Guide to drug monitoring in primary care

For some drugs there is a need for regular monitoring to ensure appropriate dosing, reduction in the risk of adverse effects and a reduction in medication errors. This guide looks at drugs which require regular monitoring in primary care. Drugs that are considered high risk should be prioritised. Many of these drugs are initiated in secondary care, but general practice plays an important role in ensuring that drugs continue to be used safely by undertaking drug monitoring and patient safety surveillance, often through a shared care arrangement. All medicines have the potential for adverse effects, so regular medication review should be routine. However, some medicines are particularly high risk due to the effects the drug has on the body and how changes in the patient's condition can affect the way the body processes the drug. These areas of risk can be mitigated by regular monitoring and assessing the results against the recommendations for prescribing. It is important that any change in monitored parameters should trigger a consideration of the medicines prescribed. Examples of high risk drugs include disease-modifying antirheumatic drugs (DMARDs), amiodarone and lithium.[1]

As part of the Network Contract Directed Enhanced Service (DES) Primary Care Networks (PCNs) are required to identify and prioritise patients who would benefit from a structured medication review (SMR). This must include patients with complex and problematic polypharmacy, specifically those on 10 or more medications and patients on medicines commonly associated with medication errors.[2]

A set of medication safety indicators have been developed as part of a programme of work to reduce medication error and promote safer use of medicines, including prescribing, dispensing, administration and monitoring. The programme of work is in response to the World Health Organisation (WHO) global challenge – Medication without Harm. The purpose of the indicators is to identify hospital admissions that may be associated with prescribing that potentially increases the risk of harm, and to quantify patients at potentially increased risk.[3]

Setting up a robust system for monitoring all high-risk medicines will reduce risks for patients and enable practices achieve safer prescribing quality indicators described in the GP contract.[1]

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Amiodarone[4-10]

Amiodarone is always initiated in secondary care or under specialist supervision. However, primary care practitioners may be expected to continue prescribing amiodarone and to monitor the person for adverse effects (depending on locally agreed shared care guidelines).[4,5]

Baseline measurements	• Chest x-ray • Electrocardiography (ECG) • Serum urea and electrolyte measurement (U&Es) • Serum potassium • Liver function tests (LFTs) - particularly transaminases • Thyroid function tests (TFTs) - FT3, FT4 and TSH.
Consider once only	• Thyroid peroxidase antibodies (TPoAb) - Can be used to help determine risk of thyroid dysfunction prior to or during amiodarone therapy. Their presence usually precedes the development of thyroid disorders.

Ongoing monitoring once stable	Frequency	Notes
REQUIRED		
LFTs	Every six months	• Treatment should be discontinued if severe liver function abnormalities or clinical signs of liver disease develop.
TFTs	Every six months And for 12 months after discontinuation	• See below for information on abnormal results for thyroid function tests. • After stopping amiodarone, continue TFT testing for up to 12 months. This is particularly important in the elderly. • A raised T3 and T4 with a very low or undetectable TSH concentration suggests the development of thyrotoxicosis.
CONSIDER		
U&Es	Every six months	• Especially if patient takes concomitant diuretics.
Chest x-ray	Every 12 months	• If pulmonary toxicity is suspected, repeat chest x-ray and lung function tests, including measurement of transfer factor, where possible. Specialist referral advised. • Suspect pneumonitis if new or progressive shortness of breath or cough develops.
Electrocardiography (ECG)	Every 12 months	

Ongoing monitoring once stable	Frequency	Notes
CONSIDER		
Ophthalmological examination	Every 12 months	• The manufacturer recommends annual eye examinations for all people taking amiodarone; however expert opinion on the use of amiodarone suggests that these are only necessary for people with visual symptoms. • If blurred or decreased vision occurs, complete ophthalmologic examination including fundoscopy promptly. • Appearance of optic neuropathy and/or optic neuritis requires amiodarone withdrawal due to the potential progression to blindness. • Unless blurred or decreased vision occurs, ophthalmological examination is recommended annually.
International Normalised Ratio (INR) for warfarinised patients	Initially ONCE weekly for first seven weeks, Then at longer intervals (depending on response), up to every 12 weeks.	• More frequent monitoring of INR both during and after amiodarone treatment is recommended. • Anticoagulant effects of warfarin are increased by amiodarone and bleeding might occur. The onset of this interaction may be slow (up to two weeks), with the peak effect occurring about seven weeks after warfarin treatment is started. • Adjust the doses of warfarin based on INR measurements. • Some recommend that the dose of warfarin should initially be reduced by 25% or 50% when amiodarone is added to established anticoagulant treatment, with increased INR monitoring until a new steady-state is achieved. • The final reduction in warfarin dose required might depend on the amiodarone maintenance dose: » Average warfarin dose reductions of 25% have been required for amiodarone 100 mg daily » 30 to 35% for amiodarone 200 mg daily » 35% for amiodarone 300 mg daily » 40 to 50% for amiodarone 400 mg daily » 65% for amiodarone 600 mg daily » These suggested reductions are broad generalisations and individual patients might need more or less. Good monitoring is essential.[10] • If established amiodarone therapy is withdrawn in a patient taking warfarin, it is likely the dose of warfarin will need increasing gradually over the first few months after amiodarone is stopped. • Be aware that amiodarone has a long half-life (25-100 days); thus, interactions may occur for some time after drug withdrawal. • Amiodarone-induced thyrotoxicosis might also alter the INR in patients taking warfarin*.

