

## **LIST OF MEDICINES TO BE USED WITH CAUTION IN PRIMARY MITOCHONDRIAL DISEASE**



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**It is important to remember that side effects can occur with any medicine in any patient. This can affect anyone taking the medicine and may not be related to your mitochondrial disease. It is therefore essential that you take the advice of your doctor and read the information given with the medicine.**

### **WHAT IS THIS LIST?**

This is a list of medicines (drugs) that should be avoided or used with caution in people affected by a primary mitochondrial disease. Patients suspected of having a primary mitochondrial disease, but in whom the diagnosis has not yet been confirmed by doctors, may also consult this list. The list was compiled by a group of experts in mitochondrial disease (doctors, pharmacists and scientists), after careful consideration and consultation.

### **WHAT IS A PRIMARY MITOCHONDRIAL DISEASE?**

This is a genetic disorder that affects the function of the mitochondria. Mitochondria are tiny power stations present inside our cells and are responsible for making the energy that powers everything that happens inside our bodies.

### **HOW IS A PRIMARY MITOCHONDRIAL DISEASE DIAGNOSED?**

Primary mitochondrial disease is diagnosed by doctors after a series of tests that may include blood and urine tests, brain scan (MRI), muscle biopsy and, most importantly, genetic testing. It is not always possible to identify the genetic cause in every affected individual, and in these cases a clinical diagnosis of “probable mitochondrial disease” may be made.

### **HOW IS PRIMARY MITOCHONDRIAL DISEASE TREATED?**

Currently, there are no cures for most mitochondrial diseases. This means that supportive treatments and medicines are extremely important. These include medicines for treating seizures (anticonvulsants), antibiotics for treating bacterial infections, medicine for

managing pain, controlling fevers, treating diabetes and heart disease, and for administering general anaesthesia safely when an operation is needed.

### **WHY DID THE LIST OF DRUGS TO BE AVOIDED NEED UPDATING?**

We saw that the existing list of medicines thought to be unsuitable (contraindicated) in patients with mitochondrial disease was very long and contained drugs that we felt could be useful in treating patients with mitochondrial disease. Therefore, we thought it was important that each medicine on the list was reviewed and updated with the latest clinical and scientific evidence.

### **WHAT WAS THE PROCESS BY WHICH THE LIST WAS REVIEWED AND UPDATED?**

Our group consisted of sixteen doctors, pharmacists and scientists and each was assigned a group of drugs to evaluate. These experts then spent two months researching the evidence for whether the medicine was harmful for mitochondrial disease patients for each of the drugs assigned to them. The group then met for a two day workshop to discuss the evidence for more than 50 drugs and decide whether or not they could safely be used in mitochondrial disease. This process of evaluating evidence is known as a Delphi workshop, and is widely accepted as a valid scientific method.

### **WHAT WERE THE CONCLUSIONS OF THE WORKSHOP?**

After a thorough review of the evidence, we concluded that most drugs on the previous list could be used safely in people affected by primary mitochondrial disease. The drugs studied and considered safe to use are listed in **TABLE 1**. The drugs considered dangerous, or to be used with caution are listed in **TABLE 2**. The drug valproic acid (an antiepileptic drug also known as sodium valproate or Epilim) should not be given to patients with mutations in a gene called *POLG* and not used in any patient who could have a primary mitochondrial disease until *POLG* mutation is ruled out. Table 2 also lists drugs that need careful evaluation and situations in which doctors may want to change the way that these medicines are used or prescribed for patients affected by particular types of mitochondrial disease.

### **WHY IS THIS LIST NOT THE SAME AS OTHER LISTS OF MEDICINES TO BE AVOIDED IN MITOCHONDRIAL DISEASES?**

This is a NEW UPDATED VERSION to replace all previous lists of medicines to be avoided in primary mitochondrial disease, based on the latest scientific and clinical evidence.

