Inherited Disorders

Introduction

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.

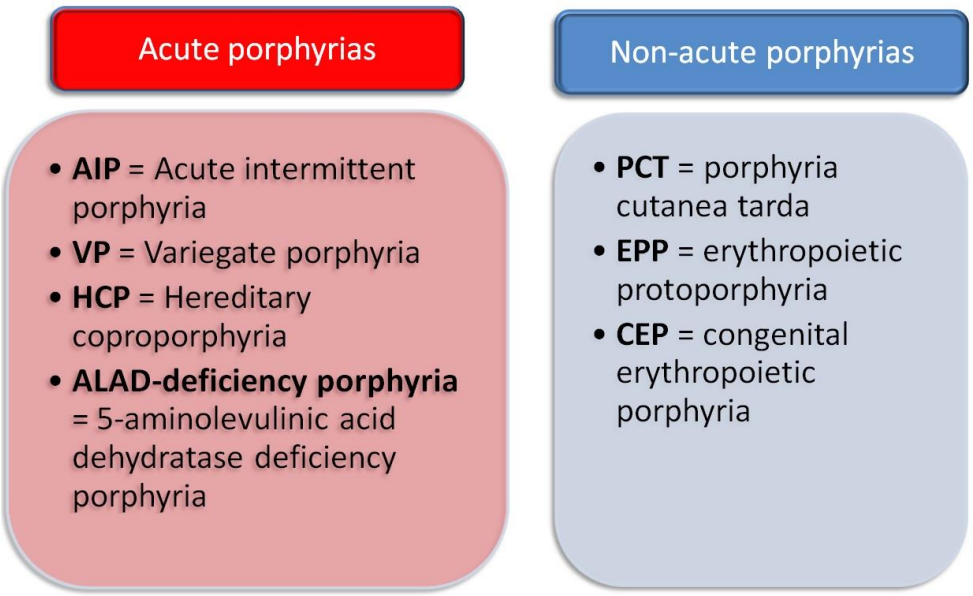
1. Porphyria

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 eight different 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 suffers from, and in particular whether it is **acute porphyria** or **non-acute porphyria**.



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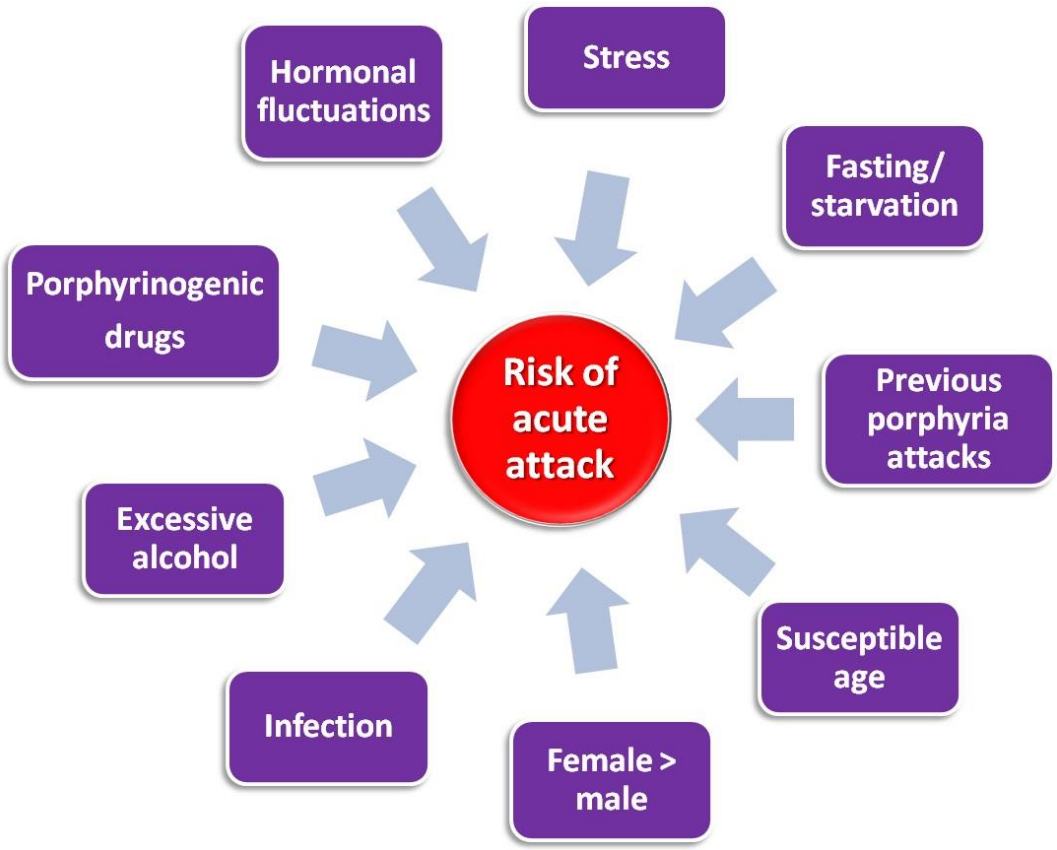
In practice, acute intermittent porphyria (AIP), variegate porphyria (VP) and hereditary coproporphyria (HCP) are the conditions that pharmacists may see presenting as an acute attack. Many factors can precipitate an acute attack by increasing the body's need for haem, and they act **cumulatively**. In patients with porphyria the haem is produced, but substrates and 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.

