

Adrenal insufficiency a guide for pharmacists and their teams

Why is this subject important?

Pharmacists and their teams are on the front line of healthcare. The services they offer are easily accessible and patients rely on pharmacists and their teams for advice and support relating to their health.

Adrenal insufficiency is a rare, potentially fatal, chronic condition which affects approximately one per 10,000 people. It has symptoms similar to other illnesses, such as type 1 diabetes mellitus and depression. If left undiagnosed and untreated, patients can become rapidly and seriously unwell and it is imperative that pharmacists and their teams have an understanding of the condition. This is so they can recognise when a patient may be suffering from symptoms associated with adrenal insufficiency or when someone may be experiencing an adrenal crisis; this may potentially save someone's life.

What will this guidance enable you to do?

- Describe what adrenal insufficiency is and what the causes are
- Identify the symptoms of adrenal insufficiency and an adrenal crisis
- Discuss with patients how a diagnosis can be made
- Outline the treatment options for patients with adrenal insufficiency
- Explain to a patient about their expected quality of life
- Identify adherence issues and be able to discuss potential solutions with patients
- Recognise opportunities to provide lifestyle advice to patients
- Give examples of organisations or persons who may be able to offer patients further support
- Identify patients who may benefit from participating in additional pharmacy services

What is adrenal insufficiency?

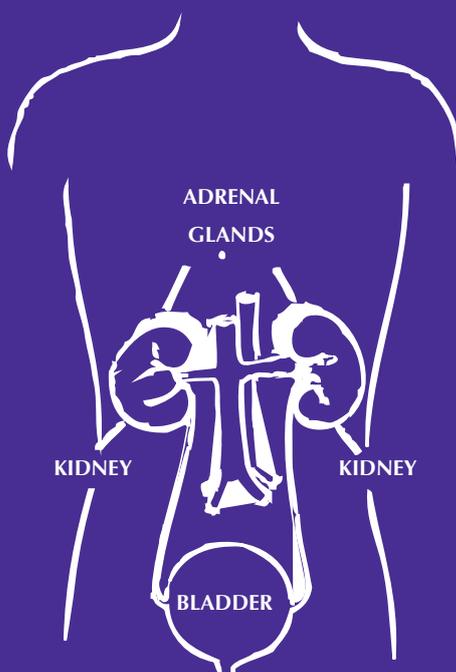
Adrenal insufficiency (also known as Addison's disease or hypoadrenalism) is a chronic, rare condition which occurs when the adrenal glands fail to produce any, or a high enough level of mineralocorticoids (for example, aldosterone), glucocorticoids (for example, cortisol) and adrenal androgens (for example, dehydroepiandrosterone (DHEA)).

The adrenal glands are positioned above the kidneys and each adrenal gland has two layers:

- Inner core layer (medulla)
 - This produces adrenaline and noradrenaline
- Outer shell layer (cortex)
 - This produces aldosterone and cortisol, and also sex hormones known as adrenal androgens, the most important being DHEA

The cortex is a critical layer, which is essential for life. It is called upon in times of intense stress, for example, serious infection, surgery or trauma. If the cortex is damaged or destroyed, the adrenal glands are unable to produce enough aldosterone and cortisol. The body is then unable to adapt to the stresses placed upon it which may lead to an adrenal crisis (see later).

Adrenal insufficiency is more common in women than men, and onset tends to be between the ages of 30–50 years of age but no age is exempt.



Causes

Adrenal insufficiency can be described as primary, secondary or tertiary depending on the cause of the condition. Primary adrenal insufficiency (Addison's disease) occurs when the adrenal cortex has been destroyed. There are different causes for primary adrenal insufficiency but 70–90 per cent of cases are due to an autoimmune disorder. The body's own immune system attacks the outer layer (cortex) of the adrenal glands; it is not known why the body acts in this way.

Other rarer causes of primary adrenal insufficiency include tuberculosis (TB) — this is uncommon in the UK but is the most common cause of Addison's disease worldwide — adrenal cancer, haemorrhage or rare hereditary diseases, such as congenital adrenal hyperplasia (CAH), a genetic defect. CAH causes enzyme defects and blocks the production of cortisol and aldosterone. In addition, it can cause signs of virilisation (when females develop male sex characteristics, for example, deepening of the voice or thick, dark facial hair) through overproduction of male hormones (androgens).

