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Cover picture

Galen (130-200 A.D.)

Scientific experimenter, showman, teacher of Pharmacy and Medicine, Galen and his rules for extracting, refining and combining drugs (galenicals), among them cold cream, fathered today's pharmaceutical compounding.

One of a series: *A History of Pharmacy in Pictures*, presented by Parke, Davis & Company.

George A. Bender, Director © 1952 Robert A. Thom, Artist

Antithyroid drugs

Antithyroid drugs are used in the pharmacological treatment of hyperthyroidism. They belong to two main classes.

- Radioiodine
- Thioureylenes

The choice of the class of drug depends on several factors including the patient's age, recurrence of hyperthyroidism, and presence of contraindications to a particular type of drug.

Thioureylenes

Initiation and maintenance

Many physicians in Sri Lanka and the UK start treatment with a thioureylene in young adults who present for the first time with hyperthyroidism. Thioureylenes are given orally. The most commonly used drug is carbimazole. Its active metabolite, methimazole is available and registered in Sri Lanka. Propylthiouracil is the other commonly used thioureylene. Both drugs act by inhibiting iodination of tyrosine residues that are part of the thyroglobulin molecule, during thyroid hormone synthesis. Thioureylenes also reduce serum thyrotropin-receptor antibody level and increase suppressor T-cell activity. The duration of a course of thioureylenes ranges from 18-24 months. Both drugs are started at a high dose, a daily dose of 40-60 mg with carbimazole or 200-400 mg with propylthiouracil. Carbimazole and methimazole can be taken once daily, but propylthiouracil is taken in divided doses. Relief of symptoms is generally observed within 2-4 weeks. The initial dose is continued until the patient is clinically and biochemically euthyroid and then reduced gradually to a maintenance dose. Adjusting of initial dose to the maintenance level is done in 4-6 weekly intervals until the maintenance dose is reached. The maintenance dose of carbimazole ranges from 5-15 mg and is adjusted to maintain T_4 and TSH within the reference range. However, it is important to remember that serum TSH level remains suppressed for weeks after normalisation of serum T_3 and T_4 levels. Reaching a stable maintenance dose takes about 3 months in most patients.

Choice of the thioureylene

Carbimazole or methimazole is the first choice unless there are known contraindications to it. Propylthiouracil is used in patients who develop hypersensitivity reactions to carbimazole. Both drugs cross the placenta and are excreted in breast milk, propylthiouracil to a lesser extent than the other. So there is a tendency to choose priopylthiouracil in pregnant hyperthyroid women. Lowest possible dose to control hyperthyroidism should be used in pregnancy to avoid foetal hypothyroidism.

Adverse effects

Rashes and pruritus are common with carbimazole but can be relieved by antihistamines. If symptoms are troublesome, carbimazole may be changed to propylthiouracil. It is important to warn the patient about agranulocytosis and neutropenia that may occur with thioureylenes. Agranulocytosis is an idiosyncratic reaction which is characterised by fever, sore throat and a granulocyte count of less than 500/mm^3. Patients should be given written advice to report signs of infection promptly, especially sore throat. Since agranulocytosis occurs rapidly, routine white cell counts are not helpful. In patients suspected to have neutropenia, carbimazole should be stopped promptly and a white cell count performed. This rare side-effect is reversible. The white cell count returns to normal within two to three weeks after the drug is stopped. Agranulocytosis is an absolute contraindication to further treatment with carbimazole, methimazole or propylthiouracil. Such patients should be treated with radioiodine. Jaundice, hepatitis, vasculitis and lupus-like syndromes are other rare, but serious, side-effects which necessitate discontinuation of thioureylenes.

Outcome of the treatment

Thioureylene therapy is usually continued for one to two years. Relapse is most likely within the first 6 months after withdrawal, but may occur years later. If a patient relapses and wishes to avoid radioiodine, thioureylene therapy may be resumed. Long term therapy appears to be safe. Most patients with Graves disease need radioiodine eventually.

Radioiodine

Radioactive sodium iodide (^{131}I) is used for the treatment of thyrotoxicosis at all ages (except pregnant and breast feeding women), especially in patients with heart disease, recurrence after surgery or medical therapy, and problems with compliance. In Sri Lanka, it is usually administered when hyperthyroidism relapses following treatment with thioureylenes or thyroidectomy. Radioiodine (isotope ^{131}I) is given orally. A single dose of

5 or 10 mCi is administered. The standard practice is to withdraw thioureylenes three to four days before giving radioiodine and resume it three to four days after radioiodine. If the patient continues be hyperthyroid, a second similar (or larger) dose of ^{131}I is given 6 months later. It is taken up and processed by the thyroid cells in the same way as the stable form of iodide. It emits beta particles and destroys thyroid tissue. Gamma rays have a cytotoxic action restricted to the thyroid cells whereas beta particles penetrate non-thyroid tissue. The cytotoxic effect of ^{131}I is delayed and reaches its maximum within 3 to 4 months. During the interim symptoms are controlled by a beta blocker, and in severe cases with carbimazole. ^{131}I has a half-life of 8 days; by two months its radioactivity has effectively disappeared.