Acute porphyria and medicines

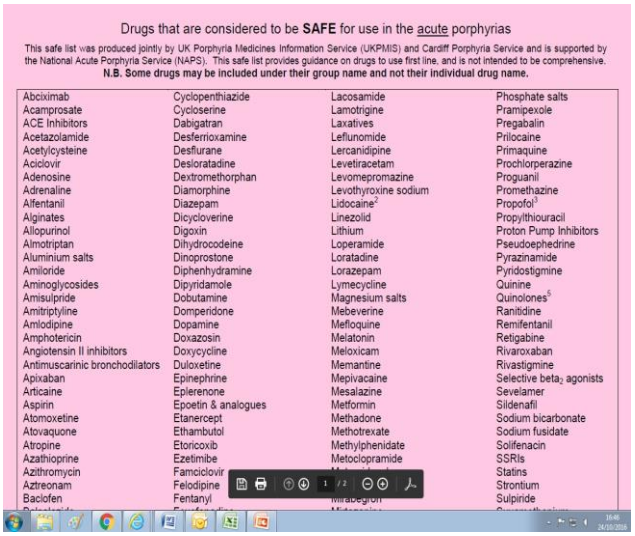
Medicines can contribute towards triggering an acute attack of porphyria in a patient with AIP, VP or HCP. There are a number of ways by which they can do this, including:

- **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 if 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. **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 personally about their precise diagnosis then you may be able to ask a relative or someone familiar with the person: *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 (type 'porphyria' into the search box). There is also a list of medicines rated as ***safe***, produced by the UK Porphyria Medicines Information Service. You should always look in ***both*** lists.



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

This safe list was produced jointly by UK Porphyria Medicines Information Service (UKPMIS) and Cardiff Porphyria Service and is supported by the National Acute Porphyria Service (NAPS). This safe list provides guidance on drugs to use first line, and is not intended to be comprehensive.
N.B. Some drugs may be included under their group name and not their individual drug name.

Abciximab	Cyclopenthiazide	Lacosamide	Phosphate salts
Acamprosate	Cycloserine	Lamotrigine	Pramipexole
ACE Inhibitors	Dabigatran	Laxatives	Pregabalin
Acetazolamide	Desferrioxamine	Leflunomide	Prilocaine
Acetylcysteine	Desflurane	Lercanidipine	Primaquine
Aciclovir	Desloratadine	Levetiracetam	Prochlorperazine
Adenosine	Dextromethorphan	Levomepromazine	Proguanil
Adrenaline	Diamorphine	Levothyroxine sodium	Promethazine
Alfentanil	Diazepam	Lidocaine[2]	Propofol[3]
Alginates	Dicycloverine	Linezolid	Propylthiouracil
Allopurinol	Digoxin	Lithium	Proton Pump Inhibitors
Almotriptan	Dihydrocodeine	Loperamide	Pseudoephedrine
Aluminium salts	Dinoprostone	Loratadine	Pyrazinamide
Amiloride	Diphenhydramine	Lorazepam	Pyridostigmine
Aminoglycosides	Dipyridamole	Lymecycline	Quinine
Amisulpride	Dobutamine	Magnesium salts	Quinolones[5]
Amitriptyline	Domperidone	Mebeverine	Ranitidine
Amlodipine	Dopamine	Mefloquine	Remifentanil
Amphotericin	Doxazosin	Melatonin	Retigabine
Angiotensin II inhibitors	Doxycycline	Meloxicam	Rivaroxaban
Antimuscarinic bronchodilators	Duloxetine	Memantine	Rivastigmine
Apixaban	Epinephrine	Mepivacaine	Selective beta$_2$ agonists
Articaine	Eplerenone	Mesalazine	Sevelamer
Aspirin	Epoetin & analogues	Metformin	Sildenafil
Atomoxetine	Etanercept	Methadone	Sodium bicarbonate
Atovaquone	Ethambutol	Methotrexate	Sodium fusidate
Atropine	Etoricoxib	Methylphenidate	Solifenacin
Azathioprine	Ezetimibe	Metoclopramide	SSRIs
Azithromycin	Famciclovir		Statins
Aztreonam	Felodipine		Strontium
Baclofen	Fentanyl		Sulpiride

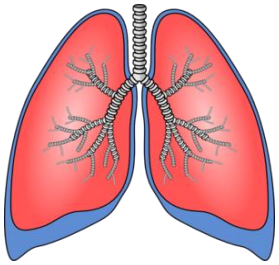
When advising on the safety of any medicine, you should point out that any risk from a medicine is cumulative with other precipitants of an acute attack such as infection etc (see previous page). If you cannot find out if a medicine is safe, or you are uncertain, then you can contact the following services for advice:

- **UK Porphyria MI Service** (UKPMIS) Tel. 029 20742251 (Monday to Friday 8.45am to 5.30pm; Saturdays 9.00am to 12.45pm)
- **National Acute Porphyria Service** (NAPS) Tel. 029 20747747 (available 24/7)

You can also phone NAPS for advice on managing an acute attack.