Secondary adrenal insufficiency (which is sometimes also referred to as Addison's although this is technically inaccurate) occurs less frequently than primary adrenal insufficiency. It occurs when another part of the body is affected by a condition or disease which in turn leads to the adrenal glands being affected. The most common cause of secondary adrenal insufficiency is when a patient develops a pituitary tumour. The pituitary gland is found at the base of the brain and the tumour may affect the ability of the pituitary glands to produce the messenger hormone, adrenocorticotropic hormone (ACTH), which is vital as it stimulates the adrenal glands into action.

Tertiary adrenal insufficiency arises when the production of corticotrophin-releasing hormone from the hypothalamus is disrupted, and as in secondary adrenal insufficiency, ACTH production is affected.

Symptoms

The symptoms of adrenal insufficiency are non-specific, and are often similar to the symptoms of depression or flu:

- A**ppetite loss, unintentional weight loss
- D**iscolouration of the skin
- D**ehydration
- I**ncreased thirst and need to urinate frequently
- S**alt, soy sauce or liquorice cravings
- O**ligomenorrhoea (irregular or infrequent periods in women)
- N**o energy or motivation (fatigue, lethargy), low mood
- S**ore/painful, weak muscles and joints

Further symptoms – these can occur gradually over months/years

- Abdominal, joint or back pain
- Chronic exhaustion leading to depression
- Diarrhoea
- Discolouration of skin, lips and gums (creases of palms, scars and pressure points)
- Muscle cramps
- Nausea and vomiting
- Postural hypotension, which can lead to dizziness and fainting
- Reduced libido, especially in women

Adrenal crisis

- It is important to be aware of the symptoms of an adrenal crisis — it can be fatal if left untreated
- It occurs when the levels of aldosterone and cortisol in the body fall
- A patient may have been experiencing no, or some symptoms, when it occurs
- It can occur very quickly, be very severe and can lead to coma or death if left untreated

Symptoms which may indicate an adrenal crisis

- Abdominal pain
- Confusion
- Dizziness
- Fever
- Headache
- Hypotension
- Pale, cold clammy skin
- Rapid, shallow breathing
- Severe dehydration
- Severe drowsiness/unconsciousness/sleepiness
- Severe muscle weakness
- Severe, persistent vomiting and diarrhoea

There is also a risk that if treatment is delayed then the brain may not get enough oxygen which could lead to permanent brain damage

If a patient is suspected of experiencing an adrenal crisis this must be treated as an emergency situation because the blood pressure is low and the emergency services should be called

Diagnosis

When adrenal insufficiency is suspected a GP may/is likely to:

- Consider the patient's symptoms and examine the skin for discolouration
- Review the patient's medical records and enquire about a family history of other autoimmune conditions
- Take the patient's blood pressure, at a sitting and standing position, to see if they are suffering with postural hypotension
- Order blood tests to check a patient's levels and low sodium, high potassium or low cortisol may be indicative of adrenal insufficiency

Further blood tests may be carried out by an endocrinologist to see if the patient has low aldosterone, high ACTH, low glucose or positive adrenal antibodies (antibodies which attack the adrenal gland) — these all are signs that a patient could have adrenal insufficiency. Additional testing may also be required, such as a synacthen stimulation test, a thyroid function test or a scan of the adrenal glands to confirm the diagnosis.

Treatment

Once diagnosed with adrenal insufficiency, most patients will need to take medicines on a daily basis for the rest of their lives. This is because most causes cannot be cured, therefore, the condition needs to be managed and continuous treatment is required. Treatment is with corticosteroids and the aim of treatment is to replicate the missing cortisol and aldosterone that a patient's body can no longer produce.

Hydrocortisone is taken to replace cortisol (glucocorticoid replacement)

- Hydrocortisone is considered as the first-line drug because:
 - It is the closest imitation of what the body produces
 - It is absorbed into the body quicker than other corticosteroids — after taking on an empty stomach it is almost all absorbed by the stomach and in the bloodstream after 30 minutes
 - It can be easily measured in the bloodstream — monitoring of dosage is easier
- The daily adult daily dose of hydrocortisone is usually 15–30mg, split into two or three doses, but this is dependent on absorption, body weight and metabolism
- Dexamethasone or/prednisolone can also be used but are less common

Not all hydrocortisone preparations are indicated for use by patients with adrenal insufficiency — pharmacists should check product literature to ensure the product they are supplying is indicated.