*The INR of a patient stabilised on warfarin and amiodarone was noted to increase from about 2 to 5.5 after he developed amiodarone-induced thyrotoxicosis. Another three well-described cases of this potential interaction have been reported. Thyrotoxicosis potentiates the effect of warfarin, and as a result less warfarin would be required to prolong the prothrombin time.[10]

Abnormal results[6]

Hypothyroidism

In clinically euthyroid patients, amiodarone may cause isolated biochemical changes (increase free-T4, slight decrease/normal free-T3). However, there is no reason to discontinue unless there is clinical or further biological (TSH) evidence of thyroid disease. The following advice is available:

- Free T4 is low; TSH is greater than 4.5 mU/L
  - Consider treating with levothyroxine if amiodarone is considered essential
- Free T4 is normal; TSH is greater than 10 mU/L; duration is over six months
  - Consider treating with levothyroxine or repeat again in three months
- Free T4 is elevated; TSH is greater than 4.5 mU/L; duration is less than three months
  - Observe and repeat in three months

Hyperthyroidism

- High circulating free T4 is associated with high or high/normal free T3 and undetectable TSH:
  - A diagnosis of amiodarone-associated hyperthyroidism is possible
  - Withdraw amiodarone and seek specialist referral
  - Clinical recovery usually occurs within a few months but precedes normalisation of TFTs
  - Severe cases, sometimes resulting in fatalities, have been reported
- TSH is less than 0.1 mU/L, and T3 and T4 normal or minimally increased
  - Repeat test in two to four weeks
- TSH is less than 0.1 mU/L and T4 elevated, T3 elevated or 50% greater than baseline
  - Discuss urgently with a specialist who may advise amiodarone withdrawal
  - Arrange for TSH-receptor antibodies and TPO antibodies

Patient and carer advice[7]

Phototoxicity

Due to the possibility of phototoxic reactions, advise patients to shield the skin from light during treatment and for several months after discontinuing amiodarone. A wide-spectrum sunscreen to protect against both long-wave ultraviolet and visible light should be used.

Driving and skilled tasks

Advise on the effects on driving and performance of skilled tasks - corneal microdeposits may be associated with blurred vision.

Antipsychotics[11-13]

Baseline measurements	• When antipsychotics are initiated, baseline assessments should be taken in secondary care. • People with a psychotic disorder will remain under the responsibility of the secondary care team for the first 12 months, or until their condition has stabilised (whichever is longer). • Regular monitoring may subsequently be done in primary care on specialist advice or depending on the person's care plan.

Ongoing monitoring	Frequency	Notes
Bodyweight, or body mass index (BMI)	• Weekly for the first six weeks • Then at three months • Thereafter every 12 months, or more often if the person is gaining weight rapidly.	
U&Es	• Every 12 months.	• Include creatinine and estimated Glomerular Filtration Rate (eGFR).
Full blood count (FBC)	• Every 12 months.	• See separate note below regarding clozapine.
Blood lipids	• Every three months after starting treatment • Then every 12 months.	
Plasma Glucose or HbA1c	• Every three months after starting treatment • Then every 12 months.	• Additionally for clozapine and olanzapine repeat after the first month of treatment. • Ask about symptoms of hyperglycaemia (such as polydipsia, polyuria, and increased appetite). • In some cases plasma glucose and HbA1C may be monitored.
Pulse and blood pressure (BP)	• During dose titration • At each dose change.	• Not required for amisulpride, aripiprazole, trifluoperazine, and sulpiride.
ECG	• After dose changes. • Ideally, also annually.	• Mandatory for haloperidol, pimozide, and sertindole. • Not required for antipsychotics with no effect, or a low-to-moderate effect on the QT interval and where there are no other risk factors for arrhythmia.
Prolactin	• Six months after starting treatment • Then every 12 months.	• Also ask about symptoms of raised prolactin (these include low libido, sexual dysfunction, menstrual abnormalities, gynaecomastia, and galactorrhoea). • Not required for aripiprazole, clozapine, quetiapine, or olanzapine (less than 20 mg daily).

Ongoing monitoring	Frequency	Notes
LFTs	• Every 12 months.	
Creatinine kinase		• If neuroleptic malignant syndrome is suspected.
Movement disorders		• Monitor for the emergence of movement disorders.
Toxicity		• Following fatal cases involving toxicity of clozapine and other antipsychotic medicines, the MHRA advises that monitoring blood concentration of amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and sulpiride may be helpful in certain circumstances, such as patients presenting symptoms suggestive of toxicity, or when concomitant medicines may interact to increase blood concentration of these medicines.

Tests which need to be done every 12 months may be carried out at the annual physical review.