## WHAT SHOULD I DO WITH THE LIST?

It is very important that you consult your doctor whenever you are unwell. You may, however, wish to share the "[List of medicines considered safe to use](#)" and the "[List with points of attention](#)" with your doctor(s) and discuss with them what this means for you and your particular type of mitochondrial disease.

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## REFERENCE (scientific publication):

<https://onlinelibrary.wiley.com/doi/epdf/10.1002/jimd.12196>

Table 1. List of drugs studied and considered safe to use

Category	Generic name
<b>ACE inhibitors</b>	captopril, perindopril, enalapril, lisinopril
<b>Analgesics – Antipyretics</b>	acetaminophen (Paracetamol), salicylates
<b>Anesthetics</b>	articain, bupivacaine, lidocain, halothane, isoflurane, sevoflurane, barbiturates, fentanyl, ketamine, midazolam / benzodiazepine, propofol
<b>Antiarrhythmics</b>	amiodarone, beta blockers
<b>Antibiotics</b>	ceftriaxone, chloramphenicol, linezolid, quinolones, tetracyclines
<b>Antidiabetic drugs</b>	biguanide drugs (metformin), thiazolidinedione (glitazones)
<b>Antiepileptic drugs</b>	barbiturates, carbamazepine, gabapentin, levetiracetam, oxcarbazepine, perampanel, phenytoin, rufinamide, stiripentol, topiramate

Category	Generic name
Antipsychotic / neuroleptic drugs / antidepressants	amitriptyline, amoxapine, chlorpromazine, clozapine, fluoxetine, fluphenazine, haloperidol, quetiapine, risperidone
Antiretroviral drugs	eg zidovudine, abacavir
Bisphosphonates	eg pamidronate, alendronate
Cannabidiol	
Chemotherapeutics	eg carboplatin, doxorubicin, ifosfamide
Ethanol	
Fibrate drugs	clofibrate, ciprofibrate
Immunotherapeutics	interferons
NSAIDs	eg diclofenac, indomethacin, naproxen
Statins	eg cerivastatin, simvastatin
Steroids	eg hydrocortisone, dexamethason, prednisone

**PRINT TABLE 1.**

Table 2. Points of attention regarding drug prescription in patients with a mitochondrial disease

Specific drug / situation / disease causing gene	Points of attention
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*Specific drug / disease causing gene*

Valproic acid (sodium valproate)	Should be used only in exceptional circumstances. <b>Should absolutely not be given to patients with mutations in a gene called <i>POLG</i></b> or to
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**Specific drug /  
situation / disease  
causing gene**

**Points of attention**

patients with symptoms suspicious for *POLG* disease. Should not be used in patients with liver disease.

Aminoglycosides  
(antibiotics)

In case of specific mitochondrial DNA mutations (12S rRNA) these antibiotics may cause hearing loss. In emergency situations aminoglycosides could be used while the benefits of the drugs are more important than. If long-term treatment is necessary one should screen for these mutations and / or switch to another antibiotic regime.

Neuromuscular  
blocking drugs (used  
for anaesthesia)

In patients with muscle disease these drugs should preferably not be used or, if necessary, under strict monitoring.

***Specific situation***

General anaesthesia  
and surgery

The time of fasting before surgery should be as short as possible. During prolonged anaesthesia fluid and caloric intake should be guaranteed by glucose infusion, unless the patient is on a ketogenic diet.

Duration of treatment

Side effects may develop when medication is used for a longer period. It must be assessed for each individual patient whether the need for long-term treatment outweighs the possible side effects.

Kidney failure

Kidneys remove certain medicines from the blood. If the kidneys do not work properly, too much medicine remains in the blood. This may cause more side effects. Dosage and / or dosing frequency should be adjusted for these medicines.

High lactic acid in  
blood

Patients with a mitochondrial disease may have an increased blood acidity due to high lactic acid. In that case, drugs that can make the blood acidic should preferably not be used or, if necessary, under regular monitoring of