Auden , Almus and Teva livery products supplied by SNS Pharmaceuticals under PL16876/0002 are indicated for use in patients with adrenal insufficiency.

Fludrocortisone is taken to replace aldosterone (mineralocorticoid replacement)

- The daily adult dose of fludrocortisone is usually 50–300mcg, taken in the morning; dosage depends on metabolism and the amount of exercise the patient does
- Some patients may not require fludrocortisone once stabilised on hydrocortisone; also for those with secondary adrenocortical failure or steroid-induced adrenal suppression, fludrocortisone is not required because adrenal production of aldosterone is often unaffected
- The dose of fludrocortisone may need to be increased when the patient is exposed to high temperatures and/or humidity — this is to compensate for the increased salt loss from sweating

Dehydroepiandrosterone (androgen replacement)

- DHEA is an unlicensed medicine but may be prescribed by some specialists

Attaining the correct dose for the individual patient may take some time, and blood test results, symptoms and overall well-being of the patient will need to be reviewed to reach the correct dose. A patient's dose may also need further correction, if the adrenal cortex continues to decline in its production of cortisol and aldosterone. Patients should be made aware of this.

Typical patient experience / quality of life

Many patients with adrenal insufficiency will be able to lead a normal lifestyle, providing they take their medicines as instructed. However, taking steroid medicines every day does not make all of the symptoms associated with adrenal insufficiency go away. Patients may still experience symptoms such as fatigue and reduced energy levels — this is something that they may need to discuss with their specialist. There will also be some patients whose quality of life may for a time be extremely affected. This could be a result of a delayed diagnosis or other health conditions which they have as well as adrenal insufficiency.

There is always the risk that a patient may develop another autoimmune condition, for example hypothyroidism, which can be a concern but is treatable. In addition, patients need to be alert to the possibility of an adrenal crisis; while life can continue to be busy and enjoyable for many, the condition will not go away.

When should a patient take their medicines?

- Hydrocortisone is taken in two or three divided doses through the day, usually with a higher dose in the morning and a lower noon and/or evening dose; this may differ for those who work shifts
- Prednisolone and dexamethasone are slower acting so are taken once a day
- Fludrocortisone is also slower acting so is only taken once a day

Importance of taking steroid medication at the correct time of day — cortisol levels in people who have normal functioning adrenal glands, start to increase at roughly 4am and are at their peak when they wake up. They then start to reduce again throughout the day. Patients are recommended to take their largest steroid dose upon waking on an empty stomach as this will enable the body to follow a similar pattern. Shortly after going to sleep a person with healthy adrenals will have a low cortisol level. Therefore, patients should be advised to avoid taking steroid medicines late at night (the last daily dose should be taken no later than 6pm or at least four hours before going to sleep) because otherwise they may experience sleeping difficulties.

Aldosterone levels work in a similar way, hence why fludrocortisone should be taken in a morning.

Switching from a 'twice a day' dosage regimen to a 'three times a day' dosage regimen — some patients experience an energy lag —also known as 'brain fog'— which usually occurs in an afternoon. Symptoms include irritability, dizziness, feeling faint or that their blood sugar may be low. This is an indicator that the body may be low on cortisol; therefore, changing the total daily dose into three divided doses instead of two may help maintain the level of cortisol in the body and help prevent these episodes.

Taking with food — steroid medicines are usually advised to be taken with food to prevent indigestion; however, most patients with adrenal insufficiency are able to take them first thing in a morning with just water. This is because they are taking a small daily dose of steroid compared to patients with other steroid-dependent conditions (in general, a daily dose of hydrocortisone 20mg does not need to be taken with food). This means the steroid starts working in the body sooner, rather than the patient having to wait until after breakfast to feel the benefits. If a patient does suffer with indigestion from only taking the steroid medicine with water, switching to swallowing the tablets with milk or a milk substitute, for example, soya or rice milk will usually resolve the issue.

Shift workers — medicines should be taken in line with a patient's sleeping patterns so if they work night shifts the first dose should be taken upon waking and the final dose at least four hours before going to sleep even if this is in the morning.