Patient and carer advice[7]

Photosensitivity

As photosensitisation may occur with higher dosages, patients should avoid direct sunlight.

Driving and skilled tasks

Drowsiness may affect performance of skilled tasks (e.g. driving or operating machinery), especially at start of treatment; effects of alcohol are enhanced.

Clozapine[11-13]

- People taking clozapine are usually managed exclusively in secondary care, although local commissioning of clozapine monitoring services may vary and could be done by specialist services in primary care in some areas.
- Clozapine can cause neutropenia or agranulocytosis, and frequent monitoring of the FBC is required. This is carried out by the clozapine monitoring service.
- Clozapine has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation, which is very common, to very rare intestinal obstruction, faecal impaction, and paralytic ileus. People taking clozapine and their carers should be advised to seek immediate medical advice before taking the next dose of clozapine if constipation develops.

Patient and carer advice[7]

Photosensitivity

As photosensitisation may occur with higher dosages, patients should avoid direct sunlight.

Driving and skilled tasks

Drowsiness may affect performance of skilled tasks (e.g. driving or operating machinery), especially at start of treatment; effects of alcohol are enhanced.

Disease-modifying anti-rheumatic drugs (DMARDs)[14]

Treatment and initial monitoring of DMARDs is usually carried out by a specialist in secondary care. Once the person is stabilised on treatment, GPs may be asked to prescribe and monitor the DMARD as part of a local shared care protocol. Whilst absolute values are useful indicators, trends are equally important. Any rapid rise or fall, or consistent downward or upward trend in any parameter warrants extra vigilance. Monitoring of patients on more than one DMARD should be based on the DMARD which requires the most frequent monitoring.

Recommendations for the monitoring of DMARDs are in-line with National Institute for health and Care Excellence (NICE) Clinical Knowledge Summaries and may differ from the monitoring recommendations in the BNF and individual SPCs.

When to refer a person taking a DMARD[14]

For people on any DMARD, consider stopping treatment and referring urgently to rheumatology if monitoring results show any of the following:

- White cell count less than 3.5 x 109/L
- Mean cell volume more than 105 fL
  - » Check B12, folate, thyroid-stimulating hormone levels – if abnormal treat, if normal discuss with specialist team
- Neutrophils less than 1.6 x 109/L
- Creatinine has increased more than 30% over 12 months and/or calculated GFR is less than 60 mL/min
  - » Repeat in one week, if still more than 30% from baseline, withhold and discuss with specialist team
- Unexplained eosinophilia more than 0.5 x 109/L
- ALT and/or AST more than 100 U/L
- Platelet count less than 140 x 109/L
- Unexplained reduction in albumin less than 30g/L
- Blood pressure more than 140/90mmHg
  - » Manage in accordance with hypertension guidelines, unless on ciclosporin — stop treatment and discuss with specialist team
- Urinary protein 2+ or more — check mid-stream urine sample
  - » If evidence of an infection, treat appropriately
  - » If sterile and 2+ proteinuria or more persists on two consecutive measurements, withhold until discussed with specialist team

For people on any DMARD, consider stopping treatment and referring urgently to rheumatology if the person develops any of the following signs or symptoms:

- Skin/mucosal reaction — for example rash, pruritus, mouth or throat ulceration
- Sore throat
- Fever
- Unexplained bruising or bleeding
- Nausea, vomiting, diarrhoea or weight loss
- Diffuse alopecia
- Breathlessness, infection or cough.
- Peripheral neuropathy

For a person on a biologic DMARD, consider stopping treatment and referring urgently to rheumatology if the person develops any of the following:

- Cough, haemoptysis, or weight loss (symptoms of tuberculosis)
- Signs or symptoms of heart failure, or worsening heart failure
- Shortness of breath or dry cough (symptoms of interstitial lung disease)
- Skin rashes (be aware of lupus-like syndrome)
- Abdominal pain, or new abdominal symptoms

Azathioprine[14]

Ongoing monitoring	Frequency	Notes
FBC	• Every two weeks until dose is stable for six weeks • Then monthly for three months • Thereafter, at least every 12 weeks* • More frequent monitoring is appropriate in patients at higher risk of toxicity • Dose increases: Every two weeks until dose is stable for six weeks, then revert to previous schedule.	
Creatinine/ calculated GFR		
LFTs		• ALT and/or AST and albumin.

*In people heterozygous for thiopurine methyl transferase (TPMT) deficiency, monitoring should continue at monthly intervals (TPMT status should be determined before prescribing — azathioprine should not be given to people with homozygous deficiency).

Patient and carer advice[7]

Bone marrow suppression

Report immediately any signs or symptoms of bone marrow suppression, e.g. inexplicable bruising or bleeding, infection.