Adverse effects

The majority of patients will eventually become hypothyroid, which is easily managed with thyroxine replacement. Occasionally there is transient thyrotoxicosis due to radiation thyroiditis. Radiation thyroiditis severe enough to cause thyroid crisis is rare. Evidence of carcinogenesis following radioiodine is inconclusive. Pregnancy is an absolute contraindication to radioiodine therapy. Radiotherapy, if inadvertently given after the tenth week of gestation (ie. after development of the foetal thyroid), leads to congenital hypothyroidism. Women of childbearing age should be given radioiodine within 10 days of a menstrual period. If the menstrual cycles are irregular, a negative pregnancy test is a prerequisite for therapy with radioiodine. Women should avoid becoming pregnant for four months following radioiodine therapy. Clinical studies have not shown a significant risk of genetic abnormalities resulting from radioiodine therapy.

Outcome

Radioiodine therapy renders the patient euthyroid or hypothyroid in most instances. Hypothyroidism in the first 6 months after radioiodine may be transient and reassessment of replacement thyroxine therapy is needed. Permanent hypothyroidism occurs by 1 year in 50% of the patients who receive high doses of radioiodine. Long term follow up of thyroid status is essential in all patients receiving radioiodine, and after thyroidectomy.

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Drugs used in dementia

Dementia is a non-specific illness syndrome in which there is progressive cognitive decline (memory and at least one other area of higher intellectual function) beyond what might be expected from normal ageing. It is more common in the elderly but may occur at any age. There are many causes of dementia but the commonest is Alzheimer disease. In the elderly Alzheimer disease causes 60-70% of dementia cases. The frequency from the age of 60 years doubles every 5 years. It is 1% for individuals 60-64 years of age, rising to 16% in at 80-84 years of age [1].

Most of the drugs used in dementia treatment are specific for Alzheimer disease (AD), and this article will focus on the drugs used in its treatment.

Current drug treatment

Presently available drugs for dementia include anticholinesterase inhibitors and the NMDA receptor antagonist memantine. Other drugs are used but not yet proven to be effective in clinical trials.

Cholinesterase inhibitors

In AD there is depletion of acetylcholine in the brain. The enzyme choline acetyltranferase that makes choline is also reduced with loss of cholinergic receptors. The enzymes acetylcholinesterase (AChE) and butyryl-cholinesterase (BuChE) are catabolic enzymes that destroy acetylcholine. The US FDA has approved 4 cholinesterase inhibitors; tacrine, donepezil, rivastigmine and galan-tamine. Donepezil inhibits AChE whereas rivastigmine inhibits both AChE and BuChE. Galantamine also affects nicotinic receptors, but these differences do not result in differences in efficacy or tolerability [2]. Donepezil and rivastigimine are available in Sri Lanka, the cloned versions being 10 times cheaper than the original brands. Tacrine is no longer in clinical use due to its association with hepatotoxity (table 1).

Galantamine and rivastigmine have to be given twice daily and have long titration schedules, whereas donepezil is given once daily, and the starting dose of 5 mg is therapeutic. These factors are important in the patients' compliance. Donepezil and galantamine are metabolised by hepatic cytochromes and hence may interact with other drugs. Rivastigmine is metabolised at the site of action and does not affect hepatic cytochromes. Hence it is least likely to cause drug interactions.

Common adverse effects are nausea, vomiting and diarrhoea from excess cholinergic stimulation and may be minimised by increasing the dose slowly. Gastric and duodenal ulcer, gastrointestinal haemorrhage, bradycardia and seizures are less common. These drugs should be used cautiously in patients with a history of gastrointestinal bleeding and arrhythmias [3].

Memantine is licensed for use in moderate to severe dementia. It acts as an antagonist at NMDA receptors, an action which may be neuroprotective. It has few adverse effects and may be used in combination with AChE inhibitors.