Patients should be made aware that they should only take the daily dose of steroid which their body needs, and not regularly taking a higher dose which may be required during illness. Over a long period of time this can be harmful to the body and contribute to causing complications, such as osteoporosis. In general, a higher dose can be taken for a couple of days when required but patients should always revert back to their prescribed daily dose unless advised otherwise by their GP or endocrinologist.

Monitoring

Patients are typically under the care of a GP and an endocrinologist (usually seen every 6-12 months). Patients should also monitor their own health and be alert for signs of illness when they may need to look to increase the dose of their steroid medicines. They should be encouraged to report any signs of under or over treatment with their medicines and may find it useful to keep a diary to record any important health issues or changes.

Common drug interactions

Drug	Effects
Anticoagulants (coumarins) e.g. warfarin	Corticosteroids may affect the effectiveness of coumarin anti-coagulants; to avoid spontaneous bleeding close monitoring of INR or prothrombin time is required.
Antiepileptics e.g. phenytoin, carbamazepine and primidone	Can speed up the metabolism of corticosteroids so doses of corticosteroid may need to be increased (discuss with the endocrinologist).
Antituberculosis drugs e.g. rifampicin	Speeds up the rate at which the body metabolises steroid medicines. Patients will typically need to increase their dose of hydrocortisone and fludrocortisone by up to double if taking this type of medicine (discuss with the endocrinologist).
Contraceptive pill and hormone replacement therapy (HRT)	These medicines can slow down the metabolism of corticosteroids; therefore, if started on either of these types of medicines the patient's daily dose of corticosteroid may be reduced.
Diuretics e.g. thiazides, loop diuretics, acetazolamide	The potassium-depleting effects of these medicines are enhanced by corticosteroids; monitor for signs of hypokalaemia (low potassium).
Hypoglycaemic drugs including insulin	Corticosteroids in high dosage antagonise the desired action of these drugs.

This list is not exhaustive and other resources should be used to confirm drug interactions between other medicines not listed.

The main documented herbal interaction is the effects of fludrocortisone with liquorice. Liquorice root has similar stimulatory properties to aldosterone. Therefore, if a patient eats or takes medicine containing liquorice (some cough medicines contain liquorice) they may need their fludrocortisone dose reducing. Some sweets are only liquorice flavoured so should not affect the patient but the ingredients would need to be checked to confirm this.

Diet

Patients should aim to have a healthy balanced diet, with plenty of protein, vitamins and minerals, and try to limit their fat and sugar intake. They should also aim to drink plenty of fluids. Patients do not need to follow a special diet but due to being more at risk from weight gain, dehydration and developing other conditions such as osteoporosis, patients will benefit from trying to eat healthily.

Salt and other cravings — patients with adrenal insufficiency lose salt faster than people with healthy adrenals, therefore, a moderate intake of salt is sensible and in hot weather, patients should be advised to try to increase their salt intake. If a patient has a severe craving for salt they should be referred to their GP. A liquorice craving is unusual and may be indicative that a patient's fludrocortisone dose needs increasing — they should be referred to their GP. Sugar cravings are common amongst the general population; however, if a patient is developing a craving at the same time each day this could indicate that their divided doses are too far apart. Developing a craving for acid tastes, for example, lemon juice or pickle juices, is also quite common. This can normally be managed by eating mediterranean-type-snacks, for example, fresh salads with olives, pickles, salty cheeses, tuna and anchovies.



Foods high in potassium — patients tend to retain potassium so they should avoid eating large amounts of foods which are high in potassium, for example, apricots (especially dried), bananas, dates and raisins.



Protein rich foods — patients should aim to eat plenty of protein rich food in their diet, for example, beans and other legumes, dairy foods, nuts, oily fish (mackerel, salmon, sardines) and vegetables.

Fluid — patients should aim to drink a minimum of 1.5 litres water daily. Large amounts of alcohol, coffee or tea can cause dehydration so patients should try to avoid drinking large amounts of these. For every glass of alcohol, coffee or tea that a patient drinks, they should aim to drink an equivalent size glass of water. Patients should avoid sports drinks which have extra potassium in them. If patients are really thirsty and are frequently passing urine this may be an indicator that their fludrocortisone needs increasing or that the patient has developed diabetes/kidney problems — referral to the GP is required in this situation.