Ciclosporin[6,14]

Ongoing monitoring	Frequency	Notes
FBC	• Every two weeks until dose is stable for six weeks • Then monthly » People who have been stable for 12 months can be considered for reduced monitoring frequency (every three months) on an individual basis • More frequent monitoring is appropriate in patients at higher risk of toxicity • Dose increases: Every two weeks until dose is stable for six weeks, then revert to previous schedule.	
Creatinine/calculated GFR		
LFTs		• ALT and/or AST and albumin
Blood glucose		
BP		

Determinations of serum lipids, potassium (especially in renal dysfunction), magnesium and uric acid are advisable before treatment and periodically during treatment.[15]

Brand name prescribing[6]

Prescribing and dispensing of ciclosporin should be by brand name to avoid inadvertent switching. If it is necessary to switch a patient to a different brand, this should be done cautiously under specialist supervision. The patient should be monitored closely for changes in the following:

- Blood-ciclosporin concentration
- Serum creatinine
- BP
- Transplant function (where applicable)

Patient and carer advice[7]

Systemic use

Manufacturer advises avoid excessive exposure to UV light, including sunlight. In psoriasis and atopic dermatitis, avoid use of UVB or PUVA.

Topical use in the eye

Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks - increased risk of blurred vision.

Hydroxychloroquine[14,16]

- Generally no routine laboratory monitoring is required for hydroxychloroquine.
- However the SPC advises that although the risk of bone marrow depression is low, periodic blood counts are advisable as anaemia, aplastic anaemia, agranulocytosis, a decrease in white blood cells, and thrombocytopenia have been reported. Hydroxychloroquine should be discontinued if abnormalities develop.
- Consider periodic monitoring of FBC every 12 months.
- For people on long-term therapy (five years or more), an annual eye assessment (ideally including optical coherence tomography) should be carried out.
- This examination should be more frequent and adapted to the patient in the following situations:
  - Daily dosage exceeds 6.5mg/kg lean body weight. Absolute body weight used as a guide to dosage could result in an overdosage in the obese.
  - Renal insufficiency
  - Visual acuity below 6/8
  - Age above 65 years
  - Cumulative dose more than 200 g.
- Patients should have baseline formal ophthalmic examination, ideally including objective retinal assessment, for example, using optical coherence tomography, within one year of commencing an antimalarial drug.

Leflunomide[14]

Ongoing monitoring	Frequency	Notes
FBC	• Every two weeks until dose is stable for six weeks • Then monthly for three months* • Then every 12 weeks • Dose increases: Every two weeks until dose is stable for six weeks, then revert to previous schedule.	• Including white cell count and platelet count platelets
Creatinine/calculated GFR		
LFTs		• ALT and/or AST and albumin
Weight		
BP		

*If leflunomide is combined with methotrexate, continue monthly monitoring until stable for 12 months, then consider reduced frequency monitoring on an individual basis.

- More frequent monitoring is appropriate in patients at higher risk of toxicity.
- Simple dose reduction is unlikely to produce a rapid diminution of adverse effects as the half-life of leflunomide is usually two weeks (range one to four weeks). If a rapid response is required, washout may be considered by the specialist team in secondary care.

Mercaptopurine[6,17]

Ongoing monitoring	Frequency	Notes
FBC	• Monitor at weeks two, four, eight and 12 • Three-monthly then after.	
U&Es		• Including serum creatinine or eGFR
LFTs		
Methylmercaptopurine to thioguanine ratio (MeMP:TGN)	• Monitor at week four • Repeat at 12-16 weeks and annually or four weeks after changes of dose.	

Methotrexate[14]

Ongoing monitoring	Frequency	Notes
FBC	• Every two weeks until dose is stable for six weeks • Then monthly for three months* • Then every 12 weeks • Dose increases: Every two weeks until dose is stable for six weeks, then revert to previous schedule.	
Creatinine/calculated GFR		
LFTs		• ALT and/or AST and albumin

*If methotrexate is combined with leflunomide, continue monthly monitoring until stable for 12 months, then consider reduced frequency monitoring on an individual basis.

- More frequent monitoring may be required in high-risk patients.

Patient and carer advice[7]

Patients and their carers should be warned to report immediately the onset of any feature of:

- Blood disorders (e.g. sore throat, bruising, and mouth ulcers),
- Liver toxicity (e.g. nausea, vomiting, abdominal discomfort and dark urine),
- Respiratory effects (e.g. shortness of breath).

Patients should be advised to avoid self-medication with over-the-counter aspirin or ibuprofen and counselled on the dose, treatment booklet, and the use of NSAIDs.

Mycophenolate[14]

Ongoing monitoring	Frequency	Notes
FBC	• Every two weeks until dose is stable for six weeks • Then monthly for three months • Then every 12 weeks • Dose increases: Every two weeks until dose is stable for six weeks, then revert to previous schedule.	
Creatinine/calculated GFR		
LFTs		• ALT and/or AST and albumin

- More frequent monitoring is appropriate in patients at higher risk of toxicity.
- In females of child-bearing potential, exclude pregnancy whilst on treatment.

Patient and carer advice[7]

Pregnancy prevention advice - The MHRA advises that prescribers should ensure that female patients understand the need to comply with the pregnancy prevention advice, and they should be informed to seek immediate medical attention if there is a possibility of pregnancy; male patients planning to conceive children should be informed of the implications of both immunosuppression and the effect of the prescribed medications on the pregnancy.