The current NICE guidelines recommend the use of an AChE inhibitor in the management of people with Alzheimer disease of moderate severity (MMSE score 10-20). However, there is growing evidence that giving these drugs early in the disease is beneficial and that patients who are treated late have a poorer response. Even later in the disease these drugs may improve behavioural problems (panel 1).

Other drugs used in the treatment of dementia

Anti-inflammatory agents

Inflammation has been postulated as a pathogenic mechanism for the onset of AD, and anti-inflammatory drugs may be useful in its treatment. Some studies show that long term use of anti-inflammatory drugs has a protective effect on the onset of AD, but the results are not conclusive.

Statins

There is a growing body of evidence that lowering serum cholesterol retards the development of AD.

Antioxidants

There is evidence that excess accumulation of amyloid-β peptide generates free radicals, which induce neuronal death. Results of a trial of patients with moderate AD showed that Vitamin E 2,000 IU/day slowed disease progression, but later studies have shown no benefit.

Table 1. Doses of anti-dementia medicines

Drug	*Starting dose*	*Maximum dose*	*Comments*
Donepezil	5 mg daily	10 mg daily	Starting dose is therapeutic. Increase after a month if necessary to 10 mg.
Rivastigmine	1.5 mg b.d.	6 mg b.d.	Increase to 3 mg b.d. after 2 weeks or more and then to 4.5 mg b.d. after a further 2 weeks.
Galantamine	4 mg b.d.	12 mg b.d.	Increase to 8 mg b.d. after 4 weeks and then to 12 mg b.d. after another 4 weeks if necessary.
Memantine	5 mg daily	20 mg daily	The recommended target dose is 20 mg per day. The dose should be increased by 5mg weekly.

Panel 1. Principles for use of anti-dementia treatment

- Make an accurate diagnosis
- Grade the severity of dementia (mild, moderate, severe)
- Inform the patient and caregiver of reasonable treatment expectations
- Optimise the dose of medication increasing the dose slowly to minimise adverse effects
- Monitor multiple domains (cognitive, behavioural)
- Switch AChE inhibitor if patient is intolerant to current drug or shows little benefit
- Emphasise the importance of good compliance
- Continue treatment until severe phase of dementia is reached

Gingko biloba

This has been promoted as a cognitive enhancer. There are experimental data to suggest a neuroprotective effect. There are human trials to suggest its efficacy in mild to moderate AD [2]. *G. biloba* may increase the risk of bleeding.

Vascular dementia

The currently available drugs are not licensed for use in vascular dementia. There is growing evidence that AChE inhibitors as well as memantine are of benefit in vascular dementia and a trial of these drugs is worthwhile. AD is often associated with vascular changes and it is prudent to add low dose aspirin (if there is no contraindication) to reduce the effects of micro-emboli.

Behavioural disturbances in dementia

Behavioural problems are common in dementia and cause a significant distress for the patients and carers. These include agitation in the late afternoon, wandering, insomnia and paranoia. There are no definitive treatments but the following have been tried.

Antipsychotics

Typical antipsychotics have been used for many years to control the behavioural disturbances in dementia. They are effective but cause extrapyramidal side-effects. The atypical antipsychotics are better tolerated but may be less effective. In the UK concerns about a link to stroke and increased mortality have led to a reduction in the use of atypical antipsychotics. A large cohort study done in Canada did not show a difference in the incidence of strokes in patients with dementia given atypical antipsychotics and those given typical antipsychotics [5]. The warnings still remain leaving the clinicians with no clear choice. In the presence of significant distress antipsychotics have to be used. Haloperidol in a dose of 0.75-1.5 mg b.d. could be given, and the dose adjusted to balance effect and adverse effects.

All three AChE inhibitors and memantine are also effective in reducing behavioural disturbances in dementia. Benzodiazepines and trazodone are used to treat insomnia. High doses of benzodiazepines should be avoided as it can lead to confusion, paradoxical agitation and falls.

At present there is no cure for AD. There is no drug that can stop or reverse the progress of the disease. However, the use of currently available medicines can slow the decline in cognitive functions and reduce behavioural problems. They should be started early for maximum effectiveness.

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Management of acute glomerulonephritis in children

Introduction

The commonest cause of acute glomerulonephritis (AGN) in children is post-infectious acute glomerulonephritis due to nephritogenic strains of Group A β-haemolytic streptococci (APSGN). It is one of the commonest glomerular causes of haematuria in children and follows infection of the skin or the nasopharynx. AGN is an immune complex glomerulonephritis where the inflammation and proliferation of cells within the glomerulus is initiated by immunological mechanisms, which restrict glomerular blood flow and decrease filtration, resulting in the clinical features of the acute nephritic syndrome.

