Chronic heart failure 21

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Key points

- Heart failure is a common condition that affects the quality of life causing fatigue, breathlessness and oedema. It often has a poor prognosis.
- Heart failure is a maladaptive condition with haemodynamic and neurohormonal disturbances. Increased understanding of its pathophysiology and the strength of the evidence base allow a rational approach to therapeutic management.
- The aims of drug treatment are to control symptoms and to improve survival. By slowing disease progression the aim is to maintain quality of life.
- Diuretics are used for symptomatic management of heart failure, and are combined with other agents in the treatment of systolic dysfunction.
- Angiotensin converting enzyme (ACE) inhibitors and β-blockers are first-line agents in asymptomatic and symptomatic patients with systolic dysfunction.
- Angiotensin II receptor blockers (ARBs) are an alternative choice in patients intolerant of or resistant to ACE inhibitor therapy. Where use of an ARB is inappropriate, the combination of hydralazine and nitrate may still have a place.
- Aldosterone antagonists have been shown to improve morbidity and mortality when used as adjunctive therapy in patients with heart failure due to systolic dysfunction.
- Digoxin may still have a role in improving symptoms and reducing the rate of hospitalisation for patients with heart failure in sinus rhythm, but has not been demonstrated to affect mortality.
- Heart failure is a condition in which integration of pharmaceutical care within multidisciplinary models of patient care can improve clinical outcomes for patients and contribute to the continuity of care.

Chronic heart failure results from deficiency in the heart's function as a pump, where the delivery of blood, and therefore oxygen and nutrients, becomes inadequate for the needs of the tissues. Chronic heart failure is a complex condition associated with a number of symptoms arising from defects in left ventricular filling and/or emptying, of which shortness of breath (exertional dyspnoea, orthopnoea and paroxysmal nocturnal dyspnoea), fatigue and ankle swelling are the most common. The symptoms of heart failure are due to inadequate tissue perfusion, venous congestion and disturbed water and electrolyte balance. Impairment of renal function, and the associated water retention, adds to the burden placed on the heart. In chronic heart failure, the physiological mechanisms that aim to maintain adequate tissue perfusion become counterproductive and contribute to the progressive nature of the condition.

Treatment is aimed at improving left ventricular function, controlling the secondary effects that lead to the occurrence of symptoms, and delaying disease progression. Drug therapy is indicated in all patients with heart failure to control symptoms (where present), improve quality of life and prolong survival. Patients with heart failure usually have their functional status assessed and categorised using the New York Heart Association (NYHA) classification system shown in Table 21.1.

Epidemiology

Chronic heart failure is a common condition with a prevalence ranging from 0.3% to 2% in the population at large, 3–5% in the population over 65 years old, and between 8% and 16% of those aged over 75 years. Heart failure accounts for 5% of adult medical admissions to hospital. There is a loss of cardiac reserve with age, and heart failure may often complicate the presence of other conditions in the elderly. More than 10% of patients with heart failure also have atrial fibrillation as a contributory factor. This combination presents a risk of thrombo-embolic complications, notably stroke; the risk is 2% in patients in sinus rhythm, but may exceed 10% a year in patients with atrial fibrillation who are not anticoagulated and have attendant risk factors.

Table 21.1 New York Heart Association (NYHA) classification of functional status of the patient with heart failure

I	No symptoms with ordinary physical activity (such as walking or climbing stairs)
II	Slight limitation with dyspnoea on moderate to severe exertion (climbing stairs or walking uphill)
III	Marked limitation of activity, less than ordinary activity causes dyspnoea (restricting walking distance and limiting climbing to one flight of stairs)
IV	Severe disability, dyspnoea at rest (unable to carry on physical activity without discomfort)

Heart failure is a progressive condition with complex possible causes, and mortality varies according to aetiology and severity. The variable prognosis is represented by a median survival of about 5 years after diagnosis. The prognosis can be predicted according to the severity of the disease, with an overall annual mortality rate for patients with chronic heart failure estimated at 10%. Main causes of death are progressive pump failure, sudden cardiac death and recurrent myocardial infarction.

Aetiology

Heart failure may be a consequence of myocardial infarction, but as a chronic condition it is often gradual in onset with symptoms arising insidiously and without any specific cause over a number of years. The common underlying aetiologies in patients with heart failure are coronary artery disease and hypertension. The appropriate management of these predisposing conditions is also an important consideration in controlling heart failure in the community. Identifiable causes of heart failure include aortic stenosis, cardiomyopathy, mechanical defects such as cardiac valvular dysfunction, hyperthyroidism and severe anaemia. Conditions that place increased demands on the heart can create a shortfall in cardiac output and lead to intermittent exacerbation of symptoms. Symptoms of heart failure may occur as a consequence of hyperthyroidism, where the tissues place a greater metabolic demand, or severe anaemia, where there is an increased circulatory demand on the heart. Cardiac output may also be compromised by bradycardia or tachycardia, or by a sustained arrhythmia such as that experienced by patients in atrial fibrillation.

Atrial fibrillation often accompanies hyperthyroidism and mitral valve disease, where a rapid and irregular ventricular response can compromise cardiac efficiency. Improved management of the underlying causes, where appropriate, may alleviate the symptoms of heart failure, whereas the presence of mechanical defects may require the surgical insertion of prosthetic valve(s). While around 50% of patients with heart failure have significant left ventricular systolic dysfunction, the other half is comprised of patients who have either a normal or insignificantly reduced left ventricular ejection fraction (EF), although there is no consensus on the threshold for compromised EF and assessment of each patient relies mainly on clinical symptoms. These patients are referred to as having heart failure with preserved left ventricular ejection fraction (HFPEF). However, most of the available evidence from clinical trials regarding the pharmacological treatment of heart failure to date relates to those patients with heart failure due to left ventricular systolic dysfunction. Clinical symptomatic description of chronic heart failure is mild, moderate, or severe heart failure. 'Mild' is used for patients who are mobile with no important limitations of dyspnoea or fatigue, 'severe' for patients who are markedly symptomatic in terms of exercise intolerance and 'moderate' for those with restrictions in between. Trials tend to formalise these categories into NYHA Categories I–IV (Table 21.1).

Pathophysiology

In health, cardiac output at rest is approximately 5 L/min with a mean heart rate of 70 beats per minute and stroke volume of 70 mL. Since the filled ventricle has a normal volume of 130 mL, the fraction ejected is over 50% of the ventricular contents, with the remaining (residual) volume being approximately 60 mL. In left ventricular systolic dysfunction, the EF is reduced to below 45%, and symptoms are common when the fraction is below 35%, although some patients with a low EF can remain asymptomatic. When the EF falls below 10%, patients have the added risk of thrombus formation within the left ventricle and in most cases anticoagulation with warfarin is indicated.

Left ventricular systolic dysfunction can result from cardiac injury, such as myocardial infarction, or by exposure of the heart muscle to mechanical stress such as long-standing hypertension. This may result in defects in systolic contraction, diastolic relaxation, or both. Systolic dysfunction arises from impaired contractility, and is reflected in a low EF and cardiac dilation. Diastolic dysfunction arises from impairment of the filling process. Diastolic filling is affected by the rate of venous return, and normal filling requires active diastolic expansion of the ventricular volume. The tension on the ventricular wall at the end of diastole is called the preload, and is related to the volume of blood available to be pumped. That tension contributes to the degree of stretch on the myocardium. In diastolic dysfunction, there is impaired relaxation or reduced compliance of the left ventricle during diastole and, therefore, less additional blood is accommodated. In pure diastolic dysfunction, the EF can be normal but cardiac dilation is absent. Sustained diastolic dysfunction, which is a feature in a minority of patients with heart failure, may lead to systolic dysfunction associated with disease progression and left ventricular remodelling (structural changes and/or deterioration).

During systolic contraction, the tension on the ventricular wall is determined by the degree of resistance to outflow at the exit valve and that within the arterial tree, that is, the systemic vascular resistance. Arterial hypertension, aortic narrowing and disorders of the aortic valve increase the afterload on the heart by increasing the resistance against which the contraction of the ventricle must work. The result is an increased residual volume and consequently an increased preload as the ventricle overfills, and produces greater tension on the ventricular wall. In the normal heart, a compensatory increase in performance occurs as the stretched myocardium responds through an increased elastic recoil. In the failing heart, this property of cardiac muscle recoiling under stretch is diminished, with the consequence that the heart dilates abnormally to accommodate the increased ventricular load. With continued dilation of the heart the elastic recoil property can become much reduced. Failure of the heart to handle the increasing ventricular load leads to pulmonary and systemic venous congestion. At the same time, the increased tension on the ventricular wall in heart failure raises myocardial oxygen requirements, which increases the risk of an episode of myocardial ischaemia or arrhythmias.

The failing heart may show cardiac enlargement due to dilation, which is reversible with successful treatment. An irreversible increase in cardiac muscle mass, cardiac hypertrophy,

occurs with progression of heart failure and is a consequence of long-standing hypertension. While hypertrophy may initially alleviate heart failure, the increased mass is pathologically significant because it ultimately increases the demands on the heart and oxygen consumption.

A reflex sympathetic discharge caused by the diminished tissue perfusion in heart failure exposes the heart to catecholamines where positive inotropic and chronotropic effects help to sustain cardiac output and produce a tachycardia. Arterial constriction diverts blood to the organs from the skin and gastro-intestinal tract but overall raises systemic vascular resistance and increases the afterload on the heart.

Reduced renal perfusion due to heart failure leads to increased renin release from the glomerulus in the kidney. Circulating renin raises blood pressure through the formation of angiotensin I and angiotensin II, a potent vasoconstrictor, and renin also prompts adrenal aldosterone release. Aldosterone retains salt and water at the distal renal tubule and so expands blood volume and increases preload. Arginine vasopressin released from the posterior pituitary in response to hypoperfusion adds to the systemic vasoconstriction and has an antidiuretic effect by retaining water at the renal collecting duct.

These secondary effects become increasingly detrimental to cardiac function as heart failure progresses, since the vasoconstriction adds to the afterload and the expanded blood volume adds to the preload. The expanded blood volume promotes the atrial myocytes to release a natural vasodilator, atrial natriuretic peptide (ANP), to attenuate the increased preload.

The compensatory mechanisms for the maintenance of the circulation eventually become overwhelmed and are ultimately highly counterproductive, leading to the emergence and progression of clinical signs and symptoms of heart failure. The long-term consequences are that the myocardium of the failing heart undergoes biochemical and histological changes that lead to remodelling of the left ventricle which further complicates disease progression. In those patients where the condition is severe and has progressed to an end stage, heart transplantation may be the only remaining treatment option.

Clinical manifestations

The reduced cardiac output, impaired oxygenation and diminished blood supply to muscles cause fatigue. Shortness of breath occurs on exertion (dyspnoea) or on lying (orthopnoea). When the patient lies down, the postural change causes abdominal pressure on the diaphragm which redistributes oedema to the lungs, leading to breathlessness. At night the pulmonary symptoms give rise to cough and an increase in urine production prompts micturition (nocturia), which adds to the sleep disturbance. The patient can be inclined to waken at night as gradual accumulation of fluid in the lungs may eventually provoke regular attacks of gasping (paroxysmal nocturnal dyspnoea). Characteristically the patient describes the need to sit or stand up to seek fresh air, and often describes a need to be propped up by three or more pillows to remedy the sleep disturbances that are due to fluid accumulation.

Table 21.2 Clinical manifestations of heart failure

Venous (congestion)	Cardiac (cardiomegaly)	Arterial (peripheral hypoperfusion)
Dyspnoea	Dilation	Fatigue
Oedema	Tachycardia	Pallor
Hypoxia	Regurgitation	Renal impairment
Hepatomegaly	Cardiomyopathy	Confusion
Raised venous pressure	Ischaemia, arrhythmia	Circulatory failure

Patients with heart failure may appear pale and their hands cold and sweaty. Reduced blood supply to the brain and kidney can cause confusion and contribute to renal failure, respectively. Hepatomegaly occurs from congestion of the gastro-intestinal tract, which is accompanied by abdominal distension, anorexia, nausea and abdominal pain. Oedema affects the lungs, ankles and abdomen. Signs of oedema in the lungs include crepitations heard at the lung bases. In acute heart failure, symptoms of pulmonary oedema are prominent and may be life-threatening. The sputum may be frothy and tinged red from the leakage of fluid and blood from the capillaries. Severe dyspnoea may be complicated by cyanosis and shock. Table 21.2 presents the clinical manifestations of heart failure.

Investigations

Patients with chronic heart failure are diagnosed and monitored on the basis of signs and symptoms from physical examination, history and an exercise tolerance test. On physical examination of the patient, a lateral and downward displacement of the apex beat can be identified as evidence of cardiac enlargement. Additional third and/or fourth heart sounds are typical of heart failure and arise from valvular dysfunction. Venous congestion can be demonstrated in the jugular vein of the upright reclining patient by an elevated jugular venous pressure (JVP), which reflects the central venous pressure. The JVP is measured by noting the visible distension above the sternum and may be accentuated in heart failure by the application of abdominal compression in the reclining patient. Confirmation of heart failure, however, should not be based on symptom assessment alone.

Echocardiography is important when investigating patients with a suspected diagnosis of heart failure. An echocardiogram allows visualisation of the heart in real time and will identify whether heart failure is due to systolic dysfunction, diastolic dysfunction or heart valve defects. With the provision of direct access echocardiography services to doctors in primary care, an increasing number of patients can now be quickly referred to confirm or exclude heart failure due to left ventricular systolic dysfunction or other structural abnormalities. Some reports suggest that between 50% and 75% of

Table 21.3 Investigations performed to confirm a diagnosis of heart failure

Investigation	Comment
Blood test	The following assessments are usually performed: • Blood gas analysis to assess respiratory gas exchange • Serum creatinine and urea to assess renal function • Serum alanine- and aspartate-aminotransferase plus other liver function tests • Full blood count to investigate possibility of anaemia • Thyroid function tests to investigate possibility of thyrotoxicosis • Serum BNP or NT pro-BNP to indicate likelihood of a diagnosis of heart failure (screening test) • Fasting blood glucose to investigate possibility of diabetes mellitus
12-lead electrocardiogram	A normal ECG usually excludes the presence of left ventricular systolic dysfunction. An abnormal ECG will require further investigation
Chest radiograph	A chest radiograph (X-ray) is performed to look for an enlarged cardiac shadow and consolidation in the lungs
Echocardiography	An echocardiogram is used to confirm the diagnosis of heart failure and any underlying causes, for example, valvular heart disease

patients referred to direct access clinics may have normal left ventricular function, which has important implications for the selection of appropriate drug treatment. Table 21.3 shows a number of investigations that are routinely performed in the assessment of heart failure symptoms. The use of serum natriuretic peptide measurement in the diagnosis of patients with heart failure is currently limited by the lack of defined cut-off values and, therefore, measurements are only considered in combination with ECG/chest X-ray data prior to echocardiography.