Common worries for patients

Patients may have concerns about symptoms which they are experiencing, or worry about developing conditions in the future, such as osteoporosis. Pharmacists should be able to discuss these concerns with patients, be able to offer lifestyle advice and recognise when a patient should be referred to their GP.

Concern	Information
Anger	It is common to feel anger at times; however, it can indicate that a patient is taking too much hydrocortisone — advise patient to review their steroid dose with their GP.
Bruising	Steroid medicines can make patients more prone to bruising and even if patients are taking the correct dose of steroid they may still suffer with this side effect. If a patient is concerned or bruising is excessive, refer the patient to their GP.
Cardiac symptoms e.g. arrhythmia	If a patient receives too high a dose of fludrocortisone this can cause a potassium deficiency — in severe cases, this can cause cardiac symptoms such as arrhythmia. Too low a dose can cause potassium overload which may also cause cardiac symptoms — referral to the GP is required.
Cravings	Refer to "Diet" section.
Depression	This can indicate that a patient is taking too much hydrocortisone — advise the patient to review their steroid dose with their GP. A patient may actually be suffering from depression and may need to take antidepressants to control this.

Concern	Information
Dry, cracked skin	This is a common problem but if the skin is excessively dry this can be a symptom of hypothyroidism — consider referral to the GP and advise on emollient usage.
Fluid retention	Fluid balance can be affected by both fludrocortisone and hydrocortisone. Fluid retention can also be caused by other conditions, such as hypothyroidism or kidney problems — patients should be referred to their GP for further investigation.
Insomnia or sleeping difficulties	This can be a common problem within the population at large and may not be associated with the patient's condition. However, it is important to check when the patient is taking their steroid medicines and that the last dose is not too near their sleeping time — refer to "When to take medicines" section.
Headaches, recurrent	This could be a sign that a patient's cortisol level is too low — a patient's hydrocortisone dose may be too low at certain times of the day; this may be solved by adjusting the dose so it is taken in smaller, more frequent doses.
Hypoglycaemic symptoms	Patients may also experience cravings for high sugar/fat snacks. Eating a protein-rich snack, for example, poached or scrambled eggs would be a better alternative. It could also be a sign that a patient's hydrocortisone level is too low at certain times and may be solved by adjusting the dose so it is taken in smaller, more frequent doses. These symptoms could be a sign of diabetes — consider referral to the GP.
Joint aches	This could be a sign that a patient's cortisol level is too low — a patient's hydrocortisone dose may be too low at certain times of the day and may be solved by adjusting the dose so it is taken in smaller, more frequent doses.
Loss of appetite	This could be a sign that a patient's cortisol level is too low — a patient's hydrocortisone dose may be too low at certain times of the day and may be solved by adjusting the dose so it is taken in smaller, more frequent doses.
Mood swings	This can indicate that a patient is taking too much cortisol — advise patient to review their hydrocortisone dose with their GP.
Muscle wastage or weakness	Noticeable muscle wastage can signify that a patient is receiving too high a dose of hydrocortisone, especially if they are also suffering with other symptoms indicative of too high a cortisol level — refer to GP to review hydrocortisone dose. Muscle weakness can be an indicator of potassium imbalance — refer to GP to check electrolyte and renin levels.
Nausea	Mild nausea could be a sign that a patient's cortisol level is too low — a patient's hydrocortisone dose may be too low at certain times of the day and may be solved by adjusting the dose so it is taken in smaller, more frequent doses. If nausea is severe, this is a more serious indicator that cortisol levels are low and patients are close to exhaustion — patients will need to take their next dose of hydrocortisone immediately. Patients may need to increase the daily dose of their medicine — refer to GP for further advice.