Bone marrow suppression – Report immediately any signs or symptoms of bone marrow suppression, e.g. infection or inexplicable bruising or bleeding.

Penicillamine[14]

Ongoing monitoring	Frequency	Notes
FBC	• Every two weeks until dose is stable for six weeks • Then monthly • Patients who have been stable for 12 months can be considered for reduced monitoring frequency (every three months) on an individual basis • Dose increases: Every two weeks until dose is stable for six weeks, then revert to previous schedule.	
Creatinine/calculated GFR		
LFTs		• ALT and/or AST and albumin
Urinalysis		• Blood and protein

- More frequent monitoring is appropriate in patients at higher risk of toxicity
- Careful monitoring is especially necessary in the elderly, since increased toxicity has been observed regardless of renal function.

Patient and carer advice[7]

Counselling on the symptoms of blood disorders is advised. Warn patient and carers to tell the doctor or other healthcare professional immediately if sore throat, fever, infection, non-specific illness, unexplained bleeding and bruising, purpura, mouth ulcers, or rashes develop.

Sulfasalazine[14]

Ongoing monitoring	Frequency	Notes
• FBC	• Every two weeks until dose is stable for six weeks • Then monthly for three months • Thereafter, at least every 12 weeks* • After 12 months, monitoring may be discontinued if considered clinically appropriate for individual patients • Dose increases: Every two weeks until dose is stable for six weeks, then revert to previous schedule.	• Including white cell count and platelet count.
• Creatinine/calculated GFR		
• LFTs		• ALT and/or AST and albumin

*More frequent monitoring is appropriate in patients at higher risk of toxicity.

Patient and carer advice[7]

Blood disorders – Advise patients to report any unexplained bleeding, bruising, purpura, sore throat, fever or malaise that occurs during treatment.

Tacrolimus[6,14]

Baseline Monitoring	• Monitor blood pressure • ECG (for hypertrophic changes—risk of cardiomyopathy) • Fasting blood-glucose • Haematological and neurological (including visual) and coagulation parameters (clotting screen) • Electrolytes (particularly potassium) • Hepatic and renal function before treatment and routinely throughout treatment.

Note: Serum tacrolimus levels and associated dose changes in post-transplant patients are usually managed by secondary care.

Ongoing monitoring	Frequency	Notes
FBC	• Every two weeks until dose is stable for six weeks. • Then monthly. • People who have been stable for 12 months can be considered for reduced monitoring frequency (every three months) on an individual basis. • More frequent monitoring is appropriate in patients at higher risk of toxicity. • Dose increases: Every two weeks until dose is stable for six weeks, then revert to previous schedule.	
Creatinine/calculated GFR		
LFTs		• ALT and/or AST and albumin
Blood glucose		
BP		

Brand prescribing and dispensing[6]

Prescribe and dispense by brand name only. Switching between brands requires careful supervision and therapeutic monitoring by an appropriate specialist.

Patient and carer advice[7]

Avoid excessive exposure to UV light including sunlight.

May affect performance of skilled tasks (e.g. driving).

DOACs – (Direct-acting Oral Anti-coagulants)[6,7,18]

Unlike warfarin, DOACS do not require regular international normalised ratio (INR monitoring). However, regular follow up is required to review the treatment, assess for adverse effects (such as bleeding), assess for thromboembolic events and provide appropriate information and advice.

Baseline measurements	• Clotting screen • Body weight • FBC • LFTs • Serum creatinine for renal function determination based on the Cockcroft and Gault formula to calculate Creatinine Clearance (CrCl). eGFR is not recommended for determining dosing for DOACs in relation to renal function • Urea and electrolytes
Consider	• Renal function required to calculate ORBIT bleeding risk score for atrial fibrillation. • Renal function, liver function and BP required to calculate HAS-BLED bleeding risk score for atrial fibrillation. • After 1 month of starting or dose change: » DOAC review appointment*
Every three months once stable	• DOAC review appointment*

Ongoing monitoring	Frequency	Notes
FBC	• Every 12 months or more frequent if clinical concerns	
LFTs	• Every 12 months or more frequent if clinical concerns	• Consider more frequent monitoring of hepatic function if intercurrent illness occurs.
U&Es	• Every 12 months or more frequent if clinical concerns	
Serum creatinine (for creatinine clearance)	• Every 12 months or more frequent if clinical concerns	If renal function changes, increase monitoring frequency: • Where a patient shows a creatinine clearance of below 60mL/min, divide the value by 10, and use the value obtained as the monthly testing frequency. » If CrCl is 30mL/min, increase frequency to every three months; » If CrCl is 20mL/min, increase frequency to every two months.

Ongoing monitoring	Frequency	Notes
		• Consider a change in testing frequency if concomitant medicines are prescribed which may affect renal or hepatic function. • Elderly - Monitoring every six months is normally most appropriate.