Treatment of heart failure

Until the 1980s, pharmacotherapy was driven by the aim to control symptoms, when diuretics and digoxin were the mainstay of treatment. While relieving the symptoms of heart failure remains decisive in improving a patient's quality of life, a better understanding of the underlying pathophysiology has led to major advances in the pharmacological treatment of heart failure. With the introduction of angiotensin converting enzyme (ACE) inhibitors, β-blockers, angiotensin II receptor blockers (ARBs) and aldosterone antagonists, delaying disease progression and ultimately improving survival have become realistic goals of therapy. An outline of the site of action of the various drugs is schematically presented in Fig. 21.1.

In heart failure patients with co-morbid conditions known to contribute to heart failure, such as hyperthyroidism, anaemia, atrial fibrillation and valvular heart disease, attention must be given to ensuring these underlying contributing factors are well controlled. Patients with atrial fibrillation may be candidates for electrocardioversion. Tachycardia from atrial fibrillation usually requires control of the ventricular rate through suppression of atrioventricular node conduction. In patients with heart failure, the use of digoxin and/or β-blockers is recommended in such circumstances. In these patients, the use of either anticoagulant or antiplatelet agents is necessary and should be based on an assessment of stroke risk.

In patients with heart failure and preserved EF, diuretics are commonly used for symptom control and there is some limited evidence to suggest that ACE inhibitors can reduce hospitalisation. However, the use of all other agents of proven benefit in treating heart failure due to left ventricular systolic dysfunction are currently not supported by an evidence base.

There is consensus that all patients with left ventricular systolic dysfunction should be treated with both an ACE inhibitor and a β-blocker in the absence of intolerance or contraindications. The evidence base for treatment clearly shows that use of an ACE inhibitor (or angiotensin receptor blocker) and β-blocker therapy in patients with heart failure due to left ventricular systolic dysfunction leads to an improvement in symptoms and reduction in mortality. There is some evidence to suggest that either agent can be initiated first, as both appear to be just as effective and well tolerated (CARMEN 2004, CIBIS III, 2005). Beneficial effects on morbidity and mortality have also been shown for the use of ARBs, aldosterone antagonists and hydralazine/nitrate combinations when used in the treatment of chronic heart failure. Digoxin has been shown to improve morbidity and reduce the number of hospital admissions in patients with heart failure, although its effect on mortality has not been demonstrated. Table 21.4 describes the treatment of acute heart failure in the hospital setting, while Fig. 21.2 highlights the possible treatment options for patients with chronic heart failure due to left ventricular systolic dysfunction.

The selection of adjunctive therapy beyond the use of ACE inhibitor and β-blocker therapy is largely dependent on the nature of the patient and the preference of the heart failure specialist involved in the patient's care. It is accepted that there is a limit as to how many agents any one patient can tolerate; therefore, the selection of drug therapy will probably be tailored to each individual patient, meaning that treatment plans will vary.

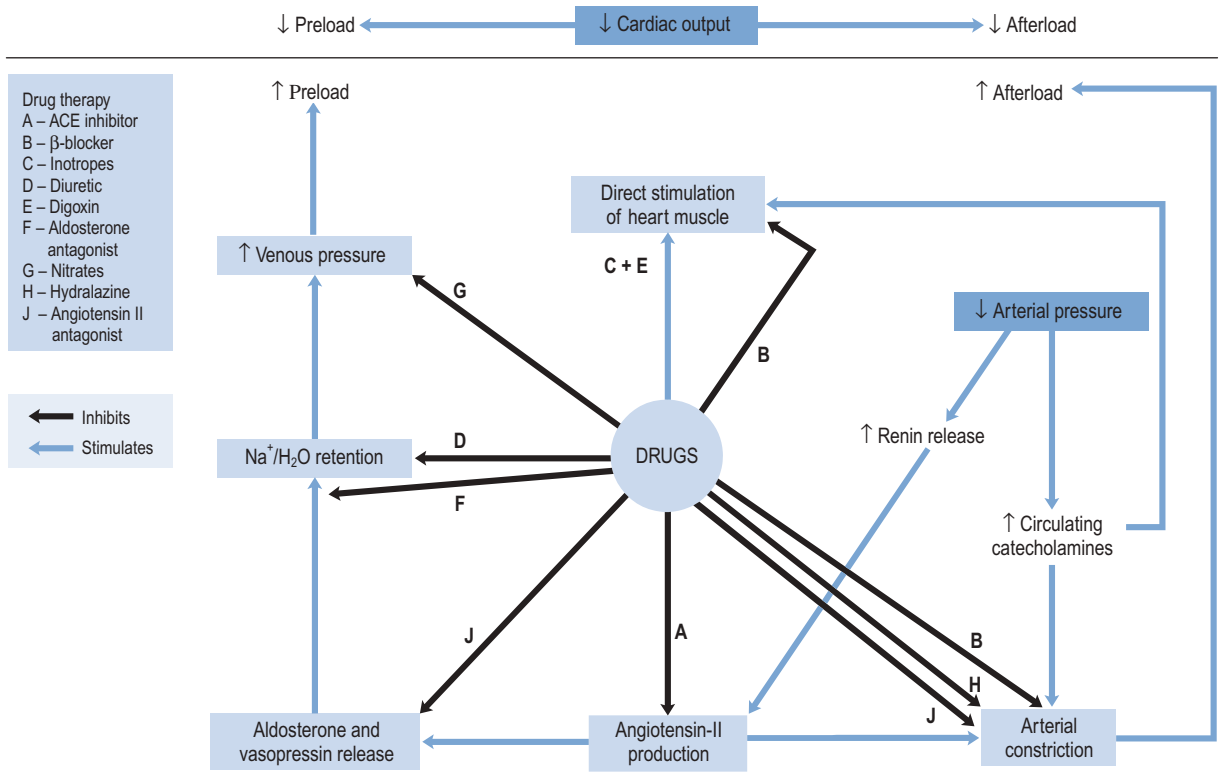


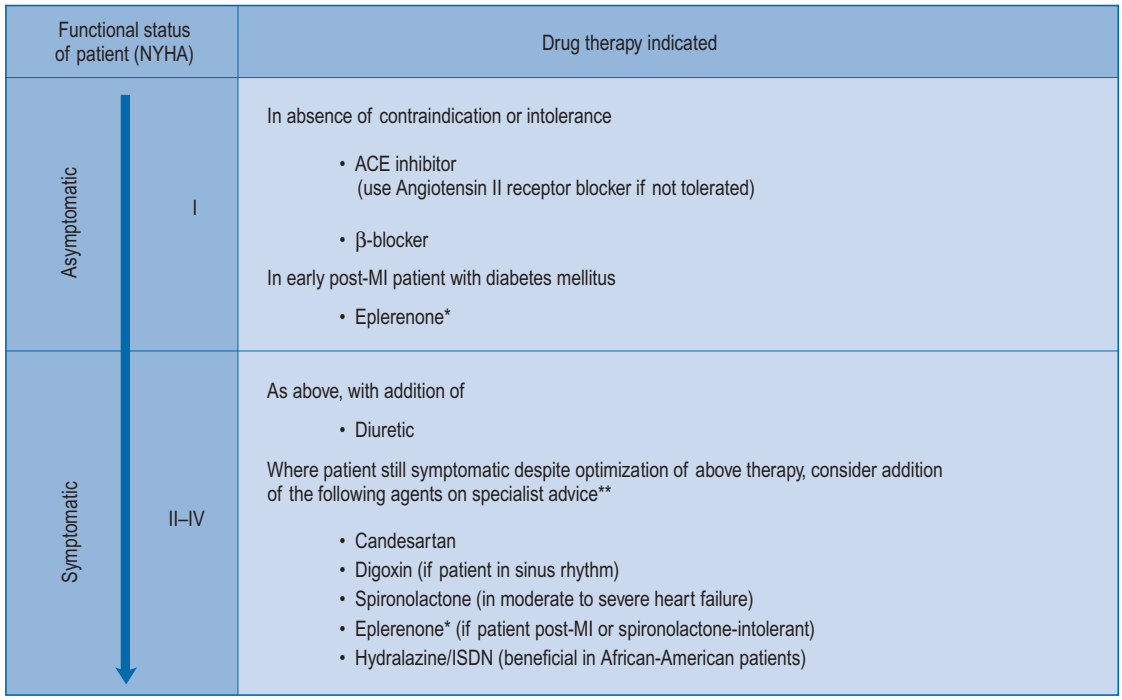
Fig. 21.1 Schematic representation of drug action in heart failure.

Table 21.4 Treatment of acute heart failure due to left ventricular systolic dysfunction in patients requiring hospitalisation

Problem	Drug therapy indicated
Anxiety	Use of intravenous opiates to reduce anxiety and reduce preload through venodilation
Breathlessness	High-flow oxygen (60–100%) may be required in conjunction with i.v. furosemide as either direct injection or 24-h infusion (5–10 mg/h). Venodilation with i.v. GTN is also effective at doses titrated every 10–20 min against systolic BP ≤ 110 mmHg
Arrhythmia	Digoxin useful in control of atrial fibrillation. Amiodarone is the drug of choice in ventricular arrhythmias
Expansion of blood volume following blood transfusion	An elevation in preload, such as can occur acutely by expansion of blood volume after a transfusion, can exacerbate the degree of systolic dysfunction. Therefore, it is necessary to continue or increase diuretic dosage during this time

Diuretics

In chronic heart failure, diuretics are used to relieve pulmonary and peripheral oedema by increasing sodium and chloride excretion through blockade of sodium re-absorption in the renal tubule. Normally, in the proximal tubule, about 70% of sodium is reabsorbed along with water. In mild heart failure, either a thiazide or more often a loop diuretic is chosen depending on the severity of the symptoms experienced by the patient and the degree of diuresis required. Thiazides are described as 'low-ceiling agents' because maximum diuresis occurs at low doses, and they act mainly on the cortical diluting segment (the point of merger of the ascending limb with the distal renal tubule) at which 5–10% of sodium is normally removed. Although thiazides have some action at this site, they fail to produce a marked diuresis since a compensatory increase in sodium re-absorption occurs in the loop of Henle, and consequently thiazides are ineffective in patients with moderate-to-severe renal impairment (eGFR <30 mL/min) or persisting symptoms. Additionally, doses above the equivalent of bendroflumethiazide 5 mg have an increased risk of adverse metabolic effects with no additional symptomatic benefit. Thiazides are, therefore, now rarely used as sole diuretic therapy and are reserved for cases where the degree of fluid retention is very mild, renal function is not compromised or as an adjunct to loop diuretics (see below).



* Therapy should be introduced within a month after acute MI
** Use of adjunctive therapy must be guided by a heart failure specialist/cardiologist, as there are certain combinations that require very close monitoring or complete avoidance according to current clinical evidence.

Fig. 21.2 Outline of treatment options for patients with chronic heart failure due to left ventricular systolic dysfunction.

Loop diuretics are indicated in the majority of symptomatic patients and most patients will be prescribed one of either furosemide, bumetanide or torasemide in preference to a thiazide. These agents are known as 'high-ceiling agents' because their blockade of sodium re-absorption in the loop of Henle continues with increased dose. They have a shorter duration of action (average 4–6 h) compared to thiazides (average 12–24 h), and produce less hypokalaemia. In high doses, however, their intensity of action may produce hypovolaemia with risk of postural hypotension, worsening of symptoms and renal failure. In practice, high doses of furosemide (up to 500 mg/day) may be required to control oedema in patients with poor renal function. In the acute situation, doses of loop diuretics are titrated to produce a weight loss of 0.5–1 kg per day.

In longer term use, patients with heart failure frequently develop some resistance to the effects of loop diuretic due to a compensatory rebound in sodium retention. In this situation, a combination of thiazide and loop diuretics has been shown to have a synergistic effect, even in patients with reduced renal function. In the UK, metolazone is also used as an adjunct to augment the effects of loop diuretics. The potentially profound diuresis produced by such a combination poses serious risks, such as dehydration and hypotension, and patients who are prescribed metolazone in addition to an existing loop diuretic must be carefully monitored. In practice, patients with oedema treated with loop diuretics may best be treated using a degree of self-management. Some patients are instructed to make upward adjustment of loop diuretic dose or to add metolazone therapy on particular days, for example, when they self-record a gain of 2 kg or more in their body weight over a short period of time.

Diuretics also have a mild vasodilator effect that helps improve cardiac function and the intravenous use of loop diuretics reduces preload acutely by locally relieving pulmonary congestion before the onset of the diuretic effect. Effective diuretic therapy is demonstrated by normalisation of filling pressure. Therefore, continued elevation of the JVP suggests a need for more diuretic unless otherwise contraindicated. Intravenous furosemide must be administered at a rate not exceeding 4 mg/min to patients with renal failure, since it can cause ototoxicity when administered more rapidly.

Details of diuretic therapy used in left ventricular systolic dysfunction are summarised in Table 21.5.

ACE inhibitors

ACE inhibitors are indicated as first-line treatment for all grades of heart failure due to left ventricular systolic dysfunction, including those patients who are asymptomatic. These agents exert their effects by reducing both the preload and afterload on the heart, thereby increasing cardiac output.

