

# 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.

## 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 bigger molecules such as haemoglobin, myoglobin, and cytochrome. Porphyrias lead to accumulation of neurotoxic and/or phototoxic haem precursors, 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**.

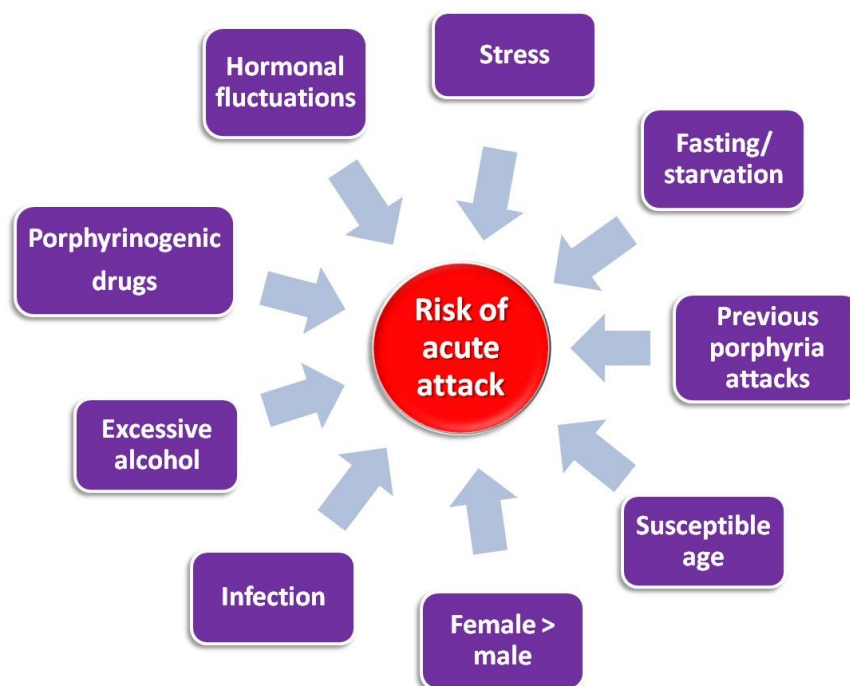
#### Acute porphyrias

- **AIP** = Acute intermittent porphyria
- **VP** = Variegate porphyria
- **HCP** = Hereditary coproporphyrin
- **ALAD-deficiency porphyria** = 5-aminolevulinic acid dehydratase deficiency porphyria

#### Non-acute porphyrias

- **PCT** = porphyria cutanea tarda
- **EPP** = erythropoietic protoporphyria
- **CEP** = congenital erythropoietic porphyria

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



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.

### 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 5.30pm; Saturdays and Sundays 9.00am to 12.45pm)
- **National Acute Porphyria Service (NAPS)** Tel. 029 2184 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.



**UKPMIS**  
UK Porphyria Medicines  
Information Service



**NHS**

National Acute  
Porphyria Service



**GIG**  
Cardiff and Vale  
University Health Board

**2021 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 2184 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	Belatacept	Clozapine	Enoxaparin
Acamprosate	Belimumab	Co-amoxiclav	Ertacapone
Acebutolol	Bendroflumethiazide	Co-beneldopa	Epinephrine
Acetazolamide	Benralizumab	Co-careldopa	Eplerenone
Acetylcysteine	Benzyloxyphenol	Codeine phosphate	Epoetin
Aciclovir	Betahistine	Co-fluampicil <sup>1</sup>	Eprosartan
Acidinium bromide	Betamethasone	Colchicine	Ergocalciferol
Adalimumab	Betaxolol	Colecalciferol	Ertapenem
Adenosine	Bevacizumab	Colesevelam	Ertugliflozin
Adrenaline	Bezafibrate	Colestipol	Escitalopram
Alfitercept	Bisacodyl	Colestyramine	Esmolol
Alentuzumab	Bisoprolol	Contrast media –	Esomeprazole
Alendronic acid	Budesonide	gadolinium-based	Etanercept
Alfacalcidol	Bumetanide	Contrast media – Gastrografin®	Ethambutol
Alfentanil	Bupivacaine	Contrast media – Iodine-based	Etoricoxib
Alginates (e.g. Gaviscon®)	Buprenorphine	COVID-19 vaccines	Exenatide
Peptac®)	Calcitriol	Cyclizine	Ezetimibe
Allopurinol	Calcium polystyrene sulfonate	Cycloserine	Famciclovir
Almotriptan	Calcium salts	Dabigatran	Felodipine
Alogliptin	Canagliflozin	Dalteparin	Fenofibrate
Alpha tocopherol/tocopherol	Canakinumab	Danaparoid	Fentanyl
Alteplase	Candesartan	Dapagliflozin	Fexofenadine
Aluminium salts	Captopril	Darbepoetin	Filgrastim
Amantadine	Carbimazole	Deflazacort	Flucloxacillin <sup>1</sup>
Amikacin	Carboprost	Demeclocycline	Flucytosine
Amiloride	Carvedilol	Denosumab	Fludrocortisone
Aminophylline	Casoprolungin	Desferrioxamine	Flumazenil
Amisulpride	Cefaclor	Desflurane	Fluxetine
Amitriptyline	Cefadroxil	Desloratadine	Fluhenazine

The UKPMIS acute porphyria 'safe' list

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.

SPS has some guidance on the topic including;

- [Prescribing in patients with non-acute porphyria](#)
- [Prescribing topical medicines in patients with porphyria](#)
- [Providing travel advice to with patients with porphyria](#)
- [How should haem arginate be administered for the management of acute porphyria?](#)
- [Providing advice to patients undergoing dental treatment](#)

## 2. Cystic fibrosis

Cystic fibrosis (CF) is a disorder usually diagnosed at birth through newborn screening programmes. Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene result in faulty production of the CFTR protein. This protein regulates the movement of chloride and bicarbonate ions and water across membranes. This means that secretions in certain parts of the body such as the lungs, pancreas and gut, become very thick and are difficult to clear.