Clinical features

Five to 12-year old children are usually affected and typically present 1-2 weeks after a streptococcal pharyngitis with sudden onset of the acute nephritic syndrome with gross haematuria, oedema, and varying degrees of reduced GFR manifesting as oliguria and hypertension.

Urine analysis shows proteinuria and haematuria with dysmorphic red cells and granular casts on microscopy. Oedema is characteristically periorbital but generalised oedema may be present, with pleural effusions and ascites occurring rarely.

Investigations

Estimation of serum creatinine and electrolytes are useful in the initial management. Confirmation of the aetiology is not essential but a low serum complement C3 level with a normal C4 level in the acute stage of the illness is found in APSGN. Evidence of antecedent streptococcal infection is by demonstrating an elevated antibody titre to streptococcal antigens. Anti-streptolysin O titre (ASO) rarely rises after streptococcal skin infections but a significantly raised titre of either anti-DNase B or anti-hyaluronidase antibodies is found in APSGN.

Initial management

In the acute stage of the illness bed rest is advocated. Meticulous monitoring of the fluid balance is mandatory. Blood pressure should be monitored regularly and the body weight recorded daily. On admission the fluid intake is the insensible loss calculated as 400 ml/m^2/day. Thereafter the intake should match the urine output. Initial diet is without any added salt, and food items rich in potassium are withheld if serum K+ is elevated.

Drugs

Routine use of diuretics is not recommended. Hypertension if symptomatic needs treatment. With the onset of diuresis in a few days the patient becomes normotensive. Oral penicillin is given for 10 days to limit spread of nephritogenic streptococci but this does not affect the natural history of the disease. Diuretic therapy is indicated for treatment of cardiac failure.

Panel 1. APSGN presenting as acute nephritic syndrome

- 5 to 12 years (rare <3 years)
- Follows skin or throat infection with group A β-haemolytic streptococci
- Macroscopic or microscopic haematuria
- Periorbital oedema
- Oliguria
- Hypertension
- Initially raised serum creatinine and potassium
- Low complement C3 and normal C4
- Raised anti-DNase or anti-hyaluronidase titres

Panel 2. Management of APSGN

- Bed rest
- Maintain a fluid balance chart
- Monitor blood pressure regularly
- Record body weight daily
- Urine analysis daily
- Diet: low salt, low potassium
- Investigations: serum creatinine, potassium
- Observe for complications

Complications

Acute renal failure is rare. Hypertensive encephalopathy and cardiac failure are possible complications in the initial phase of the illness. Hence the patient should be monitored closely for early symptoms and signs such as drowsiness, headache, difficulty in breathing, evidence of tender hepatomegaly and lung signs.

Prognosis

APSGN generally resolves spontaneously within 2 weeks and recovery is complete in over 95% of children. The child can be discharged from hospital when renal function is satisfactory and there is no macroscopic haematuria or hypertension. If microscopichaematuria persists for over 6 months, referral to a paediatric nephrologist is indicated. Unlike in rheumatic fever, recurrence of infection with nephritogenic strains of haemolytic streptococci is very rare, and secondary prophylaxis with benzathine penicillin is not indicated. Long term follow up is not required. Further investigations including a renal biopsy are indicated only very rarely.

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Preventing foot ulcers

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Summary

Foot ulceration is an unfortunate complication of a number of chronic diseases, especially diabetes mellitus. Patients with peripheral neuropathy, foot deformity or peripheral vascular disease have an increased risk of developing foot ulcers. Ulceration is often preventable and the general practitioner is in a unique position to ensure timely assessment, education, management and referral for at-risk patients. Most of the evidence for reducing the risk of foot ulcers comes from studies in diabetes. However, it is not unreasonable to apply similar principles to people with other diseases who are also at risk of developing foot ulcers.

Key words: deformity, foot ulcers, peripheral neuropathy, peripheral vascular disease, risk reduction.

(Aust Prescr 2008,31:94-6)

Introduction

Foot ulceration may be defined as the erosion of tissue or a breach of the epidermis at a site distal to the ankle.There are a number of conditions that place a person at risk of developing foot ulceration. These include, but are not limited to, diabetes (see *Aust Prescr* 2007;30:21-4), peripheral vascular disease, end-stage renal failure, vitamin B_{12} deficiency, gout, rheumatoid arthritis, scleroderma and cerebral palsy, or any other condition that affects the circulation, structure or sensation of the feet. Timely referral to a podiatrist or appropriate specialist may assist these patients to prevent or manage possible foot complications. The general practitioner has an important role in not only identifying people requiring specialist referral, but also educating those at risk about appropriate self-management and risk reduction.