ACE inhibitors act upon the renin–angiotensin–aldosterone system, and they reduce afterload by reducing the formation of angiotensin II, a potent vasoconstrictor in the arterial system. These drugs also have an indirect effect on sodium and water retention by inhibiting the release of aldosterone and vasopressin, thereby reducing venous congestion and preload. The increase in cardiac output leads to an improvement in renal perfusion, which further helps to alleviate oedema. ACE

Table 21.5 Diuretics and aldosterone antagonists used in the treatment of heart failure

Class and agent	Onset and duration of effect		Comment
Thiazide and related	**Oral**		
Bendroflumethiazide	Onset 1–2 h Duration 12–18 h		Thiazides are effective in the treatment of sodium and water retention, although there is generally a loss of action in renal failure (GFR <25 mL/min). Metolazone has an intense action when added to a loop diuretic and is effective at low GFR
Metolazone	Onset 1–2 h Duration 12–24 h		
Loop	**Oral**	**Parenteral**	
Furosemide	Onset 0.5–1 h Duration 4–6 h	Onset 5 min Duration 2 h	Loop diuretics are preferred in the treatment of sodium and water retention where renal dysfunction is evident or more severe grades of heart failure present. Agents can be given orally or by infusion, and all are effective at low GFR
Bumetanide	As above	As above	
Torasemide	Onset <1 h Duration <8 h	Onset 10 min Duration <8 h	
Aldosterone antagonist	**Oral**		
Spironolactone	Onset 7 h Duration 24 h		Can enhance diuretic effect of loop and/or thiazide. Due to slow onset of action needs 2–3 days before maximum diuretic effect reached. Spironolactone can improve survival when given as an adjunct to ACE inhibitor and diuretic therapy at a recommended dose of 25 mg daily (initial dose of 25 mg daily or on alternate days)
Aldosterone antagonist	**Oral**		
Eplerenone	Half-life 3–5 h		In early post-MI patients with symptomatic heart failure (or asymptomatic patients with diabetes mellitus), eplerenone 50 mg daily improved survival when added to optimal therapy (initial dose of 25 mg daily)

inhibitors also potentiate the vasodilator bradykinin and may intervene locally on ACE in cardiac and renal tissues.

ACE inhibitors are generally well tolerated by most patients and have been shown to improve the quality of life and survival in patients with mild-to-severe systolic dysfunction (CONSENSUS, 1987; CONSENSUS II, 1992; SOLVD-P, 1992; SOLVD-T, 1991; V-HeFT II, 1991), including those patients who have experienced a myocardial infarction (AIRE), 1993; SAVE, 1992; TRACE, 1995). When an ACE inhibitor is prescribed, it is important to ensure that the dose is started low and increased gradually, paying close attention to renal function and electrolyte balance. The dose should be titrated to achieve the target dose that has been associated with long-term benefits shown in clinical trials or (if not possible) the maximum tolerable dose. There is some evidence to suggest that high doses of ACE inhibitor are more effective than low doses in relation to reduction in mortality, although it is uncertain whether this is a general class effect (ATLAS, 1999). In clinical practice, it is possible that some patients may be treated with ACE inhibitors at doses below those used in clinical trials. As a consequence, actual outcomes in heart failure treatment may not be as good as expected from the trial findings.

The introduction of an ACE inhibitor may produce hypotension, which is most pronounced after the first dose and is sometimes severe. Patients at risk include those already on high doses of loop diuretics, where the diuretics cannot be stopped or reduced beforehand, and patients who may have a low-circulating fluid volume (due to dehydration) and an activated renin–angiotensin system. Hypotension can also occur where the ACE inhibitor has been initiated at too high a dose or where the dose has been increased too quickly after initiation. In the primary care setting, treatment must be started with a low dose which is usually administered at bedtime. In patients at particular risk of hypotension, a test dose of the shorter-acting agent captopril can be given to assess suitability for treatment before commencing long-term treatment with a preferred ACE inhibitor. Once it has been established that the ACE inhibitor can be initiated safely, the preferred option would be to switch to a longer acting agent with once- or twice-daily dosing, starting with a low dose which would be gradually titrated upwards to the recommended target (Table 21.6). Monitoring of fluid balance, blood biochemistry and blood pressure are essential safety checks during initiation and titration of ACE inhibitor therapy.

One of the most common adverse effects seen with ACE inhibitors is a dry cough and this is reported in at least 10% of patients. However, since a cough can occur naturally in patients with heart failure it is sometimes difficult to determine the true cause. ACE inhibitor therapy can also compromise renal function, although in patients in whom there is a reduction in renal perfusion due to worsening heart failure or hypovolaemia,

Table 21.6 Vasodilators used in the treatment of heart failure

	Dose	Frequency	Half-life (h)	Comment
ACE inhibitor				
Captopril	Target: 50–100 mg Start: 6.25 mg	Three times daily	8	First-dose hypotension may occur. May worsen renal failure. Adjust dose in renal failure. Hyperkalaemia, cough, taste disturbance and hypersensitivity may occur particularly with captopril
Enalapril	Target: 10–20 mg Start: 2.5 mg	Twice daily	11	
Lisinopril	Target: 20–35 mg Start: 2.5–5 mg	Once daily	12	ACE inhibitors have been shown to improve survival, with starting and target dose for those agents used in clinical trials highlighted
Ramipril	Target: 10 mg Start: 2.5 mg	Once daily (or divided dose)	13–17	
Trandolapril	Target: 4 mg Start: 0.5 mg	Once daily	16–24	
Cilazapril		Once daily	9	
Fosinopril		Once daily	11–14	
Perindopril		Once daily	25	
Quinapril		Once daily	–	
β-Blocker				
Carvedilol	Target: 25–50 mg Start: 3.125 mg	Twice daily	6–10	May initially exacerbate symptoms but if initiated at low dose and slowly titrated can improve long-term survival, even in elderly patients with heart failure
Bisoprolol	Target: 10 mg Start: 1.25 mg	Once daily	10–12	Metoprolol succinate is currently not licensed for use in the UK
Metoprolol (succinate) CR/XL formulation	Target: 200 mg Start: 12.5–25 mg	Once daily	3–7	
Nebivolol	Target: 10 mg Start: 1.25 mg	Once daily	10	Half-life of nebivolol can be 3–5 times longer in slow metabolisers
Nitrates				
Glyceryl trinitrate			1–4 min	Isosorbide dinitrate metabolised to isosorbide mononitrate. High doses needed. Tolerance can be prevented by nitrate-free period of >8 h. Protective effect against cardiac ischaemia. GTN given intravenously for sustained effect in acute/severe heart failure but limited by tolerance
Isosorbide dinitrate			1	
Isosorbide mononitrate			5	
Nitroprusside			2 min	Light sensitive. Acts on veins and arteries. Cyanide accumulation and acidosis limit treatment duration
Angiotensin II receptor blocker				
Losartan			6–9	Comparable effectiveness to ACE inhibitor in patients with ACE inhibitor intolerance, although similar effect on renal function and blood pressure. Recent evidence suggests improved survival when ARB used as adjunctive therapy. However, increased potential for deterioration in renal function and/or hyperkalaemia
Candesartan	Target: 32 mg Start: 4–8 mg	Once daily	9	
Valsartan	Target: 160 mg Start: 40 mg	Twice daily	9	
Hydralazine			2–3	Hydralazine has a direct action on arteries. Tolerance occurs. May cause drug-induced lupus and sodium retention

renal dysfunction can also occur. Therefore, there are a number of instances where ACE inhibitor intolerance can be misdiagnosed in practice. Where ACE inhibitor intolerance is suspected, patients can usually be successfully rechallenged with an ACE inhibitor once their heart failure is more stable, although careful monitoring of the patient should be undertaken during initiation and subsequent dose titration. If the increase in the patient's serum creatinine is >100% from baseline, the ACE inhibitor should be stopped, intolerance confirmed and specialist advice sought. Where the increase from baseline is 50–100%, the ACE inhibitor dose should be halved and serum creatinine concentration rechecked after 1–2 weeks. If renal function is stable and no cough or other adverse effects are reported, therapy should be continued. Where the problem persists, an alternative treatment option might be required, for example, ARB (similar benefits on morbidity and mortality, but there is a possibility of similar adverse effects on blood pressure and renal function) or hydralazine–nitrate combination.

ACE inhibitors are potentially hazardous in patients with pre-existing renal disease, as blockade of the renin-angiotensin system may lead to reversible deterioration of renal function. In particular, ACE inhibitors are contraindicated in patients with bilateral renal artery stenosis, in whom the renin-angiotensin system is highly activated to maintain renal perfusion. Since most ACE inhibitors or their active metabolites rely on elimination via the kidney, the risk of other forms of dose-related toxicity is also increased in the presence of renal failure. Fosinopril, which is partially excreted by metabolism, may be the preferred agent in patients with renal failure. ACE inhibitors are also contraindicated in patients with severe aortic stenosis because their use can result in a markedly reduced cardiac output due to decreased filling pressure within the left ventricle. Table 21.6 summarises the activity and use of ACE inhibitors.

Angiotensin II receptor blockers

Although comparisons of ACE inhibitors and ARBs have shown similar benefits on morbidity and heart failure mortality, only ACE inhibitors have been shown to have positive effects on all cause mortality. ARBs should, therefore, not be used instead of ACE inhibitors, unless the patient experiences intolerable side effects.

The use of ARBs as an adjunct to ACE inhibitor and β-blocker therapy has been associated with significant reductions in cardiovascular events and hospitalisation rate (CHARM Added, 2003). Although this finding is encouraging, the impact on mortality alone remains inconsistent and there is no clear consensus on when to use an ARB as adjunctive therapy. In studies involving patients unable to tolerate an ACE inhibitor, ARBs have been shown to be comparable to ACE inhibitors in reducing the risk of cardiovascular death and rate of hospitalisation, and in the control of symptoms in heart failure patients (CHARM Alternative, 2003; Val-HeFT, 2002). Therefore, ARBs are recommended for use as an alternative to ACE inhibitor therapy where intolerance has been confirmed. It is important to note that in patients who have renal failure secondary to ACE inhibitors, switching to an ARB is of no theoretical or practical benefit, as similar adverse effects are likely.

A recent meta-analysis has raised concerns about a possible increase of cancer in people taking ARBs (Sipahi et al., 2010). Although the implications of this are unclear it adds weight to the recommendation that ACE inhibitors, not ARBs, should be the first-line agent when selecting a drug to act on the renin-angiotensin system.

β-Blockers

Formerly, β-blockers have been contraindicated in patients with heart failure. However, the sympathetic neurohormonal overactivity that occurs in response to the failing heart has been identified as a decisive factor in the progression of ventricular dysfunction. Consequently, β-blockers have been tested in a number of clinical trials. There is now substantial evidence that β-blockers reduce mortality among patients with mild-to-moderate symptomatic heart failure (ANZ Carvedilol, 1997; CAPRICORN, 2001; CIBIS II, 1999; MERIT-HF, 1999; US Carvedilol, 1996) and those with severe heart failure (COPERNICUS, 2001). This beneficial effect also extends to the elderly heart failure population (SENIORS, 2005).

The use of β-blockers is, therefore, recommended for all patients with heart failure due to left ventricular systolic dysfunction, irrespective of age and the degree of dysfunction. However, due to their negative inotropic effects, β-blockers should only be initiated when the patient's condition is stable. There is insufficient evidence for a class effect to be assumed illustrated by the fact that in one trial, metoprolol tartrate was found to be inferior to carvedilol (COMET, 2003). Currently, nebivolol, bisoprolol and carvedilol are the only licensed β-blockers for the treatment of heart failure in the UK.

It is likely that patients will experience a worsening of symptoms during initiation of therapy and, therefore, patients are started on very low doses of β-blocker (e.g. carvedilol 3.125 mg daily) with careful titration occurring over a number of weeks or months with careful monitoring. The goal is to titrate the dose towards those used in clinical trials that have been associated with morbidity and mortality benefits (carvedilol 25–50 mg daily). Table 21.6 summarises the activity and use of β-blockers in heart failure.

Despite the demonstrated benefits, there is ongoing concern that certain subgroups of patients with heart failure continue to be undertreated with β-blockers. These groups include patients with chronic obstructive pulmonary disease (COPD), peripheral vascular disease, diabetes mellitus, erectile dysfunction and older adults. With the exception of patients with reversible pulmonary disease, who have typically been excluded from β-blocker trials (CIBIS II, 1999; MERIT-HF, 1999), there is now sufficient evidence to justify the use of β-blockers licensed for heart failure in these patients. In addition, a systematic review of trials on cardio-selective β-blockers found no clinically significant adverse respiratory effects in patients with reversible COPD, although it would be prudent to use these agents in such patients with caution and with appropriate monitoring in place (Salpeter S. et al., 2005).

Aldosterone antagonists

The use of aldosterone antagonists as an adjunct to standard treatment has been shown to have an effect on morbidity and mortality in patients with heart failure. Spironolactone has been shown to reduce mortality and hospitalisation rates in patients with moderate-to-severe heart failure (RALES, 1999). The use of eplerenone has also been shown to be associated with similar benefits in early post-MI patients with symptomatic heart failure or early post-MI diabetic patients with asymptomatic heart failure (EPHESUS, 2003, EMPHASIS-HF, 2010).

Aldosterone can cause sodium and water retention, sympathetic activation and parasympathetic inhibition, all of which are associated with harmful effects in the patient with heart failure. Aldosterone antagonists counteract these effects by directly antagonising the activity of aldosterone, providing a more complete blockade of the renin–angiotensin–aldosterone system when used in conjunction with an ACE inhibitor. Although the combination of spironolactone (at a dose of 50 mg daily or more) and an ACE inhibitor is associated with an increased risk of developing hyperkalaemia, the use of a 25-mg daily dose has been shown to have little effect

on serum potassium and provides a significant reduction in mortality. The use of spironolactone is, however, contraindicated in those patients with a serum potassium >5.5 mmol/L or serum creatinine >200 μmol/L. With eplerenone, similar contraindications exist and, therefore, close monitoring of blood biochemistry and renal function must be undertaken for use of either agent. The activity and use of spironolactone and eplerenone are summarised in Table 21.5.

