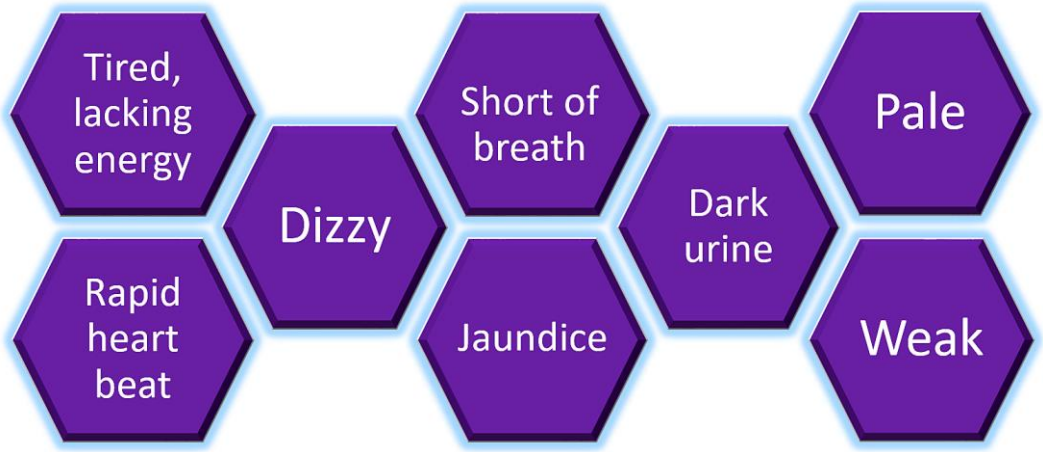
3. G6PD deficiency

Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme that protects red blood cells from damage. In patients with an inherited G6PD deficiency, certain triggers can cause red blood cells to haemolyse, potentially resulting in an 'acute haemolytic anaemia'. Some of the common triggers are summarised in the diagram here.



The main food that can trigger an acute attack is broad beans.

When a haemolytic episode occurs, the symptoms may include some or all of the following:



The duration of symptoms arising from an acute attack depends on its severity. However, the process of erythropoiesis, by which the body produces new red blood cells, is rapid and newly synthesised cells are unaffected once the trigger has gone away. People from certain parts of the world are more likely to suffer from G6PD deficiency, such as those who are of African, Middle Eastern or Mediterranean descent. It is also more common in men.

Medicines and G6PD deficiency

The genetic profile of an individual patient with G6PD deficiency affects whether a specific medicine causes an acute episode or not, and the severity of it. So while one sufferer may tolerate a particular medicine, another may react to it.

The risk of medicines provoking haemolytic anaemia, and the severity of attacks, is usually dose-dependent.

You can always check which medicines are regarded as unsafe by looking in the G6PD deficiency section of the BNF. The G6PD Deficiency Association website or App may help you further.

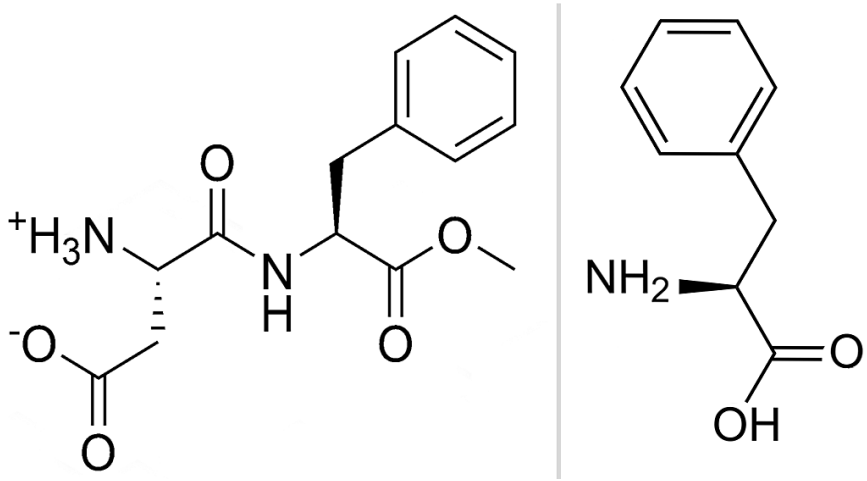
4. Phenylketonuria

Patients with phenylketonuria (PKU) are unable to break down the amino acid phenylalanine because activity of the enzyme responsible, phenylalanine hydroxylase, is reduced or absent due to genetic variation.

This allows phenylalanine to build up to potentially toxic levels. Nerve cells in the brain are particularly sensitive to this amino acid and they can become damaged when exposed to high levels.

As mentioned on the page for cystic fibrosis, in the UK, the families of infants are offered newborn screening within the first week of life for PKU.

Symptoms of **untreated** PKU can include behavioural difficulties, epilepsy, tremors, jerky movements, eczema, vomiting, and reduced pigment of the skin, hair and eyes. The main treatment is a controlled, low-protein diet to reduce intake of phenylalanine, but patients also have to take amino acid supplements to make sure they're getting all the nutrients required for normal growth and good health. Some patients may also be eligible for a relatively new treatment called sapropterin.



Chemical structure for aspartame (left) and phenylalanine (right)

People with PKU must avoid the sweetener aspartame because it is converted to phenylalanine by the body. Aspartame is found in some food and drinks, and also in some medicines. As a pharmacist you may be asked to check whether a medicine contains aspartame, or to advise on an aspartame-free alternative. It is a legal requirement for any medicine that contains aspartame to state it on the patient information leaflet. You can use the 'Advanced Search' function of the emc to search for medicines that don't contain aspartame.

Suggested questions

We have covered a diverse range of inherited disorders, so it is impossible to give you a generic list of questions to ask here. However there are a number of questions specific to **patients with porphyria**, when asked about the suitability of a medicine.

What is the age and sex of the patient?

What type of porphyria does the patient have?

- Acute Intermittent Porphyria (AIP)
- Hereditary Coproporphyria (HCP)
- Variegate Porphyria (VP)
- Erythropoietic Protoporphyria (EPP)
- Porphyria Cutanea Tarda (PCT)
- Congenital Erythropoietic Porphyria (CEP)
- ALAD-deficiency porphyria (ADP)
- Unknown

What is the current status of the patient's porphyria (i.e. active or latent)?
Does the patient have any history of drug-induced porphyria?
What is the indication for the drug in question?