Risk factors

Common risk factors for foot ulceration include peripheral neuropathy, structural deformity of the foot, peripheral vascular disease, trauma and a history of foot ulceration and/or amputation.

Peripheral neuropathy

Many of the conditions that place individuals at increased risk of developing foot ulcers share the common factor of peripheral neuropathy. In patients with peripheral neuropathy, trauma and injury can occur without them knowing. For many people this means that they cannot detect a foreign object in the shoe, or that their shoe does not fit correctly. Undetected trauma is often untreated trauma, and can have potentially limb-threatening consequences. Peripheral neuropathy may also contribute to the development of foot deformity, as well as changes in the skin.

One way to diagnose neuropathy in the clinical setting is with the 10 g Semmes Weinstein monofilament (Fig. 1). Failure to detect the monofilament at any one of the test sites (Fig. 2) indicates the presence of peripheral neuropathy.[1]

Foot deformity

Foot deformity results in increased foot pressures and when combined with an additional risk factor, such as neuropathy, places the patient at significant risk of developing a foot complication.[2] Foot deformity may be congenital, or develop as a consequence of poor footwear or as part of a disease process, especially for those with rheumatoid arthritis and diabetes. The most common foot deformities are claw or hammer toes, bunions, callus, previous surgical sites and a lowered medial longitudinal arch.

Peripheral vascular disease

Peripheral vascular disease is not often the cause of foot ulceration, but is a contributing factor in poor or delayed healing of foot ulcers.[3] A simple clinical test for diagnosing peripheral vascular disease is palpation of the foot pulses. Absence of these pulses indicates a high likelihood of peripheral vascular disease, which may warrant further investigations.[4] Assessment of the microcirculation is more difficult but can be achieved with measurement of toe pressures. A toe pressure of greater than 30 mmHg suggests a wound is likely to heal with conservative therapy.[5]

Fig. 1

Using a monofilament to assess sensation in the foot

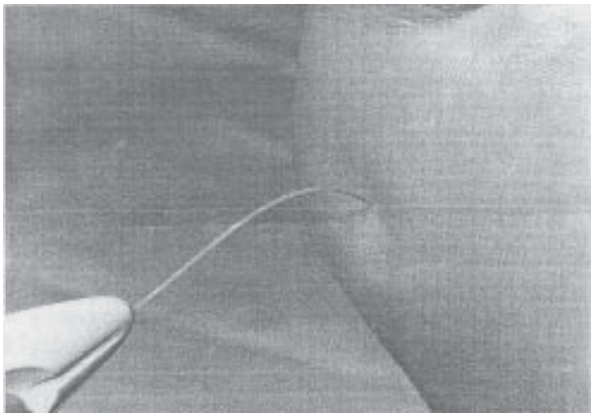
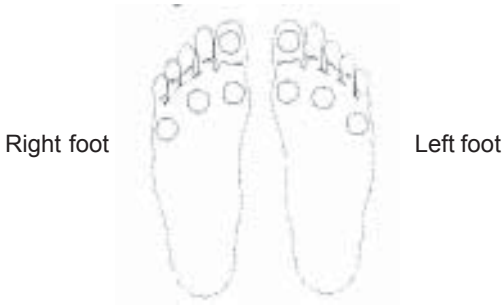


Fig. 2

Monofilament testing sites



Trauma

People often think that trauma to the foot is what precipitates foot ulceration, with little credit being given to the contribution of underlying disease process or other risk factors. Certainly, a blister from new shoes or a burn from a hot water bottle are precipitating events in ulcer formation. However, it is the consequences of the underlying disease process that result in the non-healing or problem foot ulcer. Preventing trauma often prevents foot ulceration.

History of foot ulceration or amputation

Previous ulceration or amputation are recognised as the most significant risk factors for developing further ulceration.[6] This probably represents the underlying limb pathology, and may also be related to gait changes that result from an amputation.[7,8] A person with diabetes and a history of foot ulceration or amputation must be considered at ongoing high risk for developing further ulceration and be referred to a podiatry service for

monitoring and management. There is evidence to support reduced re-ulceration and amputation rates in people with diabetes who access regular podiatry care.[9,10,11]

Preventative measures

It is important to optimise the treatment of underlying conditions, such as peripheral neuropathy, which can increase the risk of developing foot ulcers. Regular foot inspections by a general practitioner are a good opportunity to check that the feet are free from injury, but also to reiterate advice and discuss any concerns the person may have.