Currently, there is no evidence available regarding the effectiveness and safety of combining an ACE inhibitor, ARB and an aldosterone antagonist, and therefore it is recommended that this combination is avoided until more information about this particular combination becomes available.

Digoxin

Although digoxin has an established role in the control of atrial fibrillation, its place in the treatment of heart failure is still the subject of debate. There is evidence to show that when digoxin has been used to treat heart failure in patients in sinus rhythm, as an adjunct to ACE inhibitor and diuretic therapy, then worsening of symptoms occurs on withdrawal of digoxin (PROVED, 1993; RADIANCE, 1993). While the use of digoxin in heart failure in patients in sinus rhythm has no measurable impact on mortality, it reduces the number of hospital admissions (DIG, 1997). Consequently, digoxin is currently recommended for use as add-on therapy at low doses in patients with moderate-to-severe heart failure who remain symptomatic despite adequate doses of ACE inhibitor, β-blocker and diuretic treatment. Due to the lack of effect on mortality, it is unlikely that digoxin would be considered before the other adjunctive therapies available.

Digoxin is a positive inotropic agent and acts by increasing the availability of calcium within the myocardial cell through an inhibition of sodium extrusion, thereby increasing sodium–calcium exchange and leading to enhanced contractility of cardiac muscle. Digoxin increases cardiac output in patients with co-existing atrial fibrillation by suppressing atrioventricular conduction and controlling the ventricular rate. In patients with atrial fibrillation, the serum digoxin concentration usually needs to be at the higher end of the reference range (0.8–2 μcg/L) or beyond to control the arrhythmia. However, a high serum digoxin concentration is not necessarily required to achieve an inotropic effect in patients in sinus rhythm. Digoxin is also associated with both vagal stimulation and a reduction in sympathetic nerve activity, and these may play important roles in the symptomatic benefits experienced by those patients in sinus rhythm receiving lower doses. In practice, the dose prescribed will be judged appropriate by the clinical response expressed as relief of symptoms and control of ventricular rate. Routine monitoring of serum digoxin concentrations in the pharmaceutical care of the patient is not recommended, other than to confirm or exclude digoxin toxicity or investigate issues around patient compliance.

Digoxin treatment is potentially hazardous due to its low therapeutic index and so all patients receiving this drug should be regularly reviewed to exclude clinical signs or symptoms of adverse effects. Digoxin may cause bradycardia and lead to potentially fatal cardiac arrhythmias. Other symptoms associated with digoxin toxicity include nausea, vomiting, confusion and visual disturbances. Digoxin toxicity is more pronounced in the presence of metabolic or electrolyte disturbances and in patients with cardiac ischaemia. Those patients who develop hypokalaemia, hypomagnesaemia, hypercalcaemia, alkalosis, hypothyroidism or hypoxia are at particular risk of toxicity. Treatment may be required to restore serum potassium, and in emergency situations intravenous digoxin-specific antibody fragments can be used to treat life-threatening digoxin toxicity. Table 21.7 summarises the activity and use of digoxin.

Table 21.7 Inotropic agents used in the treatment of heart failure

Class and agent	Pharmacological half-life	Comment
Cardiac glycosides		
Digoxin	39 h	In renal failure, half-life of digoxin is prolonged. Dosage individualisation required. Serum drug concentration monitoring used to confirm or exclude toxicity or effectiveness. Dose of digitoxin unaffected by renal failure. CNS, visual and GI symptoms linked to digoxin toxicity. No benefit in terms of mortality, but use associated with improved symptoms and reduced hospitalisation for heart failure. Beneficial in AF, although risk of arrhythmias with high doses. If given i.v. must be administered slowly (20 min) to avoid cardiac ischaemia
Digitoxin	5–8 days	
Phosphodiesterase inhibitors		
Enoximone	4.2 h	Used only in severe heart failure as adjunctive therapy. Associated with arrhythmias and increased mortality with chronic use
Milrinone	2.4 h	
Sympathomimetics		
Dobutamine	2 min	Continuous intravenous use only. Require close monitoring in critical care setting
Dopamine	2 min	
Dopexamine	6–7 min	
Isoprenaline	>1 min	

Nitrates/hydralazine

Nitrates exert their effects in heart failure predominantly on the venous system where they cause venodilation, thereby reducing the symptoms of pulmonary congestion. The preferred use of nitrates is in combination with an arterial vasodilator such as hydralazine, which reduces the afterload, to achieve a balanced effect on the venous and arterial circulation. The combined effects of these two drugs lead to an increase in cardiac output, and there is evidence to show the combination is effective and associated with a reduction in mortality in patients with heart failure (V-HeFT I, 1986). Although the combination can improve survival, the reduction in mortality is much smaller than that seen with ACE inhibitors (V-HeFT II, 1991), especially in the white population. The combination has been shown to reduce mortality, heart failure hospitalisation rates and quality of life in patients of African descent, when added as an adjunct to optimum medical therapy (A-HeFT, 2004) and this benefit is sustained (A-HeFT, 2007).

The evidence supports the use of hydralazine 300 mg daily with isosorbide dinitrate (ISDN) 160 mg daily (although in practice an equivalent dose of isosorbide mononitrate, ISMN, is often used). Since the emergence of ACE inhibitors, with their superior effects on morbidity and mortality, the combination has mainly been reserved for patients unable to tolerate, or with a contraindication to, ACE inhibitor therapy.

Organic nitrate vasodilators work by interacting with sulphydryl groups found in the vascular tissue. Nitric oxide is released from the nitrate compound and this in turn activates soluble guanylate cyclase in vascular smooth muscle, leading to the vasodilatory effect. Plasma nitric oxide concentrations are not clearly related to pharmacological effects because of their indirect action on the vasculature. Depletion of tissue sulphydryl groupings can occur during continued treatment with nitrates, and is partly responsible for the development of tolerance in patients with sustained exposure to high nitrate doses. Restoration of sulphydryl groupings occurs within hours of treatment being interrupted; therefore, nitrate tolerance can be prevented by the use of an asymmetrical dosing regimen to ensure that the patient experiences a daily nitrate-free period of more than 8 h.

In the acute setting, glyceryl trinitrate (GTN) is frequently administered intravenously, along with a loop diuretic, to patients with heart failure to relieve pulmonary congestion. When using this route of administration, it is important that a Teflon-coated catheter is used to avoid adsorption of the GTN onto the intravenous line.

ISDN can be given orally and is completely absorbed; however, only 25% of a given dose appears as ISDN in serum with 60% of an oral dose being rapidly converted to ISMN. ISMN is longer acting and, therefore, most of the accumulated effects of a dose of ISDN are attributable to the 5-isosorbide mononitrate metabolite. Consequently, a 20-mg dose of ISDN is approximately equivalent to a 10-mg dose of ISMN. In practice, nitrate preparations are usually given orally in the form of ISMN, and intravenously in the form of GTN (see Table 21.6).

Hydralazine has a direct action on arteriolar smooth muscle to produce arterial vasodilation. Its use is associated with the risk of causing drug-induced systemic lupus erythematosus (SLE). SLE is an uncommon multisystem connective tissue disorder that is more likely to occur in patients classified as slow acetylators of hydralazine, which accounts for almost half the UK population.

Inotropic agents

The use of inotropic agents (except digoxin) is almost exclusively limited to hospital practice, where acute heart failure may require the use of one or more inotropic agents, particularly the sympathomimetic agents dobutamine and dopamine, in an intravenous continuous infusion. These agents have inotrope-vasodilator effects which differ according to their action on α, β_1, β_2 and dopamine receptors (β_1-agonists increase cardiac contractility, β_2-agonists produce arterial vasodilation, dopamine agonists enhance renal perfusion). With dopamine, low doses (0–2 µcg/kg/min) have a predominant effect on dopamine receptors within the kidneys to improve urine output, intermediate doses (2–5 µcg/kg/min) affect β_1-receptors, producing an inotropic effect, and high doses (10 µcg/kg/min) have a predominant action on α-adrenoreceptors. Dobutamine has a predominantly inotropic and vasodilator action due to the action of the (+) isomer selectively on β-adrenoreceptors (see Table 21.7). Tolerance to sympathomimetic inotropic agents may develop on prolonged administration, particularly in patients with underlying ischaemia, and is also associated with a risk of precipitating arrhythmias.

Noradrenaline (norepinephrine) is an α-adrenoreceptor agonist where its vasoconstrictor action limits its usefulness in severely hypotensive patients such as those in septic shock. Adrenaline (epinephrine) has β_1, β_2 and α-adrenoreceptor agonist effects and is used in patients with low vascular resistance. However, it is more arrhythmogenic than dobutamine and should be used with caution.

Phosphodiesterase inhibitors are rarely used in clinical practice as a consequence of trials showing an increased risk of mortality (PROMISE, 1991).

Other agents

Direct-acting vasodilators such as sodium nitroprusside are rarely used except in the acute setting when they are given by continuous infusion. Vasodilation occurs as a result of the catalysis of nitroprusside in vascular smooth muscle cells to produce nitric oxide. The fact that nitric oxide production in this instance is via a different route when compared to the catalysis of GTN (where there is a need for sulphydryl groups) may explain why there is little tolerance seen with nitroprusside. In patients with impaired renal function thiocyanate, a metabolic product of nitroprusside can accumulate over several days, causing nausea, anorexia, fatigue and psychosis.

Patients with coronary heart disease may be candidates for calcium-blocking antianginal vasodilators. However, some of these agents can exacerbate co-existing heart failure, since their negative inotropic effects offset the potentially beneficial arterial vasodilation. Amlodipine and felodipine have a more selective action on vascular tissue and, therefore, a less pronounced

effect on cardiac contractility than other calcium antagonists and should be the agents of choice where appropriate.

In hospitalised patients in whom compromised respiratory function remains despite medical management of heart failure, the treatment options include mechanical ventilation, continuous positive airway pressure ventilation and the use of intra-aortic balloon pumping.

Guidelines

Several groups have produced evidence-based consensus clinical guidelines for the management of chronic heart failure. The focus of the various guidelines tends to be on chronic medication use (National Institute for Health and Clinical Excellence, 2010; American College of Cardiology/American Heart Association Task Force on Practice Guidelines, 2009; European Society of Cardiology, 2008; Scottish Intercollegiate Guidelines Network, 2007). All guidelines confirm that ACE inhibitors and β-blockers should be given to all patients with all grades of heart failure, whether symptomatic or asymptomatic, in the absence of contraindication or intolerance.

In ACE inhibitor-intolerant patients, the preferred alternative is an ARB. However, it should be remembered that where ACE inhibitor intolerance is due to renal dysfunction, hypotension or hyperkalaemia, similar effects could be expected with an ARB. If an ARB is an unsuitable alternative, the use of hydralazine/nitrate combination or digoxin could be considered, although the latter combination of agents has no effect on mortality. For patients with symptomatic heart failure, a loop diuretic is usually recommended to treat oedema and control symptoms. In heart failure patients who are still symptomatic despite being on optimum therapy (ACE inhibitor, β-blocker with/without a diuretic), the use of adjunctive therapies is recommended which can include ARB, aldosterone antagonists, hydralazine/nitrate combination and digoxin where the patient is still in sinus rhythm.

There is also debate as to whether diastolic dysfunction is a true diagnosis. The cause of 'apparent' heart failure symptoms can in many cases be attributed to another disease/condition such as respiratory disease, obesity or ischaemic heart disease. However, there may also be some patients in whom the cause of heart failure symptoms remains uncertain. Therefore, specific recommendations for the drug treatment of diastolic heart failure are still lacking.

Patient care

Heart failure remains poorly understood by the general public, amongst whom only 3% were able to identify the condition when presented with a list of typical symptoms. Patients with heart failure are often elderly and often include patients with co-morbidity such as coronary heart disease and hypertension. Other complications include renal impairment, polypharmacy and variable adherence to prescribed medication regimens. Where renal function is compromised, careful attention to dosage selection is required for drugs excreted largely unchanged in the urine. Patients with heart failure are at particular risk of fluid or electrolyte imbalance, adverse effects and drug interactions. Consequently, careful monitoring is indicated to help detect problems associated with suboptimal drug therapy, unwanted drug effects and poor patient adherence.

A number of therapeutic problems may be encountered by the patient with heart failure. Notably, heart failure often complicates other serious illness, and is a common cause of hospital admission. In addition to monitoring clinical signs and symptoms in the acute setting, there should be monitoring of fluid and electrolyte balance, assessment of renal and hepatic function, and performance of chest radiograph, electrocardiograph and haemodynamic measurements where appropriate.

Patient education and self-monitoring

The patient must be in a position to understand the need for treatment and the benefits and risks offered by prescribed medication before concordance with a treatment plan can be reached. Appropriate patient education is necessary to encourage an understanding of their condition, inform patients of the extent of their condition and how prescribed drug treatment will work and affect their daily lives. It is also important to encourage them to be an active participant in their care where appropriate. Specific advice should be given to reinforce the timing of doses and how each medication should be taken. Patients also need to be advised of potentially troublesome symptoms that may occur with the medication, and whether such effects are avoidable, self-limiting or a cause for concern.

Patients should be made aware that diuretics will increase urine production, and that doses are usually timed for the morning to avoid inconvenience during the rest of the day or overnight. However, there are cases where patients are advised that they can alter the timing of the dose(s) if required to suit their lifestyle or social commitments, with the agreement of their doctor. There are also some patients who use a flexible diuretic dosing regimen, where they can take an extra dose of diuretic in response to worsening signs or symptoms as part of an agreed self-management protocol. To use such a regimen, the patient has to monitor and record their weight on a daily basis, and have clear instructions to take an extra dose of diuretic when a notable increase in weight is detected as a result of fluid retention, and when to seek medical attention. It is also important for patients to be aware of signs and symptoms of drug toxicity with medicines such as digoxin, for example anorexia, diarrhoea, nausea and vomiting, and be aware of the action to be taken should these symptoms occur.