2. Cystic fibrosis

Cystic fibrosis (CF) is a disorder usually diagnosed in childhood in which a genetic mutation disrupts the movement of chloride 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. CF is a complex condition, and we offer only a very basic introduction here.

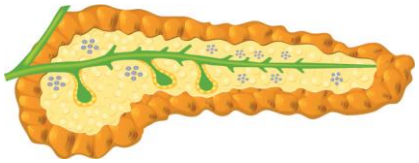


Chronic respiratory complications

Mucous accumulates in the lungs which becomes 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 they typically die from lung-related causes. So preventing chronic chest infection is 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 colistin, and oral azithromycin has been given as a long-term oral prophylaxis.

Gastrointestinal 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 also 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.

Cystic fibrosis and the pharmacist

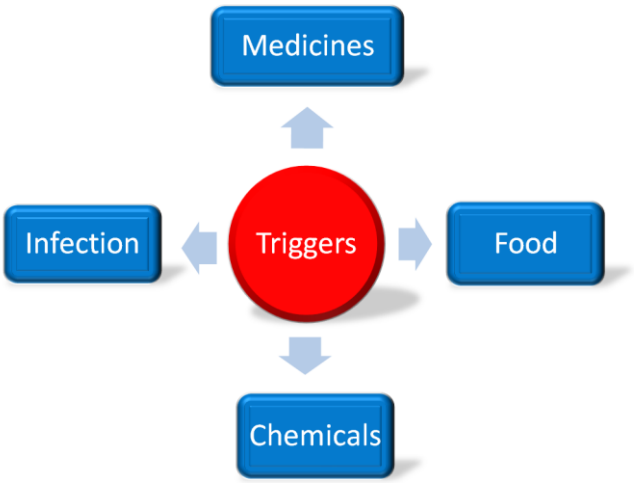
Patients with CF handle medicines differently, but every patient is different so it's difficult to make generalisations. The absorption of medicines may be altered because of the effects that CF has on the gut. Some people need bigger doses of medicines or more frequent dosing because CF may enhance 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 of the patients are children and the special care with which medicines are generally used in this age group is discussed in the children 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, may be given via an unlicensed route, or be taken at larger than expected doses. Hospital pharmacists can show patients how to administer medicines, and help them with adherence and monitoring of therapy. You can also organise communications about ongoing supplies of medicines by providing appropriate information to primary care colleagues such as GPs and community pharmacists.

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 safeguards red blood cells and protects them from damage. When there is an inherited G6PD deficiency, certain triggers can cause an acute illness because red blood cells become unstable and break down or haemolyse. This is called acute haemolytic anaemia, and 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, then symptoms may include some or all of the following:

The duration of symptoms arising from an acute attack depend 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

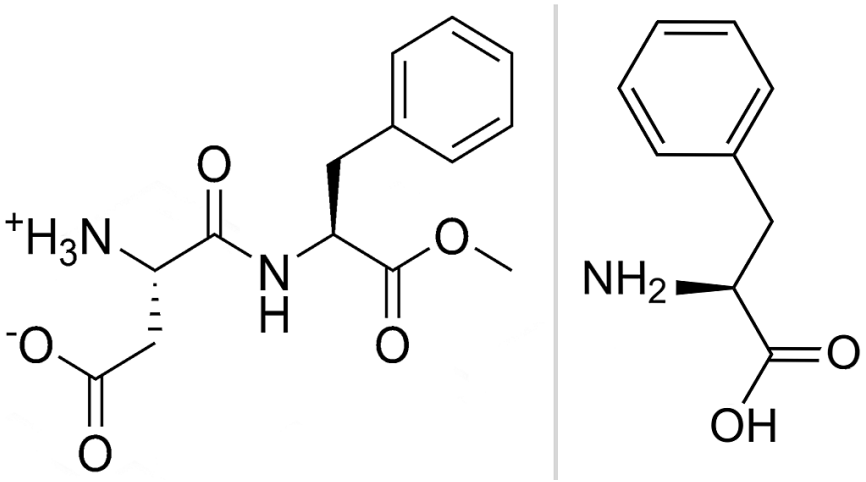
The genetic make-up of the individual patient with G6PD deficiency affects whether a specific medicine causes an acute episode or not, and the severity of it. So while one sufferer may tolerate a particular medicine, another may react to it. However, the effect of medicines is usually dose-related as well: the risk of provoking haemolytic anaemia is greater with bigger doses, and bigger doses also cause more severe symptoms.

You can always check to see which medicines are regarded as unsafe by looking in the G6PD deficiency section of the BNF.

4. Phenylketonuria

Patients with phenylketonuria (PKU) are unable to break down the amino acid phenylalanine because 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.



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 foods such as drinks, chewing gums, 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.