Life expectancy for people with CF has gradually been increasing with interventions such as physiotherapy and long-term antimicrobial prophylaxis. However the recent introduction of medicines that restore CFTR function ([‘CFTR modulators’](#)) has significantly improved the quality of life and health outcomes for some patients with CF.

### Chronic respiratory complications

In patients with CF, mucous 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. Most people who die of CF each year are young adults, and this is typically due to lung-related causes. 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 mucous, and medicines such as inhaled dornase alfa or hypertonic saline reduce the viscosity of lung secretions. Acute infections are treated with inhaled antibiotics such as tobramycin or colistimethate sodium, and oral azithromycin has been given as a long-term oral prophylaxis.

### Other complications

Damage to the pancreas results in its digestive enzymes not reaching the bowel in sufficient quantity, and this can give rise to malnutrition. In children this dietary deficiency can affect growth. Patients with CF take pancreatic enzyme supplements orally (pancreatin), and 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 older patients with CF can develop diabetes 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. The absorption of medicines may be altered because of the effects that CF has on the gut. Some people need higher doses of medicines or more frequent dosing because CF may enhance drug clearance. At the same time, patients may be smaller than expected for their age and thinner, and generally have little body fat, and this affects [volume of distribution](#). Many patients with CF are children and the special care required with medicines in this age group is discussed in our [children's tutorial](#).

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.

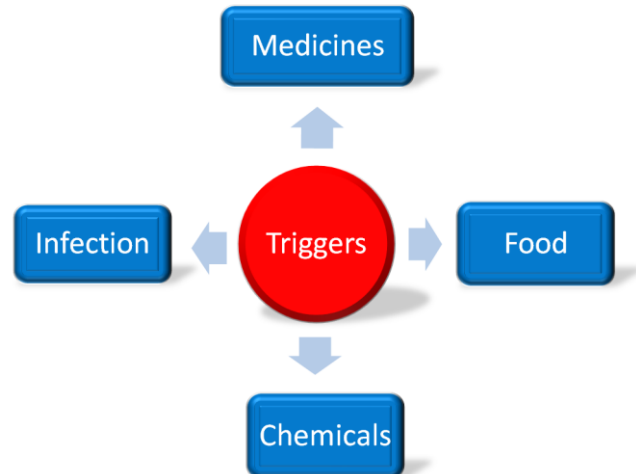


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Specialist cystic fibrosis pharmacists are experts at medicines optimisation in this group of patients, so you should try to contact one for advice before making a significant intervention.

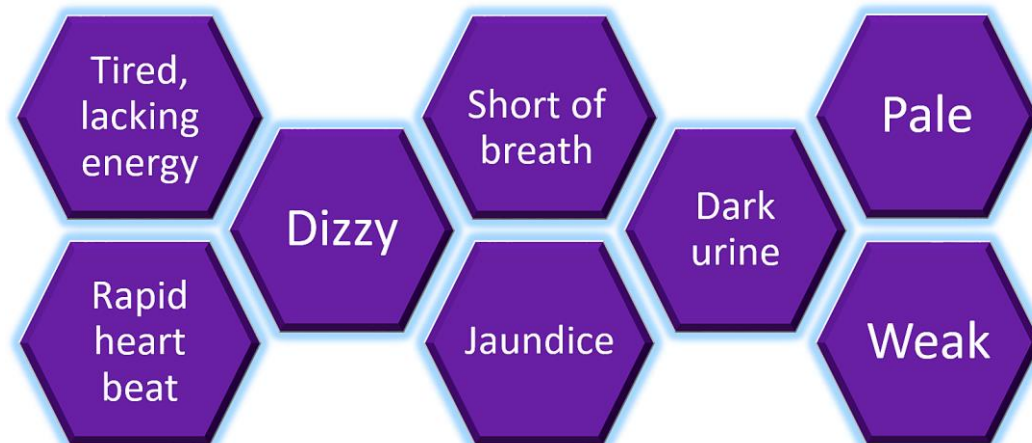
### 3. G6PD deficiency

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 make-up of the 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.

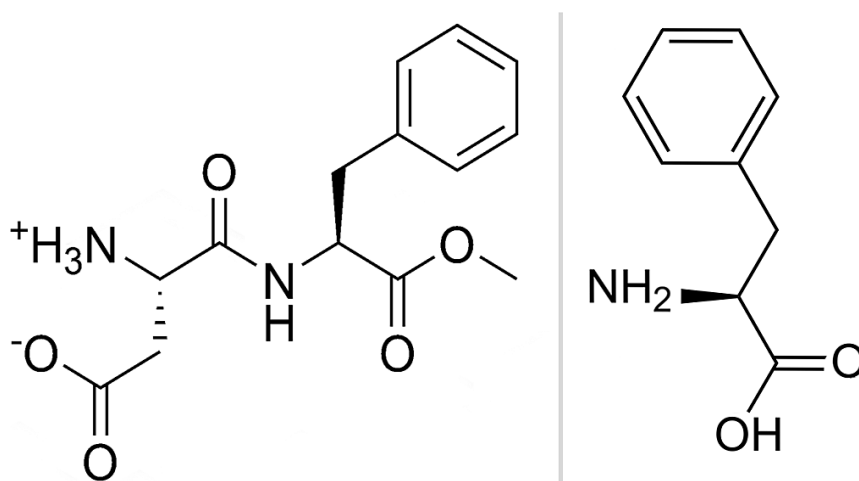




## 4. Phenylketonuria

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. 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.

Symptoms of 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.



*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 Protoporphyrria (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?**