Timing of doses is also important. If a nitrate regimen is being used, then patients must be made aware that the last dose of the nitrate should be taken mid to late afternoon to ensure that a nitrate-free period occurs overnight, thus, reducing the risk of nitrate tolerance. However, patients with prominent nocturnal symptoms require separate consideration. Where β-blockers are introduced, it is important that the patient is aware of the need for gradual dose titration due to the risk of the medication aggravating heart failure symptoms. Certain medicines for

the treatment of minor ailments that are available for purchase over the counter without a prescription can aggravate heart failure, such as ibuprofen, antihistamines and effervescent formulations. It is important that patients know what action to take if their symptoms become progressively worse, and whom to contact when necessary for advice. Table 21.8 provides a general patient education and self-monitoring checklist, highlighting the typical areas where advice should be given.

Monitoring effectiveness of drug treatment

Therapeutic effectiveness is confirmed by assessing the patient for improvements in reported symptoms such as shortness of breath and oedema, and for noticeable changes in exercise tolerance. Oedema is often visible and remarked upon by patients, especially in the feet (ankles) and hands (wrists and fingers). Increased oedema may be reflected by an increase in the patient's body weight, and can be more easily assessed if the patient routinely records their weight and reviews this on a daily basis. Questions about tolerance to exercise are also useful in identifying patients who may be experiencing difficulties with their condition or where the treatment plan is suboptimal. Onset or deterioration of symptoms is often slow and patients are more inclined to adapt their lifestyle gradually by moderating daily activities to compensate. This should be borne in mind whenever a patient assessment is undertaken.

Identifying the symptoms of poor heart failure control can be complicated by many factors, such as the presence of conditions like arthritis and parkinsonism which can also affect a patient's mobility. Poor control of respiratory disease, presenting as an increased shortness of breath or exacerbation of other respiratory symptoms, can also be mistaken for loss of control of heart failure. Therefore, consideration of these and other factors is necessary in the interpretation of presenting symptoms, as a deterioration in symptoms may not be solely due to worsening heart failure or ineffective heart failure medication.

Dietary factors can lead to loss of symptom control, where failure to restrict sodium intake may contribute to an ongoing problem of fluid retention. Simple dietary advice to avoid processed foods and not to add salt to food should be reinforced.

Table 21.8 Patient education and self-monitoring in the treatment of heart failure

Topic	Advice	Comment
Diuretics	• Will cause diuresis • Timing of dose • Flexible dosing (where indicated)	Monitor for incontinence, muscle weakness, confusion, dizziness, gout, unusual gain in weight within very short time-period (few days). Use of diary to record and monitor daily weight can help identify when to take an agreed extra dose of diuretic. Patient also able to adjust time of dose to suit lifestyle where necessary
ACE inhibitors	• Improve symptoms • Avoid standing rapidly	Monitor for hypotension, dizziness, cough, taste disturbance, sore throat, rashes, tingling in hands, joint pain
β-Blockers	• Symptoms worsen initially • Gradual increase in dose	Monitor for hypotension, dizziness, headache, fatigue, gastro-intestinal disturbances, bradycardia
Cardiac glycosides	• Report toxic symptoms	Monitor for signs or symptoms of toxicity, such as anorexia, nausea, visual disturbances, diarrhoea, confusion, social withdrawal
Nitrates	• Timing of dose • Postural hypotension • Avoid standing rapidly	Monitor for headache, hypotension, dizziness, flushing (face or neck), gastro-intestinal upset. Ensure asymmetrical dosing pattern for nitrates to provide nitrate-free period and reduce risk of tolerance developing
Potassium salts	• Administration of dose (soluble + non-soluble)	Monitor for gastro-intestinal disturbances, swallowing difficulty, diarrhoea, tiredness, limb weakness. Ensure patient knows how to take their medication safely, for example, swallow whole immediately after food, or soluble forms to be taken with appropriate amount of water/fruit juice and allow fizzing to stop
Purchased medicines	• Choice of medicines	Ensure patient is aware of need to seek advice when purchasing medicines for minor ailments. Ask pharmacist to confirm suitability when selecting
Understanding the condition	• What heart failure is • Impact on lifestyle • Treatment goals	Ensure patient understands their condition, treatment goals and complications that may impact on their quality of life. Important to motivate the patient with respect to lifestyle modification and achievement of agreed treatment goals relative to the degree of heart failure present (asymptomatic, mild, moderate or severe symptoms)
Health issues	• Diet; sodium intake • Alcohol intake • Smoking • Exercise • Other risk factors	Issues related to diet, alcohol consumption, smoking habit, regular gentle exercise (walking). Other associated risk factors, for example, hypertension, ischaemic heart disease, need to be addressed where appropriate

According to some manufacturers, the absorption of ACE inhibitors, for example, captopril, perindopril, may be slowed by food or antacids and, therefore, patients should be advised to take the dose before food in the morning to ensure maximum effect.

Patients with heart failure may often receive suboptimal drug treatment, due to the fact that they are not prescribed first-line therapy, such as ACE inhibitors and β-blockers, and the dosage is below the recommended target dose. All patients at risk of suboptimal treatment need to be routinely identified, and this will require the involvement of health care professionals in the monitoring of symptoms and the individualisation of each patient's therapeutic plan.

In an effort to systematically identify whether a patient's therapeutic plan adheres to the current evidence base for treatment, and whether any changes might be required to optimise therapy, the audit tool shown in Box 21.1 could be used in routine practice. The tool has been derived from published consensus-based clinical guidelines, and could underpin a more comprehensive medication review.

Monitoring safety of drug treatment

A number of issues around the safe use of medication must be considered, especially in those patients with co-morbidity and/or a high number of prescribed medicines. In these patients there is an increased risk of drug–drug and drug–disease interactions (Tables 21.9-21.11). It is important to be aware of clinically important interactions and to investigate potentially problematic combinations, as well as to regularly assess the patient for any signs or symptoms of drug therapy problems. Monitoring for problems such as negative inotropic effects, excessive blood pressure reduction, and salt and fluid retention should be undertaken and, where appropriate, laboratory measurement of serum drug concentration (digoxin) or physiological markers (potassium, creatinine) should be performed to confirm or exclude adverse effects. Patients started on an ACE inhibitor should have renal function and serum electrolytes checked at 1 and 3 months after starting therapy, and 6 monthly once a maintenance dose is reached.

Potential problems with diuretic therapy

The use of diuretic therapy for sodium and water retention is common in the treatment of heart failure, although there can be a number of problems for the patient to contend with. Elderly patients in particular are at risk from the unwanted effects of diuretics. The increase in urine volume can worsen incontinence or precipitate urinary retention in the presence of an enlarged prostate, while overuse can lead to a loss of

Table 21.9 Monitoring the effectiveness of drug treatment in patients with heart failure

Consider	Monitor for	Comment
Clinical markers	• Poor symptom control • Achievement of agreed treatment goals	Signs or symptoms of undertreatment or advancing disease need to be addressed (dyspnoea, breathlessness and/or fatigue). The aim is for good symptom control and either maintenance or improvement in quality of life. Persisting symptoms or hospitalisation may indicate a revision of drug therapy or the addition of other agents where appropriate
Interactions	• Drug–drug interactions	Some interactions may result in reduced effectiveness and require dosage adjustment or change in choice of drug
Compliance	• Formulation acceptability • Dose timing and interval • Unusual time interval between requests for prescription medication	Poor adherence can result from drug being ineffective (over- or under-use), experience of side effects, a complicated drug regimen or patient behaviour (intentional non-adherence or forgetfulness). Reasons need to be identified and addressed where possible, for example, adjusting frequency and timing of doses, review choice of formulation, education. Initiation of devices to improve compliance should be considered where appropriate
Evidence-based prescribing	• Implementation of evidence-based guidelines • Audit of prescribed treatment for heart failure	The drug of choice for a particular patient may not reflect the evidence base for treatment for patients with heart failure. It is important to ensure evidence-based treatments are considered for every patient, and choices of medication confirmed or changed where appropriate. Audit of guideline recommendations to help confirm that treatment plans are optimal can be systematically applied to help assess appropriateness of treatment (see Box 21.1)
Multidisciplinary working	• Input from other health care professionals	It is important to be aware of what care has already been provided to minimise the risk of giving conflicting advice to the patient or duplicating work already done. It may also allow reinforcement of key information. There is an increasing evidence base for the benefits of multidisciplinary models of care for chronic heart failure patients

Box 21.1 Criteria for the assessment of drug treatment in a patient with chronic heart failure (Scottish Intercollegiate Guidelines Network, 2007)

Need for drug therapy (all patients)

1. Is an ACE inhibitor prescribed?
2. If intolerant to ACE inhibitor, is an ARB prescribed?
3. If intolerant to an ACE inhibitor and ARB, is H/ISDN prescribed?
4. Is a β-blocker prescribed?
5. Has patient received pneumococcal vaccination?
6. Has patient received influenza vaccination?

Need for drug therapy (as appropriate)

7. If symptomatic on optimised doses of ACE inhibitor and BB, is an aldosterone antagonist or candesartan prescribed?
8. If symptomatic on optimised therapy with ACE inhibitor I, BB and ARB/aldosterone antagonist, is digoxin prescribed?
9. If post-MI, is an antiplatelet and statin prescribed?
10. In AF, is thrombo-embolic prophylaxis prescribed?

Need for dose titration

11. If an ACE inhibitor I is prescribed, target dose achieved?
12. If an ARB is prescribed, target dose achieved?
13. If a BB is prescribed, target dose achieved?
14. If warfarin prescribed, is dose titrated to INR?

Medication safety

15. Aggravating drugs avoided (if possible):
    - (a) NSAIDs
    - (b) Tricyclic antidepressants
    - (c) Some antihistamines (e.g. diphenhydramine)
    - (d) Dihydropyridine calcium channel blockers (except amlodipine or felodipine)
    - (e) Diltiazem, verapamil
    - (f) Glitazone anti-diabetics
    - (g) Minoxidil
    - (h) Itraconazole and other azole antifungals
    - (i) Macrolide antibiotics
    - (j) Corticosteroids
    - (k) Tadalafil
    - (l) Lithium

ACE inhibitor, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BB, β-blocker; H, hydralazine; INR, international normalised ratio; MI, myocardial Infarction.

control of heart failure and worsening of symptoms. Rapid diuresis with a loop diuretic leading to more than a 1-kg loss in body weight per day may exacerbate heart failure due to an acute reduction in blood volume, hypotension and diminished renal perfusion, with a consequent increase in renin release. Prolonged and excessive doses of diuretics can also contribute to symptoms of fatigue as a consequence of electrolyte disturbance and dehydration. The adverse biochemical effects of excessive diuresis include uraemia, hypokalaemia and alkalosis. Diuretic-induced glucose intolerance may affect diabetic control in type 2 diabetes, but more commonly diuretics reveal glucose intolerance in patients who are not diagnosed as being diabetic. Diuretics also increase serum urate leading to hyperuricaemia, although this may not require a change in drug therapy if symptoms of gout are absent (estimated incidence of 2%).

Hyponatraemia may occur with diuretics, and is usually due to water retention rather than sodium loss. Severe hyponatraemia (serum sodium concentration of less than 115 mmol/L) causes confusion and drowsiness. It commonly arises when potassium-sparing agents are used in diuretic combinations.

Diuretics may also lead to hypokalaemia as a result of urinary sodium increasing the rate of K^+/Na^+ exchange in the distal tubule. Serum potassium concentrations below 3.0 mmol/L occur in less than 5% of patients receiving diuretics. The occurrence of hypokalaemia is hazardous for patients receiving digoxin and also for those with ischaemic heart disease or conduction disorders. It is more commonly found with thiazide diuretics than loop agents, and is more likely to occur when diuretics are used for heart failure than for hypertension. This is probably due to the fact that higher doses are used and there is an associated activation of the renin–angiotensin system. Patients with a serum potassium level of less than 3.5 mmol/L require treatment with potassium supplements or the addition of a potassium-sparing diuretic. The use of a potassium-sparing diuretic is considered to be more effective at preventing hypokalaemia than using potassium supplements. Prevention of hypokalaemia requires at least 25 mmol of potassium, while treatment requires 60–120 mmol of potassium daily. Since proprietary diuretic-potassium combination products usually contain less than 12 mmol in each dose, their use is often inappropriate.

Potassium supplements are poorly tolerated at the high doses often needed to treat hypokalaemia, and a liquid formulation is more preferable to a solid form. This is mainly due to the fact that solid forms can produce local high concentrations of potassium salts in the gastro-intestinal tract, with the risk of damage to the tract in patients with swallowing difficulties or delayed gastro-intestinal transit. In patients with deteriorating renal function or renal failure, the use of potassium supplements or potassium-sparing diuretics might cause hyperkalaemia, and therefore careful monitoring of these agents is essential.

Potential problems with ACE inhibitor and ARB therapy

ACE inhibitors are the cornerstone of the treatment of heart failure, but there are also risks associated with their use. ARBs, which also act on the renin–angiotensin–aldosterone system, pose similar risks to those recognised for ACE inhibitors. Both agents can predispose patients to hyperkalaemia through a reduction in circulating aldosterone; therefore, potassium supplements or potassium-retaining agents should be used with care when co-prescribed, and careful monitoring of serum potassium should be mandatory. Although potassium retention can be a problem with ACE inhibitors and ARBs, it can also be an advantage by helping to counteract the potassium loss that can result from the use of diuretic therapy. However, since this effect on potassium cannot be predicted, laboratory monitoring is still necessary to confirm that serum potassium concentration remains within safe limits.