Patients should be educated about how to reduce their risk of developing foot ulcers (Table 1). This is especially important for people with peripheral vascular disease who are more likely to require a referral for expert assessment, monitoring and management than those with neuropathy. People with early stage vascular disease should be encouraged to 'move it or lose it' to maintain their circulation, with the exception of people who currently have an active foot problem.

Table 1. Foot care for patients at risk of foot ulcers [12]

Advice	*Points to highlight*
Daily foot inspection	Check between the toes and underneath the feet
	Look for any breaks in the skin, areas of rubbing or signs of infection
First aid for injuries	Apply antiseptic (e.g. povidone-iodine) to the injury, followed by a protective cover (e.g. dry dressing such as cutiplast)
	Seek expert assistance when an injury is not healing
Self-care	Wash feet daily and dry thoroughly, especially between toes
	Daily use of an emollient to prevent drying and cracking of the feet, such as sorbolene
	Filing in preference to cutting of nails. If nails are cut this should be straight across and the nail edge should be left longer than the most distal aspect of the nail sulcus (see Fig. 3).
	Use of a pumice to reduce callus development. This should only be undertaken when a person has no neuropathy and has had a safe technique demonstrated to them by their podiatrist or general practitioner.
Risk reduction	Never walk barefoot
	Beware of sources of heat (heaters, hot water bottles) as a cause of trauma
	Treat tinea infections promptly with an appropriate topical antifungal such as terbinafine preparations. Any breach of the epidermis increases the risk of bacterial infection.
Well-fitting footwear	Wear shoes with a wide and deep toe box (should be able to freely move toes inside)
	Shoes should have leather upper, minimal internal seams, firm fastenings (laces or velcro), a firm heel counter (the rear of a shoe should be able to hold its shape under firm pressure) and a cushioning sole
	New shoes should be worn in slowly to minimise the risk of the shoe causing a foot ulcer. A podiatrist usually recommends starting at one hour a day, increasing the time the shoe is worn by an hour each day as long as no problems are detected.

The most basic but important advice for individuals with neuropathy is to inspect their feet daily for signs of trauma. This can be difficult for some people with visual or physical disabilities. Where a family member or carer is not available, most people are able to adequately perform this function using a good quality magnifying mirror to inspect the plantar surface of the foot. Patients should also be advised to inspect their footwear for foreign objects before wearing, and check their shoes are a good fit.

People with foot deformity should be educated on the importance of purchasing well-fitting footwear, and for more severe cases that are affecting day-to-day function, a referral to a podiatrist or orthotist for pressure-relieving orthoses and/or specialist footwear may be of assistance. The best advice people can be given is to seek professional help as soon as a foot problem develops, or is not resolving. Any person identified as being at high risk for ulceration should not only receive detailed education on risk reduction, but should also be referred for podiatry care.

Conclusion

Foot ulceration is preventable with suitable assessment, management and education. The regular access and individual relationships that people with a chronic disease have with their general practitioner provide excellent opportunities to reduce the risk of foot ulceration. When individuals at high risk develop a foot complication, they should be promptly referred to specialist health professionals with expertise in managing these conditions to maximise wound healing and reduce the risk of lower limb amputation.

Fig. 3

Correctly cut big toe nail

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Management of anxiety disorders

Anxiety is a normal emotion experienced by practically everyone. Its manifestations are psychological, physical or a combination of these. Anxiety disorders are classified in the International Classification of Diseases ICD-10, under the category 'Neurotic, stress related and somatoform disorders' [1]. The predominant symptom in these conditions is anxiety, though a mixture of anxiety and depression often coexist. The main anxiety disorders are phobic anxiety disorders which include agoraphobia, social phobia and other specific phobias, generalised anxiety disorder, panic disorder and obsessive compulsive disorder.

Clinical features

Panic disorder

The main feature is recurrent attacks of unpredictable, severe anxiety. Sudden onset of palpitations, chest pain, choking sensation, dizziness and feelings of unreality are common. There is secondary fear of dying, losing control or going mad. Biological models of panic disorder describe dysregulation of the serotonergic system and GABA-benzodiazepine receptor complex as possible mechanisms in the aetiology of panic disorder.

Generalised anxiety disorder

Generalised anxiety disorder (GAD) is defined as excessive and uncontrollable worry and anxiety about everyday life situations. It is a chronic disorder associated with substantial somatisation, high rates of comorbid depression and other anxiety disorders, and significant disability [2].