*DOAC review appointment should include:

- Assess compliance with treatment and reinforce advice regarding the importance of a regular dosing schedule.
- Enquire about the presence of any adverse effects such as bleeding and re assess HAS-BLED score.
- Look for signs of bleeding or anaemia.
- Assess for the presence of thromboembolic events (e.g. symptoms of stroke, or breathlessness – may suggest a pulmonary embolism).
- Ask the person if they have been taking any other medicines including any bought over-the-counter.
- Assess and minimise modifiable risk factors for bleeding, such as uncontrolled hypertension, medication predisposing to bleeding and excessive alcohol intake.
- Give appropriate information and advice on DOAC treatment.

Abnormal results[6]

Responding to abnormal results for DOACs is dependent on the individual medicine prescribed.

Apixaban

Renal function - Take action if creatinine or creatinine clearance abnormal:

- If CrCL less than 15mL/min or in patients undergoing dialysis, apixaban use is not recommended.
- If CrCL 15-29mL/min and apixaban prescribed for prevention of recurrent DVT, PE, and treatment of DVT or PE, then continue with caution.
- If CrCL 15-29mL/min and apixaban prescribed for prophylaxis of stroke and systemic embolism in a person with NVAF, reduce dose to 2.5mg twice daily.
- When used in prophylaxis of stroke, If serum creatinine is greater than 133micromol/L, apixaban prescribed for stroke, and patient either 80 years or older or less than 60kg, reduce dose to 2.5mg twice daily.

Decreased haemoglobin or bleeding

- If there is an unexplained fall in haemoglobin or haematocrit, occult bleeding may be present (apixaban can cause bleeding from any site). Stop treatment and seek specialist advice.

Hepatic impairment - Use with caution in mild or moderate hepatic impairment:

- Child Pugh A or B.
- ALT/ AST over two times the upper limit of normal.
- Total bilirubin over 1.5 times the upper limit of normal.

Avoid apixaban in:

- Severe impairment.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.

HAS-BLED

- If the patient's HAS-BLED score is more than 3, there is high risk of bleeding and apixaban should be used cautiously, with regular intervals.

Dabigatran

Renal function - Take action if creatinine clearance abnormal:

- CrCL less than 30mL/min: CrCL less than 30mL/min dabigatran use is contraindicated.
- CrCL 30-50mL/min: a reduction in dose is recommended see summary of product characteristics.

Hepatic function - Use with caution in:

- Mild to moderate impairment.
- ALT/ AST over two times the upper limit of normal.
- Total bilirubin over 1.5 times the upper limit of normal.

Avoid dabigatran in:

- Severe impairment.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.

Reduce dose in elderly or if verapamil prescribed

- If the patient is elderly or taking concomitant verapamil, consult product literature for advice on dose reduction.

Edoxaban

Renal function - Take action if creatinine clearance abnormal:

- CrCL less than 15mL/min: edoxaban is contraindicated. Assess for bleeding and seek advice regarding alternative anticoagulant therapy.
- CrCL 15-50mL/min: reduce dose to 30mg once daily.
- CrCL over 95mL/min: re-evaluate treatment choice and consider alternative. A trend towards decreasing efficacy with increasing creatinine clearance has been observed compared to well managed warfarin.

HAS-BLED

- If the person's HAS-BLED score is more than three, there is high risk of bleeding and edoxaban should be used cautiously, with regular intervals.

Rivaroxaban

Renal function - Take action if creatinine clearance abnormal:

- CrCL less than 15mL/min: CrCL less than 15mL/min rivaroxaban use is not recommended.
- CrCL 15-49mL/min: consult product literature for indication specific advice.

Hepatic impairment

- Manufacturer advises avoid in hepatic disease with coagulopathy and clinically-relevant bleeding risk including patients with moderate to severe cirrhosis.

Bleeding

- Patients should be monitored for signs of bleeding or anaemia; treatment should be stopped if severe bleeding occurs.

Lithium[6,7,12]

Lithium salts have a narrow therapeutic/toxic ratio and should therefore not be prescribed unless facilities for monitoring serum-lithium concentrations are available.

Baseline measurements	• Body weight or BMI • Cardiac function · especially in patients with cardiovascular disease or at risk who may require ECG • eGFR • Serum calcium • TFTs - patients should be euthyroid before initiation • U&Es

After started or dose changed	Frequency	Notes
Lithium levels	• At one week; then weekly until levels stable; then every three months for first year	• Lithium levels should be measured 12 hours post-dose (take sample just prior to time of next dose).

Ongoing monitoring	Frequency	Notes
Lithium levels	• Then every three to six months thereafter	• Lithium levels should be measured 12 hours post-dose (take sample just prior to time of next dose) • If a patient is considered at-risk (see below) continue monitoring every three months • Additional serum-lithium measurements should be made if a patient develops significant intercurrent disease or if there is a significant change in a patient's sodium or fluid intake.
BMI (or body weight)	• Every six months	• If a patient is considered at-risk (see below) continue monitoring every three months.
U&Es	• Every six months	• If a patient is considered at-risk (see below) continue monitoring every three months. • If the person's urea, or creatinine levels become elevated or if the eGFR declines over two or more tests, consider measuring lithium levels more frequently than three monthly.
eGFR	• Every six months	• If a patient is considered at-risk (see below) continue monitoring every three months.
calcium	• Every six months	• If a patient is considered at-risk (see below) continue monitoring every three months.
TFTs	• Every six months	• If a patient is considered at-risk (see below) continue monitoring every three months.
ECG	• Before treatment repeat as and when clinically necessary	• Only if there is a risk factor for, or existing, cardiovascular disease.