The use of an aldosterone antagonist as adjunctive therapy with an ACE inhibitor (or ARB if the patient is ACE inhibitor intolerant) can be safely undertaken with minimal effects on the serum potassium concentration, provided that recommended target doses for the aldosterone antagonist are not

Table 21.10 Common drug–drug interactions with prescribed heart failure medication

Drug	Interacts with	Result of interaction
Diuretic	NSAIDs	Decreased effect of diuretic and increased risk of renal impairment
	Carbamazepine	Increased risk of hyponatraemia
	Lithium	Excretion of lithium impaired (thiazides worse than loop diuretics)
ACE inhibitor or ARB	NSAIDs	Antagonism of hypotensive effect. Increased risk of renal impairment
	Ciclosporin	Increased risk of hyperkalaemia
	Lithium	Excretion of lithium impaired
	Diuretics	Enhanced hypotensive effect. Increased risk of hyperkalaemia with potassium-sparing drugs
Digoxin	Amiodarone	Increased digoxin level (need to halve maintenance dose of digoxin)
	Propafenone	Increased digoxin level (need to halve maintenance dose of digoxin)
	Quinidine	Increased digoxin level (need to halve maintenance dose of digoxin)
	Verapamil	Increased risk of AV block
	Diuretics	Increased risk of hypokalaemia and therefore toxicity
	Amphotericin	Increased cardiac toxicity if hypokalaemia present
Nitrates	Sildenafil	Increased hypotensive effect
	Heparin	Increased excretion of heparin
Spironolactone	Digoxin	Spironolactone may interfere with measurement of digoxin serum levels, resulting in inaccurate interpretation
β-Blocker	Amiodarone	Increased risk of bradycardia
	Diltiazem	Increased risk of AV block and bradycardia
	Verapamil	Increased risk of hypotension, heart failure and asystole

Table 21.11 Common drug–disease interactions with prescribed heart failure medication

Drug	Concurrent disease	Potential outcome
Diuretic	Prostatism	Urinary retention/incontinence
	Hyperuricaemia	Exacerbation of gout
	Liver cirrhosis	Encephalopathy
ACE inhibitor	Renal artery stenosis	Renal failure
	Severe aortic stenosis	Exacerbation of heart failure
	Renal impairment	Renal failure
	Hypotension	Hypotension and cardiogenic shock
β-Blocker	Asthma	Bronchoconstriction/ respiratory arrest
	Bradyarrhythmias	Exacerbation of heart failure
	Hypotension	Further hypotension and cardiogenic shock
Digoxin	Bradyarrhythmias	Exacerbation of heart failure
	Renal impairment	Exacerbation of heart failure and digoxin toxicity leading to cardiac arrhythmias

exceeded (see Table 21.5). Although this is usually the case, laboratory monitoring of potassium is mandatory to ensure patient safety. Heparin therapy has also been shown to increase the risk of hyperkalaemia when used alongside ACE inhibitor or ARB therapy, and therefore a similar approach to monitoring should be taken when co-prescribed.

When initiating ACE inhibitor or ARB therapy, volume depletion due to prior use of a diuretic increases the risk of a large drop in blood pressure occurring following the first dose. As a consequence, diuretic treatment is usually withheld during the initiation phase of therapy in an effort to minimise this effect.

A dry cough, which may be accompanied by a voice change, occurs in about 10% of patients receiving an ACE inhibitor. It is more common in women and is associated with a raised level of kinins. Rashes, loss or disturbances of taste, mouth ulcers and proteinuria may also occur with ACE inhibitor therapy, particularly with captopril. These unwanted effects tend to be more common in patients with connective tissue disorders.

A number of ACE inhibitors are administered as pro-drugs, so close monitoring is advised in patients with liver dysfunction, as this could reduce the benefits associated with their use. Most ACE inhibitors are dependent on the kidney for excretion, and require careful dosage titration in patients with existing renal dysfunction. Differences in the pharmacokinetic characteristics do not fully explain the differences in duration of action seen with the ACE inhibitors, as this is also related to ACE binding affinity. Throughout treatment the dose must be individualised to obtain maximum benefit in relation to symptom relief and survival, with minimum side effects. When the experience of adverse effects requires a review of therapeutic alternatives, ARBs can be considered as an alternative treatment option. Although the side effect profile of ARB therapy is very similar to that of ACE inhibitors, it is not identical.

Potential problems with β-blocker therapy

Until recently, the use of β-blockers was contraindicated in patients with heart failure due to negative inotropic and chronotropic effects. However, β-blockers have clearly been shown to be safe and effective in patients with heart failure and should be used in all patients in the absence of contraindications or intolerance. Initiation of treatment and titration of dose must be done under close supervision, with very small dose increments used to minimise transient worsening of heart failure symptoms. Titration of the dose to target is normally performed over a number of weeks or months, and close patient monitoring is required to ensure safety is not compromised. The maximum tolerable dose for a patient may be below the target dose and may limit further dose titration. Monitoring for excessive bradycardia or rapid deterioration of symptoms is necessary to ensure patient safety, while also monitoring the patient's prescribed dose to ensure that dosage increments are gradual and the patient is not subjected to an overall worsening of symptoms.

Potential problems with digoxin therapy

Although digoxin has been shown to reduce hospitalisation rates for patients with heart failure, its use is associated with a range of adverse effects including non-specific signs and symptoms of toxicity such as nausea, anorexia, tiredness, weakness, diarrhoea, confusion and visual disturbances. Digoxin also has the potential to cause fatal arrhythmias. It slows atrioventricular conduction and produces bradycardia, but it may also cause various ventricular and supraventricular arrhythmias. Digoxin toxicity typically causes conduction disturbances with enhanced automaticity leading to premature ventricular contractions. Patients at particular risk are those with myocardial ischaemia, hypoxia, acidosis or renal failure.

The appropriateness of digoxin dosage should be guided by assessment of the patient's renal function (from serum creatinine and creatinine clearance determinations) and from the patient's pulse rate. Renal function may also be affected by drug therapy or loss of control of heart failure; therefore, any medicine which affects in digoxin clearance will have an impact on the serum digoxin concentration. The possibility of a high serum digoxin concentration should also be considered in any patient whose health deteriorates or who shows signs and symptoms of potential digoxin toxicity.

Potential problems with other cardiovascular drugs

There are a number of other cardiovascular drugs that may be prescribed for patients with diseases or conditions other than heart failure, with some agents capable of worsening or aggravating symptoms. Patients with coronary artery disease may be candidates for calcium-blocking antianginal vasodilators. However, some of these agents, for example, diltiazem and verapamil, can exacerbate co-existing heart failure, since their negative inotropic effects offset the potentially beneficial arterial vasodilation. Second-generation dihydropyridines such as amlodipine and felodipine have a preferential action on the vasculature. They have less pronounced effects on cardiac contractility than other calcium antagonists, and this makes them the agents of choice where a limitation of the heart rate is not required.

Symptoms of fainting or dizziness on standing may indicate a need to review diuretic or vasodilator therapy. Patients should be reassured about mild postural effects and given advice to avoid standing from their chair too quickly. The patient and the health care team need to confirm the safety of the patient's treatment plan regularly, and be vigilant for any signs or symptoms suggesting otherwise.

A summary of monitoring activity required to ensure the safety of drug use is outlined in Table 21.12.

Table 21.12 Monitoring the safety of drug treatment in patients with heart failure

Consider	Monitor	Comment
Clinical markers	Side effects Toxicity Adverse drug reactions	There is a need to monitor for signs/symptoms of overtreatment with prescribed medication, such as diuretics (dehydration) and digoxin (nausea and vomiting). Look for signs of patient intolerance, allergy, serious adverse effects or troublesome side effects. Document unexpected adverse drug reactions if reported
Laboratory markers	Changes in organ function Biochemical changes Haematological changes Suspected digoxin toxicity	Renal function assessment and implications for drug choice and dosage individualisation required, especially in the elderly and for initiation or titration of ACE inhibitor therapy (creatinine, potassium, urea). Hypokalaemia can lead to digoxin toxicity, and serum drug concentration measurement may be performed to confirm or exclude toxicity. Haematological side effects with some drugs have been reported, for example, ACE inhibitors, therefore, laboratory checks may be required in response to clinical signs/symptoms presented
Interactions	Drug–drug interactions Drug–disease interactions	Some interactions may result in harm to the patient
Co-morbidity	Drug selection for concomitant conditions	The presence of heart failure may influence treatment choice for co-existing diseases or conditions, for example, coronary artery disease, thyroid disease, respiratory disease. Where possible, ensure drugs known to worsen heart failure are avoided or used with caution, for example, non-steroidal anti-inflammatory agents or corticosteroids in rheumatoid arthritis

Potential problems with non-cardiovascular agents

A number of agents should be avoided or used with caution in patients with heart failure because of their known negative inotropic or pro-arrhythmic effects that may aggravate symptoms of heart failure (see Box 21.1). In particular, the use of non-steroidal anti-inflammatory drugs (NSAIDs) should be actively discouraged where possible. Not only do NSAIDs cause fluid retention and put patients at increased risk of bleeding, especially if they are already taking antiplatelets or anticoagulants, there is also an increased risk of acute renal failure, particularly in those on long-term use and in the elderly. Recent articles have described the synergistic/cumulative adverse renal effects of combinations of ACE inhibitors or ARBs with diuretics and NSAIDs, which are particularly common in patients with heart failure.

Case studies

Case 21.1

Mr GF, a 57-year-old, suffered a myocardial infarction 12 months ago and at the time was also found to have left ventricular systolic dysfunction on echocardiography. He is currently asymptomatic (NYHA I). At your request, he has agreed to see you for a medication review regarding his drug therapy. He has a history of type 2 diabetes mellitus (8 years) and his current prescription includes enalapril 10 mg twice daily, gliclazide 80 mg twice daily, bisoprolol 5 mg daily, aspirin 75 mg daily, and a glyceryl trinitrate spray to use when required.

Question

1. Is the current treatment plan for heart failure optimal?

Answer

1. Mr GF has echocardiographic evidence of left ventricular systolic dysfunction, but has no signs or symptoms of heart failure at present. Therefore, the absence of diuretic therapy is expected, although enquiry into the presence/absence of symptoms would form part of any review and would be included in the patient monitoring.

   He is prescribed an ACE inhibitor at the recommended target dose (enalapril 10–20 mg twice daily) and treatment with this agent is optimal at present. There is scope for a further increase in dose should the need arise. When we consider β-blocker therapy, the current dose of bisoprolol (5 mg daily) is below the recommended target and should, therefore, be titrated to a dose of 10 mg daily or maximum tolerable dose. This titration should be implemented gradually over a period of weeks or months with close monitoring of blood pressure and heart rate. Regular assessment of the patient for side effects or signs and symptoms of heart failure should also be undertaken, as each incremental rise in β-blocker dose may be accompanied by a worsening (or in this case, appearance) of heart failure symptoms. When considering other potential changes to the treatment plan for heart failure, there may have been an opportunity for the introduction of eplerenone at the time of his myocardial infarction provided this was done within 14 days of the event. However, given that the myocardial infarction was 12 months ago, the use of eplerenone would not be indicated based on the current evidence.

   With Mr GF's history of myocardial infarction and type 2 diabetes mellitus, his cardiovascular risk is high and he should, therefore, also be prescribed lipid-lowering therapy (regardless of his serum cholesterol measurement), for example, a statin.

Case 21.2

Mrs JM, 66 years old, presents with a new prescription for candesartan 4 mg daily. On checking her medication record she has been prescribed lisinopril 20 mg daily, bisoprolol 10 mg daily and furosemide 40 mg daily for the last 6 months to treat her heart failure. Her blood pressure was measured 2 weeks ago and was 128/78 mmHg.

Question

1. How do you respond to the new prescription?

Answer

1. It is unclear from the information given whether candesartan is prescribed as an adjunct to ACE inhibitor therapy (provided the dose has been optimised) or as an alternative to ACE inhibitor due to intolerance. If being used as an adjunct, it is also unclear whether the patient also has an intolerance to aldosterone antagonists. Therefore, it is important to confirm the intended use of candesartan in this case through speaking to the patient and/or prescriber. If candesartan is being used as an alternative to either the ACE inhibitor or aldosterone antagonist, it is important to establish the reason for intolerance and ensure the therapeutic choice is appropriate for the patient. Patients are usually found to be intolerant of ACE inhibitors for three main reasons: dry cough, hypotension or compromised renal function. As heart failure can produce symptoms of a dry cough, it can sometimes be difficult to ascertain whether the ACE inhibitor or the heart failure is responsible. Dry cough occurs secondary to the inhibition of bradykinin metabolism and is generally identified shortly after initiation of an ACE inhibitor or after a dose increase; therefore, inquiry into the timing of symptoms attributed to ACE inhibitor intolerance is important. If the reason is due to persistent dry cough, an ARB would be a suitable alternative. However, if the ACE inhibitor intolerance is related to hypotension or renal dysfunction, it is likely an ARB would induce similar adverse effects and, therefore, other alternatives may need to be discussed with a heart failure specialist. In patient's intolerant of an aldosterone antagonist, the main reasons tend to be related to hyperkalaemia or unacceptable side effects such as gynaecomastia in men, gastro-intestinal intolerance and renal dysfunction.

   If candesartan is being used as adjunctive therapy, which is supported by the current evidence base for treatment, careful introduction and titration of dose must be undertaken due to the increased risk of hypotension, renal dysfunction and hyperkalaemia (ACE inhibitors and ARBs are both potassium conserving). The addition of candesartan would normally be under the guidance of a heart failure specialist, and should be initiated at a low dose and gradually titrated up to the target (32 mg daily) or maximum tolerable dose. It is important to note that dose increases during the titration period should be at least 2 weeks apart. Although Mrs JM has a normal blood pressure measurement at present, it is unclear whether renal function or blood biochemistry has previously been checked and it is important that this is confirmed prior to starting candesartan. The monitoring plan for Mrs JM should include regular checks of blood pressure, serum creatinine (and estimation of renal function), serum potassium and clinical assessment for any signs/symptoms of adverse effects/intolerance. This should be done

7–14 days after initiation and final dose titration. As the addition of candesartan should improve heart failure symptom control, regular patient monitoring will allow an assessment of the effectiveness of therapy.