Obsessive compulsive disorder

The essential feature of this disorder is recurrent obsessional thoughts or compulsive acts [1]. Obsessional thoughts are ideas, images or impulses that enter an individual's mind again and again in a stereotyped form. Common themes in obsessional thoughts are contamination, doubts, and sexual and blasphemous thoughts. The compulsive acts or rituals are carried out to reduce the anxiety. Cleaning rituals (especially hand-washing), repeated checking, repeating numbers or words in a pattern are common rituals.

Anxiety disorders respond well to cognitive behaviour therapy and pharmacotherapy. This article will discuss the pharmacotherapy of anxiety disorders.

Phobic anxiety disorders

Anxiety is evoked only by certain well-defined situations or objects [1]. At other times the person has no symptoms. Agoraphobia is characterised by fear of open spaces and the presence of crowds, resulting in fear of leaving home, entering shops, crowds, public places or travelling alone in trains, buses or planes. Social phobias often start in adolescence and are centred on a fear of scrutiny by other people leading to avoidance of social situations. Specific phobias are phobias restricted to highly specific situations such as proximity to particular animals, heights, thunder, darkness, flying, sight of blood and injury, or fear of exposure to certain diseases such as HIV/AIDS.

Treatment of anxiety disorders

Cognitive behaviour therapy (CBT) and medication are effective in the treatment of anxiety disorders. The main classes of medication used are specific serotonin reuptake inhibitors (SSRI), serotonin noradrenaline reuptake inhibitors (SNRI), tricyclic antidepressants and benzodiazepines. SSRIs have greater safety in overdose and better tolerability and are recommended as first-line treatment. Choice between SSRIs depends on the acceptability of particular side-effects for the individual

patient and the cost. Tricyclics have the disadvantage of cardiovascular and anticholinergic side-effects and are unsafe in overdose. Benzodiazepines are of limited use because of sedation, memory difficulties, impairment of motor skills, falls, tolerance and dependence. The side-effects of venlafaxine (SNRI) are similar to those of SSRIs, but a small proportion may develop raised blood pressure. Hence blood pressure monitoring is recommended. The therapeutic doses of medications for anxiety disorders are given in the table.

Panic disorder

The SSRIs, SNRIs, tricyclics and benzodiazepines are equally effective in treating panic disorder [3]. SSRIs are recommended as first-line treatment and all SSRIs are of equal efficacy. Because SSRIs, SNRIs and tricyclics take 4-6 weeks to act, benzodiazepines which have a rapid onset of action are used as an adjunct initially in treating patients with very distressing symptoms.

Starting doses of SSRI, SNRI and tricyclics are lower than the doses used for depression as they can initially exacerbate anxiety and other symptoms of panic disorder [3]. The dose is titrated according to response. Therapeutic effect can be delayed and may take up to 6 weeks. Treatment should be continued for at least 8 months. Antidepressants should be tailed off over several weeks. About 50% of patients may relapse after medication is withdrawn.

In addition to an antidepressant short term use of a benzodiazepine for 4-6 weeks to control symptoms is used in clinical practice. This ensures a rapid control of symptoms and relieves the initial exacerbation of anxiety sometimes caused by antidepressants. Alprazolam is effective in preventing panic attacks, reducing anticipatory anxiety and avoidance. Alprazolam 0.25 mg three times a day is given initially and the dose titrated to a maximum of 2-3mg/day over the first 2 weeks depending on symptom control. Clonazepam can be used as a once daily dose.

Generalised anxiety disorder

Cognitive behaviour therapy is as effective as pharmacotherapy in GAD. The antidepressants SSRIs, SNRIs, tricyclic antidepressants and benzodiazepines are effective in treating GAD. In addition buspirone and pregabalin (a structural analogue of gamma-aminobutyric acid GABA) are reported to be effective.

Table. Effective dose range of antidepressants and benzodiazepines for anxiety disorders

	Starting dose for generalised anxiety and panic disorder/day	*Therapeutic dose for generalised anxiety and panic disorder/day*	*Maximum dose for obsessive compulsive disorder/day*
SSRI			
Citalopram	10 mg	20-40 mg	80 mg
Escitalopram	5-10 mg	10-20 mg	40 mg
Fluoxetine	10 mg	20-40 mg	80 mg
Fluvoxamine	25-50 mg	100-200 mg	300 mg
Paroxetine	10 mg	20-40 mg	60 mg
Sertraline	25 mg	100-200 mg	200 mg
SNRI			
Venlafaxine XR	37.5 mg	150-225 mg	225 mg
Tricyclics			
Imipramine	10 mg	100-300 mg	Not effective
Clomipramine	10-25 mg	50-150 mg	250 mg
Benzodiazepines			
Alprazolam	0.75 mg (given as tds)	2-4 mg	Not effective
Clonazepam	0.5-1.0 mg	1-2 mg	Not effective

SSRIs are used as first-line treatment [2]. Treatment is with low initial doses and gradual titration. If there is poor response after 12 weeks of treatment with the maximum tolerable dose switching to another SSRI or SNRI (venlafaxine or duloxetine) is recommended. Treatment should be continued for 18 months.