Patients at risk of lithium toxicity and in whom more frequent monitoring may be warranted include:

- Age 65 years and older
- Taking drugs that interact with lithium - see current BNF for full list of known lithium interactions.
- Risk of impaired renal function: e.g. eGFR declines over two or more tests; or urea and creatinine elevated
- At risk of impaired thyroid function
- Raised calcium levels or other complications
- Significant change in a patient's sodium or fluid intake
- Have poor symptom control or poor adherence
- The last serum-lithium concentration was 0.8 mmol/litre or higher

Abnormal results[6]

Lithium toxicity

- Lithium toxicity occurs at serum lithium concentrations of approximately 1.5 mmol/L and above, but may occur despite an apparently normal plasma level. The risk of toxicity is greater in people with hypertension, diabetes, congestive heart failure, chronic renal disease, schizophrenia, or Addison's disease.
- Signs and symptoms of lithium toxicity include increasing diarrhoea, vomiting, anorexia, muscle weakness, lethargy, dizziness, ataxia, lack of coordination, tinnitus, blurred vision, coarse tremor of the extremities and lower jaw, muscle hyper-irritability, choreoathetoid movements, dysarthria, and drowsiness.
- If lithium toxicity is suspected, do an urgent lithium level immediately and seek specialist advice.
- Referral to secondary care may be required depending on the severity of symptoms and the certainty of toxicity. Use clinical judgement to determine the urgency of referral.

Renal function

Monitor dose and blood levels more closely and assess the rate of renal function deterioration in the following circumstances:

- Elevated urea levels
- Elevated creatinine levels
- Decline in eGFR

Patient and carer advice[7]

Patients should be advised to report signs and symptoms of lithium toxicity, hypothyroidism, renal dysfunction (including polyuria and polydipsia), and benign intracranial hypertension (persistent headache and visual disturbance).

Maintain adequate fluid intake and avoid dietary changes which reduce or increase sodium intake.

May impair performance of skilled tasks (e.g. driving, operating machinery).

Advice patients to avoid taking Over the Counter NSAIDS (i.e. ibuprofen).

Mesalazine[6,7,19]

Baseline measurements	• FBC • LFTs • Serum creatinine (for creatinine clearance) or eGFR • U&Es • Urine dipstick.

Monitoring until stabilised	Frequency	Notes
• FBC	• Test 14 days after starting treatment • Then four, eight and 12 weeks • Then every three months.	
• LFTs		
• Serum creatinine (for creatinine clearance) or eGFR		
• U&Es		
• Urine dipstick		

Ongoing monitoring once stable	Frequency	Notes
• FBC	• Every six months or annually based on the person's risk factors.	
• LFTs Renal function		• More frequently in renal impairment.
• U&Es		
• Urine dipstick		
• Serum creatinine (for creatinine clearance) or eGFR	• Every six months for the first four years then annually.	

Haematological investigations - Perform haematological investigations if patient develops unexplained bleeding, bruising, purpura, anaemia, fever or sore throat. Stop if suspicion or evidence of blood dyscrasia.

Valproate and sodium valproate[6,7,20]

Valproate should only be initiated in adults and children by, or on the recommendation of, a specialist.

Valproate must not be used in any woman or girl able to have children unless there is a pregnancy prevention programme (PPP) in place. This is designed to make sure patients are fully aware of the risks and the need to avoid becoming pregnant.

Healthcare professionals who seek to prescribe valproate to their female patients must make sure they are enrolled in the PPP. This includes the completion of a signed risk acknowledgement form when their treatment is reviewed by a specialist, at least annually.

Baseline measurements	• BMI • Clotting screen including bleeding time and coagulation tests • FBC • LFTs • Pregnancy Test – see advice about use of Valproate in Women and Girls.

Monitoring until stabilised	Frequency	Notes
• LFTs	• Periodically within first six months	• Especially in patients most at risk, and those with a prior history of liver disease.

Ongoing monitoring once stable	Frequency	Notes
• BMI	• After six months and then annually	
• FBC		
• LFTs		

If used for bipolar disorder, additionally monitor:
• Cardiovascular status, including pulse and BP • Metabolic status, including fasting blood glucose, glycosylated haemoglobin (HbA1c) • Blood lipid profile.

FBC (including platelet count), bleeding time and coagulation tests are recommended before surgery and in cases of spontaneous bruising or bleeding.

Abnormal results[6]

Hepatic effects

Raised liver enzymes are usually transient but patients should be assessed clinically and FBC (including platelets) and liver function (including prothrombin time and coagulation tests) monitored until return to normal. Discontinue if abnormal liver function.

Haematological effects

Discontinue if abnormally prolonged prothrombin time or blood dyscrasias.

Pancreatitis

In case of pancreatitis, valproate should be discontinued.