Case 21.3

Mr HS, 72 years old, is admitted to hospital with increasing shortness of breath at rest. He has a previous medical history of severe left ventricular systolic dysfunction, confirmed by echocardiography, and angina. Before admission he had been taking the following medication: lisinopril 10 mg daily, furosemide 80 mg each morning and 40 mg at 2 pm, digoxin 62.5 µcg each morning, ISMN SR 60 mg daily, glyceryl trinitrate spray 1–2 doses as required, aspirin 75 mg dispersible each morning. His chest X-ray shows severe pulmonary oedema, his blood pressure is 110/70 mmHg and serum urea and electrolytes are within normal range. During the admission, carvedilol 3.125 mg twice daily is started.

Questions

1. What therapeutic options would you choose to treat the acute symptoms presented by Mr HS at the beginning of his admission?
2. Was the addition of bisoprolol appropriate for this patient?
3. What other drug treatment options might be considered for this patient in the longer term?

Answers

1. The administration of furosemide by the intravenous route is necessary as there is decreased absorption of oral furosemide secondary to gastro-intestinal oedema in acute heart failure. The administration of i.v. furosemide allows rapid serum levels to be achieved which has the benefit of producing venodilation (reducing the preload) which helps improve symptoms long before there is diuresis. Only after the oedema has resolved should the patient revert back to oral administration of diuretics. At this time, the dosage can be adjusted to maintain an appropriate fluid balance. Where diuresis is inadequate with an oral loop diuretic alone, the addition of a thiazide diuretic such as bendroflumethiazide or metolazone should be considered. Metolazone should be given initially at low dose of 2.5 mg daily, or less often if required, to avoid rapid diuresis leading to hypotension and/or renal failure.
2. Although there is good evidence to show that β-blocker therapy is safe and effective for patients with NYHA stage IV heart failure, it is not currently recommended that it should be initiated in patients with acute symptoms of heart failure. Where β-blocker therapy is indicated, initiation should occur when the patient's heart failure has been stable for at least 2 weeks and started at a very low dose on specialist advice (i.e. carvedilol 3.125 mg twice daily). The dose should be titrated gradually over a period of months towards the recommended target dose where appropriate, provided the patient tolerates each increment. In Mr HS's case, however, there is evidence to suggest that β-blocker use at discharge can be done safely in patients with heart failure, with positive effects on survival for both heart failure and coronary heart disease.
3. There is also scope to increase the dose of lisinopril to 20–35 mg daily provided the patient can tolerate the higher dose, as this is associated with greater benefits on morbidity and mortality. Based on his systolic blood pressure and assuming satisfactory renal function, there is no reason why this option cannot be explored and it would be reasonable to delay any titration of dosage until the symptoms become more stable. This is important since the use of large doses of loop diuretics in acutely ill patients may predispose to ACE inhibitor-induced renal impairment. An aldosterone antagonist (or angiotensin receptor blocker if patient tolerance poor) could be added to Mr HS's existing drug therapy. If the patient is poorly controlled on optimised doses of ACE inhibitor and β-blocker. Either addition would show benefits on morbidity and mortality if added to the existing treatment plan. The decision to initiate the angiotensin receptor blocker would usually lie with a heart failure specialist based on the individual patient. As Mr HS approaches end-stage heart failure, there may be a need to focus solely on symptom relief.

Case 21.4

Mrs FM, a 70-year-old with chronic asthma and mild heart failure, has been prescribed naproxen 250 mg three times daily. On inspection of her medication record, it is discovered that she is also receiving:

Furosemide 40 mg each morning
Ramipril 5 mg in the morning
Prednisolone 5 mg daily
Salbutamol inhaler two puffs four times daily when required
Salmeterol 50 µcg inhaler one puff twice daily
Beclometasone 250 µcg inhaler two puffs twice daily
Omeprazole 10 mg daily

When asked her about symptom control she told that she is still breathless at night which, in addition to her painful knee, is keeping her awake.

Questions

1. Do you think Mrs FM should be taking naproxen?
2. What other aspects of this patient's medication regimen could be improved?
3. What is the likely effect of the prescribed therapy on serum potassium concentrations?

Answers

1. NSAIDs such as naproxen can exacerbate asthma and heart failure by inducing bronchospasm and by causing fluid retention, respectively. They can also lead to upper gastro-intestinal problems, particularly when co-prescribed with oral steroids. It would be worth checking what has been tried already. If the painful knee is responsive to a simple analgesic such as paracetamol, this would be the preferred option. Alternatively, if an NSAID is necessary and tolerated, the use of ibuprofen in low dosage would be slightly less likely to have an effect on respiratory and renal function, although it may still aggravate symptoms of heart failure. Further investigation into the persistence of respiratory symptoms is required as it is unclear whether the patient's breathlessness is due to an exacerbation of her asthma or a worsening of her heart failure, and therefore the interpretation of this symptom is difficult.
2. The clinical nature of the breathlessness is not easy to determine, and therefore makes the solution to this case uncertain at this stage. A number of issues, which also include confirming both diagnoses, should be considered. It is important to establish whether the patient is receiving maximum benefit from inhaled treatment. Inhaler technique must be checked and improved if necessary and the dose of beclometasone optimised. A regular regimen of salbutamol is not advisable since it may impair control of asthma by masking the onset of exacerbations. A review of the need for an oral steroid should be undertaken, and any reduction in the use of an oral steroid must be done gradually to avoid exacerbation of the asthma and ensure that the patient does not experience adrenal insufficiency.

Reduction of the oral steroid dose may benefit the heart failure. Although the prednisolone dose is low its impact on treated heart failure is probably low but nevertheless should be taken into account in the review of its use.

When considering the treatment of heart failure, application of the criteria set identified the following were not met in Mrs FMs treatment:

- **Not achieved target dose of ACE inhibitor**
- **Not prescribed any aldosterone antagonist**
- **Not prescribed candesartan**
- **Potentially aggravating drug prescribed (NSAID, naproxen)**

There is scope to increase the dose of ramipril to 5 mg twice daily if tolerated, which is the target dose in heart failure patients. However, as β-blocker is contraindicated in this patient, consideration may be given to an adjunctive therapy such as an aldosterone antagonist, for example spironolactone. If the patient was known to be intolerant of an aldosterone antagonist, an ARB, for example candesartan, could be added instead. The decision around which agent to select first may come down to personal choice if symptoms are moderate. An increase in the dose of furosemide could also be considered provided the breathlessness is due to heart failure.

3. Mrs FM is receiving a number of medications with the potential to affect serum potassium. Diuretics, oral and inhaled steroids (high dose) and β-agonists can reduce potassium, while ACE inhibitors can increase potassium. It is impossible to predict the extent to which each agent will affect potassium, especially with inhaled treatments as the dose normally needs to be high before there is any significant systemic absorption. Determination of serum potassium is necessary and if it remains low under the current treatment plan, or is at risk of being altered due to changes in drug dosage such as an increase in ramipril to 5 mg twice daily, then close observation will be required.

Case 21.5

Mr CH, a 78-year-old, regularly visits your pharmacy for his medication and has moderately symptomatic heart failure (NYHA III). During a recent review with his primary care doctor, Mr CH described worsening of his heart failure symptoms. His doctor has said he could take an extra dose of furosemide 40 mg if required, but Mr CH would need to be referred back to the hospital cardiology consultant before changing any other medication. He is currently prescribed ramipril 5 mg daily, nebivolol 2.5 mg daily and furosemide 40 mg daily. His blood pressure has been measured as 103/62 mmHg (heart rate 54 bpm) and he has an estimated creatinine clearance of 20 mL/min.

Questions

1. What is the rationale behind the decision to refer Mr CH to the cardiology consultant?
2. What other drug treatment options might be considered?

Answers

1. Mr CH is prescribed both ACE inhibitor and β-blocker therapy in accordance with the evidence base for treatment. As Mr CH has symptomatic heart failure (NYHA III), he is also prescribed furosemide in response to signs and symptoms of fluid retention. When Mr CH reports deterioration in the control of his heart failure symptoms, the prescriber must consider what treatment options are available for Mr CH and make any necessary changes.

   Neither the ACE inhibitor nor β-blocker is prescribed at the recommended target dose (see Table 21.6); therefore, there is scope to titrate the dose of either agent to the target dose which should result in improvement of symptoms and a reduced need for diuretic therapy. However, there may be reluctance to increase the dose of ACE inhibitor possibly due to the fact that Mr CH has a relatively low blood pressure and compromised renal function (estimated creatinine clearance 20 mL/min). However, it is unclear whether Mr CH is receiving maximally tolerated doses and whether his apparent hypotension is indeed symptomatic. Similarly, there may be reluctance to increase the dose of β-blocker due to a low blood pressure and heart rate (54 bpm). As both options may adversely affect the patient, the doctor has decided to treat the symptoms with additional diuretic when required as a short-term solution prior to Mr CH's appointment with the cardiology consultant. Advice should be sought from a heart failure specialist where a patient may be poorly tolerant of ACE inhibitor or β-blocker, or where there is a risk of hypotension or renal failure in susceptible individuals. In Mr CH's case, specialist supervision is required for optimisation of therapy.
2. It is unlikely that there will be much scope to add further medication, and optimising either ACE inhibitor or β-blocker therapy will be limited due to their effects on blood pressure and/or renal function. Mr CH may be a likely candidate for cardiac resynchronisation therapy (CRT) and should probably be assessed for this. An ECG would confirm his eligibility for therapy if his QRS duration was >120 ms, and would be likely to improve his symptoms and survival. It may also help increase his blood pressure and renal function to a point where further optimisation of ACE inhibitor and β-blocker dose might be possible.

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22 Arrhythmias

S. Sporton and S. Antoniou

Key points

- Arrhythmias are common and should be treated only if they cause symptoms or threaten haemodynamic failure.
- An understanding of the ionic basis of the cardiac action potential is important because drugs used in the treatment of cardiac arrhythmias act by altering the function of the transmembrane ion channels.
- The heart is designed to work most efficiently in sinus rhythm. Any arrhythmia compromises cardiac function.
- Non-pharmacological treatments for arrhythmias are becoming more common.
- Atrial fibrillation is the most common arrhythmia and is associated with an increased risk of thromboembolic stroke. All patients with atrial fibrillation should undergo assessment of their stroke risk.
- Antiarrhythmic drugs are grouped by the Vaughan–Williams classification based on their ability to block the movement of specific ions across the myocardial cell membrane.
- All antiarrhythmic drugs are also proarrhythmic in some circumstances.
- While drug treatment has been the mainstay of arrhythmia treatment, it is often of limited efficacy and may be associated with significant toxicity.
- ß-Blockers and amiodarone are the most commonly used antiarrhythmic drugs.

Normal cardiac electrophysiology

The normal cardiac rhythm, sinus rhythm, is characterised by contraction of first the atria and then the ventricles (systole) followed by relaxation (diastole) during which the heart refills with blood before the next cardiac cycle begins. This orderly sequence of contraction and relaxation is regulated by the heart's electrical activity. Heart muscle cells (myocytes) are electrically active and capable of generating action potentials, which initiate contraction of the myocyte through a process known as excitation–contraction coupling. Adjacent myocytes form electrical connections through protein channels called gap junctions. An action potential in one myocyte causes current flow between itself and adjacent myocytes which in turn generate their own action potentials and in this way an 'activation wavefront' spreads though the myocardium, resulting in a wave of contraction.

Cardiac action potential

An understanding of the ionic basis of the cardiac action potential is important because drugs used in the treatment of cardiac arrhythmias act by altering the function of transmembrane ion channels. Inherited abnormalities of ion channel function ('channelopathies') are an important cause of sudden cardiac death due to arrhythmia and are increasingly implicated in the pathogenesis of other arrhythmias including atrial fibrillation (AF).

The phospholipid membrane of cardiac myocytes is spanned by numerous proteins known as ion channels, whose permeability to specific ions varies during the cardiac cycle resulting in a resting (diastolic) membrane potential, diastolic depolarisation in cells with pacemaker activity, and action potentials.

The resting membrane potential of –60 to –90 mV occurs because the intracellular potassium (K^+) concentration is much higher than the extracellular K^+ concentration as a result of a transmembrane pump known as Na^+–K^+–ATPase, which pumps K^+ ions into the cell in exchange for sodium (Na^+) ions. K^+ ions diffuse out of the cell through selective K^+ channels (the inward rectifier current or I_{K1}) unaccompanied by anions, resulting in a net loss of charge and thus a negative resting, diastolic or phase 4, transmembrane potential (Fig. 22.1A).