Obsessive compulsive disorder

Cognitive behaviour therapy which includes exposure and response prevention and SSRIs are used as first-line treatment. Weekly CBT sessions and daily homework for 13-20 weeks are recommended. The tricyclic antidepressant clomipramine is as effective as SSRIs but because of unpleasant side-effects it is used mainly in patients not responding to SSRIs. Pharmacological treatment used initially may reduce symptom severity and improve cooperation with psychological therapy. Combining CBT with an SSRI is more effective in reducing symptoms and preventing relapse than monotherapy with either CBT or SSRI. New evidence suggests that venlafaxine (SNRI) may be effective in treating OCD. Tricyclics other than clomipramine and benzodiazepines are not recommended for treatment of OCD [4].

Fluoxetine is commenced at a dose of 20 mg/day and titrated to a maximum of 80 mg/day according to response. Response may take 10-12 weeks. Treatment should be continued for 1-2 years and tailed off over several months [4].

In about 30% residual symptoms remain despite initial treatment. If a patient has not responded adequately to a trial of 8-12 weeks of treatment which includes 4-6 weeks at the maximum tolerable dose, change of medication should be considered. CBT can be added if not already provided. Switching to another SSRI to clomipramine or venlafaxine and augmenting with an atypical antipsychotic are second-line treatment strategies. The atypical antipsychotics risperidone 1-4 mg, quetiapine 50-400 mg and olanzapine 5-20 mg and the typical antipsychotic haloperidol 2-10 mg are used for augmentation of SSRI in non-responders [4].

Social anxiety disorder

Also known as social phobia responds well to CBT and exposure therapy. CBT is more effective than pharmacotherapy. First-line pharmacological treatment is SSRIs [5]. Venlafaxine is used as second-line treatment. Gabapentin, pregabalin, valproic acid, clonazepam and monoamine oxidase inhibitors though effective are not widely used. Treatment should be continued for 6 months.

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Self-assessment questions

(And clinical physiology in small doses)

*Select the **best** response in each question*

1. Radioactive sodium iodide (^{131}I) oral solution used in the treatment of hyperthyroidism
   a. is contraindicated in all adults below the age of 35 years.
   b. exercises its therapeutic action for a maximum of 2 weeks after the initial dose.
   c. is processed by the thyroid gland in the same manner as the stable isotope.
   d. causes hypothyroidism in about 40-50% of treated patients by 10 years.
   e. significantly increases the risk of leukemia and cancer in recipients.

2. In euthyroid non-pregnant adults
   a. the molar activity ratio of T_3 to T_4 is about 2:1.
   b. the secretory ratio of T_3 to T_4 is about 1:5.
   c. about 2% of T_4 in the plasma is not protein bound.
   d. about 3% of T_3 in the plasma is not protein bound.
   e. most of the T_3 in plasma is derived from monodeiodination of T_4 in peripheral tissue.

3. Carbimazole used in the management of hyperthyroidism
   a. is converted to its active metabolite methimazole after oral dosing.
   b. is preferably given 8-hourly.
   c. the initial daily dose is 5-10 mg.
   d. acts principally by inhibiting iodide uptake by the thyroid gland.
   e. suppresses TSH secretion by a direct action on the pituitary.

(See next page for answers)

Answers to self-assessment questions

Question 1. The correct response is **c**. Radioactive iodine may be used at all ages above 20 years (except during pregnancy and breast feeding), exercises its action for several months after dosing, causes hypothyroidism in over 75-80% of recipients by 10 years, and does not increase the risk of malignancy.

Question 2. The correct response is **e**. The molar activity ratio of T_3 to T_4 is about 1:4. Only about 0.05% of the plasma T_4 is unbound, whereas about 0.5% of T_3 is unbound which explains its higher molar activity ratio. The secretory ratio of T_3 to T_4 is 1:15.

Question 3. The correct response is **a**, hence the more rational drug for use is methimazole, which is available in Sri Lanka. The initial dose of canbimazole is 40 - 60 mg a day, which may be given as a single dose or 12-hourly. It inhibits iodination of tyrosine moieties in the thyroglobulin molecule, and has no direct action on TSH secretion.

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