Patient and carer advice[6,7]

Blood or hepatic disorders

Patients or their carers should be told how to recognise signs and symptoms of blood or liver disorders and advised to seek immediate medical attention if symptoms develop.

Pancreatitis

Patients or their carers should be told how to recognise signs and symptoms of pancreatitis and advised to seek immediate medical attention if symptoms such as abdominal pain, nausea, or vomiting develop.

Warfarin[6,7,18]

Anticoagulants are usually initiated in secondary care, a dedicated clinic in a hospital, or an outreach clinic in primary care.

Baseline measurements	• BP • Clotting Screen - The base-line prothrombin time should be determined but the initial dose should not be delayed whilst awaiting the result • eGFR or serum creatinine for creatinine clearance • FBC • LFTs • TFTs • Renal function required to calculate ORBIT bleeding risk score for atrial fibrillation • Renal function, liver function and BP required to calculate HAS-BLED bleeding risk score for atrial fibrillation.

Monitoring until stabilised or after dose changed	Frequency
• INR	• Measure INR daily, or on alternate days, until within therapeutic range (usually between 2-3, ideally 2.5) on two consecutive occasions. • Although the INR may be measured each day after starting warfarin, a meaningful INR can only be obtained three to four days after starting treatment. • Then, twice weekly for one to two weeks • Then weekly measurements • Obtain two consecutive INR measurements are within the therapeutic range before reducing testing frequency • A number of patient groups require particular care and close monitoring in the early stages of warfarin therapy. These include patients with: » Hypothyroidism or hyperthyroidism » Familial history of polymorphisms of CYP2CP or VKORC1 » HASBLED score more than three. • Then at longer intervals (depending on response), then up to every 12 weeks. • Increase frequency if high risk patient, poor control, or interacting medicine - see Current BNF for full list of known warfarin interactions. • Consider more frequent monitoring at least every one to two weeks if high risk patient, poor control or an interacting medicine is co-prescribed.

Ongoing monitoring once stable	Frequency
• INR	• Review current BNF for full list of known warfarin drug interactions. • See below for a list of possible aggravating factors for over coagulation and increased risk of bleeding. • Poor control may occur where: » Two INR values higher than five, or one INR value higher than eight, occur within the past six months » Two INR values less than 1.5 occur within the past six months » Time in therapeutic range (TTR) is less than 65% • Interacting medicines - Patients who are prescribed a drug that may interact with warfarin should have an INR test performed after three to five days - see Current BNF for full list of known warfarin interactions. • Those who have had a change in warfarin dose as a result of an interacting drug will need to resume usual maintenance dose following cessation of that drug.

Aggravating factors for over-coagulation include:

- Severe hypertension
- Liver disease including alcoholic liver disease
- Renal failure
- Highly variable INRs.

Aggravating factors for increased risk of bleeding include:

- History of gastrointestinal bleeding
- Uncontrolled hypertension
- Cerebrovascular disease
- Serious heart disease
- Risk of falling
- Thrombocytopenia
- Anaemia
- Coagulation disorders
- Malignancy
- Trauma
- Renal insufficiency
- Morbidity changes (such as intercurrent illness, or exacerbations of chronic conditions)
- Recent change in medication
- Difficulties with adherence.

Poor control

Where there is poor control, reassess anticoagulation and increase testing frequency.

Abnormal results[18]

- If the international normalized ratio (INR) is outside the therapeutic range, ask the person about any changes in order to find a cause of the out-of-range result. For example, ask about:
  - Adherence to warfarin treatment, for example if they have missed any doses or taken too much.
  - Use of other medications, including over-the-counter products, vitamins, and herbal or homeopathic remedies.
  - Use of alcohol or illicit drugs.
  - Food and drink intake (for example green vegetables and cranberry juice).
  - Their general health:
    - Weight loss, acute illness (such as gastroenteritis), and smoking cessation can increase the effect of warfarin.
    - Weight gain, diarrhoea, and vomiting can reduce the effect of warfarin.
- If the person has major bleeding, stop warfarin, and refer urgently for intravenous treatment with phytomenadione (vitamin K1) and dried prothrombin complex concentrate (factors II, VII, IX, and X), or fresh frozen plasma if dried prothrombin complex is unavailable.
- If the INR is high and is:
  - Greater than eight with minor bleeding — stop warfarin and give phytomenadione by slow intravenous injection. The dose of phytomenadione may be repeated after 24 hours if the INR is still too high.
    - Restart warfarin when the INR is less than five.
  - Greater than eight with no bleeding — stop warfarin and give phytomenadione by mouth using the intravenous preparation orally (off-label use). The dose of phytomenadione may be repeated after 24 hours if the INR is still too high.
    - Restart warfarin when the INR is less than five.
  - Between five to eight with minor bleeding — stop warfarin and give phytomenadione by slow intravenous injection.
    - Restart warfarin when the INR is less than 5.
  - Between five to eight with no bleeding — withhold one or two doses of warfarin and reduce subsequent maintenance dose.
- If there is unexpected bleeding at therapeutic levels — always investigate possibility of underlying cause, such as unsuspected renal or gastrointestinal tract pathology.

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