Concern	Information
Osteopenia and osteoporosis	Patients who take the minimum daily dose of hydrocortisone which they require, should not be at increased risk of bone thinning; however, if patients are regularly over medicating on their steroid medicine they are increasing their risk of developing osteopenia and osteoporosis. Encourage patients to eat a diet rich in calcium and vitamin D, participate in weight-bearing exercises and for post-menopausal women, advise on the benefits of taking HRT. Patients may need to be prescribed a bisphosphonate if diagnosed with one of these bone conditions.
Puffy/moon face	If also suffering with other symptoms listed, it could be an indicator that a patient needs to reduce their hydrocortisone dose. It can also be caused by other conditions, for example, hypothyroidism — refer to GP for further advice.
Thinning skin	If skin thinning is sudden and noticeable, and the patient is suffering with this and other listed symptoms, it could be an indicator that a patient needs to reduce their hydrocortisone dose — refer to GP for further advice.
Thirst	Refer to “Diet” section.
Weight gain	Steroid medicines can increase a patient’s appetite and they can also make it difficult for a patient to lose weight. If a patient is experiencing weight gain they may benefit from gradually reducing their steroid dose — refer to GP for further advice. Encourage patients to eat a healthy, balanced diet and participate in exercise — signpost to local services who may be able to assist, for example, gyms or weight loss organisations.
Vertigo	If vertigo is severe then this is a more serious indicator that cortisol levels are low and patients are close to exhaustion — patients will need to take their next dose of hydrocortisone immediately. Patients may need to increase the daily dose of their medicine — refer to GP for further advice.

Other useful points to discuss with patients

- Ensure patients who have been diagnosed are aware that they are entitled to a medical exemption certificate which will allow them to receive their NHS prescriptions free of charge
- Encourage patients to have the annual flu vaccination each Autumn
- Advise patients and encourage them to wear a MedicAlert tag to alert people in an emergency to their condition, for example, it could state "adrenal insufficiency, steroid dependent"
- Recommend to patients that they carry a steroid card on their person which will again alert others to the fact they are steroid dependent
- Patients should also be encouraged to carry an emergency crisis letter which can be downloaded from the Addison's Disease Self Help Group (ADSHG) website (this is also available in different languages if a patient is travelling abroad)
- Advise patients that the ADSHG has also produced a manual which can be downloaded free-of-charge from their website that covers a range of topics including medication, diet, exercise, travelling, managing adrenal crisis, pregnancy and looking after children with Addison's disease
- Check whether patients have an emergency injection kit at home (usually hydrocortisone) and anti-emetic tablets — this is good preparation in case they develop a serious illness or are involved in an accident and there is a delay before they can get medical attention
- If patients increase the level of exercise they do, or start doing physically demanding exercise, they may need to increase the steroid dose they take before exercising — this should be discussed with their GP
- The Auden Mckenzie formulation of hydrocortisone 10mg tablets has scoring/breaklines intended to divide into equal doses.

Signposting patients

- Addison's Disease Self Help Group
- Living with Congenital Adrenal Hyperplasia
- The Pituitary Foundation

Website: www.addisons.org.uk

Website: www.livingwithcah.com

Website: www.pituitary.org.uk

Reflection — pharmacy services

Having read the leaflet, spend some time thinking about the services that your pharmacy offers and whether patients with adrenal insufficiency would benefit from participating in them. For example, patients may be suitable for a medicines use review (MUR) and as demonstrated in this leaflet, there is plenty of information and advice that can be provided to this group of patients.

Further information

Further information can be found by referring to the references as well as the following:

- You and your hormones: www.youandyourhormones.info
- Myth vs. fact – adrenal fatigue factsheet (Aug '10) produced by Hormone Foundation and the Endocrine Society: www.hormone.org/hormones-and-health/myth-vs-fact/adrenal-fatigue
- Society for Endocrinology: www.endocrinology.org/

References

- Addison's Disease Self Help Group crisis letter:
www.addisons.org.uk/info/emergency/soscrisisletter.pdf
- Baker, S.J. and White, K. (2003) Living with Addison's disease. An owner's manual for individuals with the disease. Addison's Disease Self Help Group:
www.addisons.org.uk
- Wass, J., Howlett, T., Arlt, W. et al. (2009) Diagnosing Addison's: a guide for GPs. Addison's Disease Self Help Group:
www.addisons.org.uk
- Wass, J., Howlett, T., Arlt, W. et al. (2007) Caring for the Addison's patient: information for GPs. Addison's Disease Self Help Group:
www.addisons.org.uk
- MedicAlert: www.medicalert.org.uk/
- NHS choices: www.nhs.uk/Conditions/Addisons-disease/Pages/Introduction.aspx
- NICE CKS: <http://cks.nice.org.uk/addisons-disease#!topicsummary>
- Summary of product characteristics: hydrocortisone tablets 10mg (Auden Mckenzie (Pharma Division) Ltd)
- WASS BMJ LEADER