Certain specialised myocytes form the cardiac conduction system and these cells have pacemaker activity, that is, they are capable of generating their own action potentials due to gradual depolarisation of the transmembrane potential during diastole (phase 4), referred to as the pacemaker potential (Fig. 22.1B). The pacemaker potential occurs as a result of (i) a gradual reduction in an outward K^+ current called the delayed rectifier (I_K) current, (ii) increasing dominance of an inward current of Na^+ and some Ca^{2+} ions known as I_f (f stands for 'funny') and (iii) an inward calcium current I_{Ca} through voltage-gated calcium channels. As a result of the pacemaker potential, the transmembrane potential gradually becomes less negative until a threshold potential is reached at which an action potential is triggered. The rate of depolarisation of the pacemaker potential, and hence the heart rate, is influenced by the autonomic nervous system. Sympathetic nervous system activation and circulating catecholamines increase the heart rate by binding to $ß_1$-adrenoreceptors leading to an increase in intracellular cyclic AMP, which results in changes to the permeability of the various ion channels

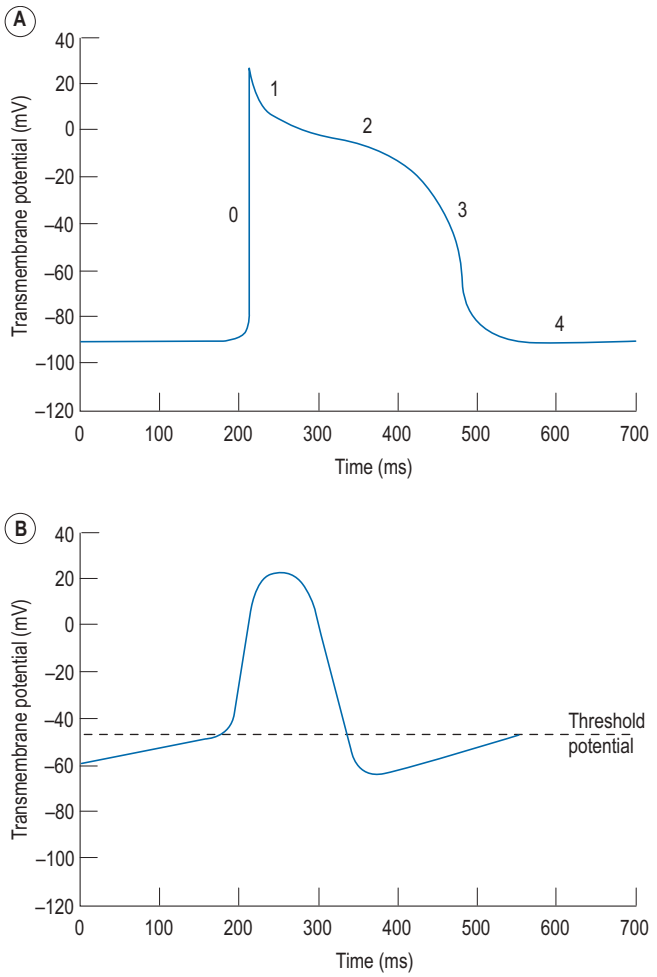

Fig. 22.1 The cardiac action potential. (A) An action potential from ventricular myocardium. During diastole (phase 4), the resting transmembrane potential is constant at –90 mV. The upstroke (phase 0) of the action potential is due to the rapid influx of Na^+ ions. The early phase of repolarisation (phase 1) is due to efflux of K^+ ions, followed by a plateau phase (phase 2) at about 0 mV during which influx of Ca^{2+} ions is balanced by efflux of K^+ ions. Towards the end of diastole, influx of Ca^{2+} ions diminishes and efflux of K^+ ions increases, resulting in repolarisation (phase 3) back to the negative resting membrane potential. (B) An action potential from the sinus node. During diastole (phase 4), there is progressive depolarisation towards a threshold potential at which an action potential is triggered. The upstroke (phase 0) of the action potential is less steep than in ventricular myocardial cells because the sinus node cells lack 'fast' Na^+ channels and so depolarisation is dependent upon influx of Ca^{2+} ions.

responsible for the pacemaker current. Parasympathetic nervous system activation, mediated by muscarinic cholinergic receptors, has the opposite effect.

The rapid depolarisation of the cardiac action potential (Fig. 22.1A, phase 0) occurs because of a rapid increase in the permeability of the cell membrane to Na^+ ions, which enter rapidly through 'fast' Na^+ channels in a current known as I_{Na}. The I_{Na} current is brief as the 'fast' Na^+ channels inactivate rapidly. The early phase of repolarisation (phase 1) is due to closure of the fast Na^+ channels, an outward K^+ current known as I_{to} (to – transient outward) and a further K^+ current known as the ultra-rapid component of the delayed rectifier current or I_{Kur}. The plateau phase (phase 2) of the cardiac action potential occurs because the inward movement of Ca^{2+} ions (I_{Ca}) is balanced by the outward movement of K^+ ions. Repolarisation (phase 3) occurs as I_{Ca} diminishes and two further components of the delayed rectifier (I_K) current known as the rapid (I_{Kr}) and slow (I_{Ks}) components predominate, with an important contribution from I_{K1}.

There is considerable variation in the expression of transmembrane ion channels in different parts of the heart, with corresponding variation in the morphology of the action potential. The most marked example is that myocytes in the sinus and AV nodes contain few Na^+ channels. The upstroke of the action potential in these cells is due, predominantly, to the influx of Ca^{2+} ions and, therefore, is considerably slower than the upstroke in other myocytes (Fig. 22.1B). The variation in ion channel expression throughout the heart is essential for normal cardiac function, helps to explain the pathophysiology of many inherited and acquired diseases complicated by cardiac arrhythmia and accounts for the relative selectivity of antiarrhythmic and other drugs for certain parts of the heart.

Refractoriness

The action potential of cardiac myocytes differs from that seen in nerve cells by the presence of a plateau phase during which the myocyte is electrically inexcitable and refractory, that is, incapable of generating another action potential. It is only towards the end of repolarisation (phase 3) that the myocyte regains excitability. The time interval between the onset of the action potential and the regaining of electrical excitability is known as the refractory period. Under most circumstance the refractory period of a cardiac myocyte corresponds closely to the duration of the cardiac action potential and, therefore, drugs that prolong action potential duration (APD) prolong the refractory period.

Normal cardiac conduction

During normal sinus rhythm (Fig. 22.2), an activation wavefront begins in the sinus node, a group of cells with pacemaker activity on the upper free wall of the right atrium. The rate of diastolic depolarisation and hence the rate of discharge of the sinus node is increased by sympathetic nerve stimulation, circulating catecholamines or sympathomimetic drugs mediated by $ß_1$-adrenoreceptors on the cell membranes of the sinus node myocytes. Parasympathetic (vagus) nerve stimulation exerts the opposite effect, mediated by muscarinic cholinergic receptors.

An activation wavefront spreads across the atrial myocardium, leading to atrial contraction and generating the P wave on the surface electrocardiogram (ECG; Fig. 22.3). The last part of the atria to be activated is the atrioventricular (AV) node, the electrical and structural properties of which result in a slow conduction velocity, allowing atrial emptying to be completed before ventricular contraction begins

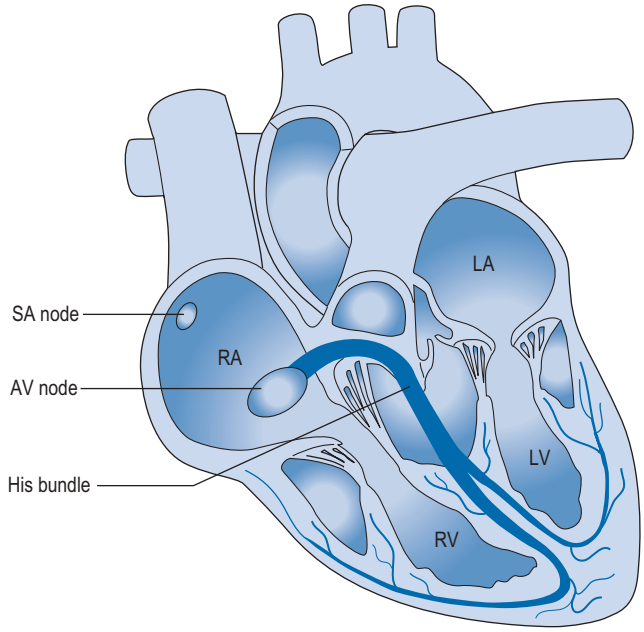

Fig. 22.2 The normal cardiac conduction system. During sinus rhythm, an activation wavefront spreads from the sinus (sinoatrial – SA) node across the atrial myocardium before entering the atrioventricular node. The activation wavefront then enters the bundle of His, which penetrates the annulus fibrosus and forms the only electrical connection between the atria and ventricles. The bundle of His divides into right and left bundle branches which ramify into a subendocardial network of Purkinje fibres that transmit the activation wavefront rapidly across the ventricles. Activation of the ventricles proceeds from endocardium to epicardium.

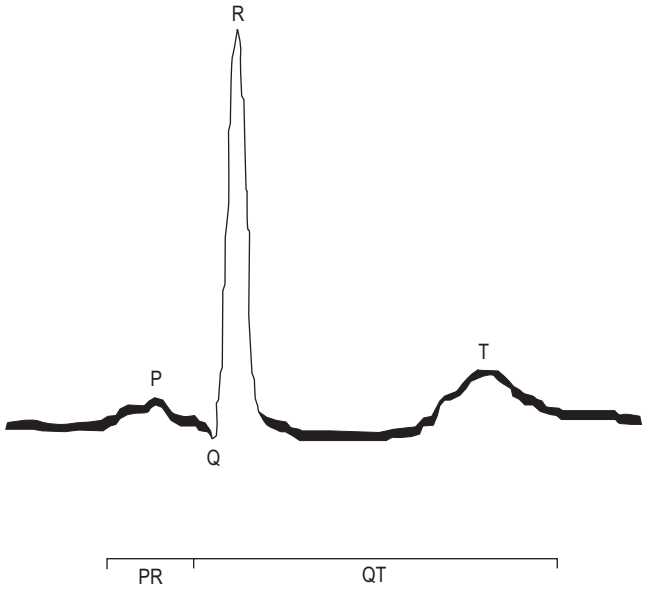

Fig. 22.3 The normal electrocardiogram (ECG). The P wave results from activation (depolarisation of the atria). The PR interval is isoelectric as the activation wavefront proceeds slowly through the atrioventricular node. The QRS complex reflects activation of the ventricles and is large compared to the P wave because of the much greater mass of the ventricular myocardium, and brief, reflecting extremely rapid conduction in the His–Purkinje system. The T wave represents ventricular repolarisation.

and represented by the PR interval on the ECG. Conduction velocity in the AV node is increased by sympathetic nerve stimulation, circulating catecholamines or sympathomimetic drugs, mediated by $ß_1$-adrenoreceptors while parasympathetic (vagus) nerve stimulation exerts the opposite effect via muscarinic cholinergic receptors.

The atria and ventricles are electrically isolated from each other by the annulus fibrosus, the electrically non-conductive fibrous tissue forming the valve rings. In the normal heart, there is just one electrical connection between the atria and ventricles, the bundle of His, which conveys the activation wavefront from the AV node and penetrates the annulus fibrosus before dividing into the right and left bundle branches. The bundle branches ramify into a sub-endocardial network of Purkinje fibres, which convey the activation wavefront rapidly across the ventricles ensuring near-simultaneous contraction of the ventricular myocardium, and are represented by the narrow QRS complex of the ECG. Finally, the activation wavefront spreads from endocardium to epicardium. A wave of repolarisation then spreads across the ventricles resulting in the T wave. The QT interval on the ECG, therefore, represents the duration of ventricular depolarisation and repolarisation. There is an inverse relationship between the time to activation of different areas of the ventricular myocardium and APD such that the latest areas to be activated have the shortest APD. The purpose of this relationship is that repolarisation is rapid and uniform throughout the ventricular myocardium, which serves to maintain electrical stability.

Arrhythmia mechanisms

Cardiac arrhythmias occur because of abnormalities of impulse formation or propagation.

Abnormal impulse formation

Abnormal automaticity

Automaticity is another term for pacemaker activity, a characteristic possessed by all cells of the specialised cardiac conduction system during health and, potentially, by other cardiac myocytes during certain disease states. The rate of firing of a pacemaker cell is largely determined by the duration of the phase 4 diastolic interval (Fig. 22.4). This in turn is determined by (i) the maximum diastolic potential following repolarisation of the preceding action potential, (ii) the slope of diastolic depolarisation due to pacemaker currents and (iii) the threshold potential for generation of a new action potential. In the healthy state, there is a hierarchy of firing rates within the specialised conduction system with the highest rate in the sinus node followed by the AV node and then the His–Purkinje system. The sinus node is, therefore, the dominant pacemaker and determines the heart rate, while the pacemaker activity in the distal conduction system is 'overdriven' by the sinus node. Abnormal automaticity describes either accelerated pacemaker activity in cells of the distal cardiac conduction system such that they escape from overdrive

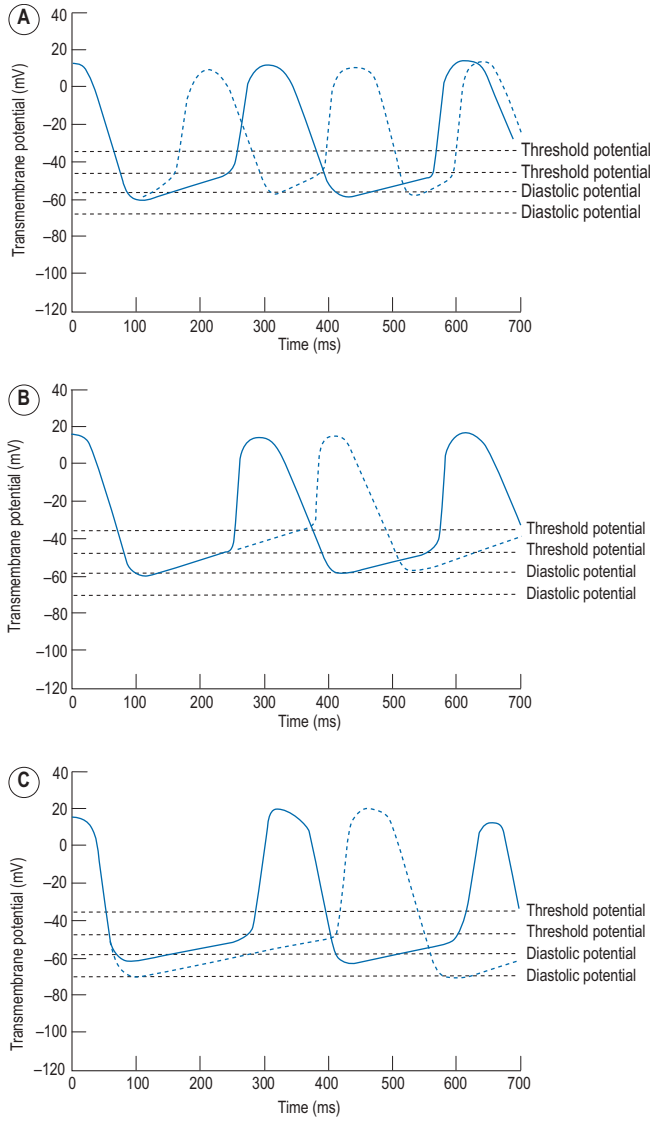

Fig. 22.4 Abnormal automaticity. A sinus node action potential is shown (in bold) with a characteristic slow upstroke. Following repolarisation, gradual diastolic depolarisation occurs as a result of pacemaker currents. When the threshold potential is reached a further action potential is generated. The rate of firing of the pacemaker cell is governed largely by the duration of the diastolic interval which is in turn determined by (A) the slope of diastolic depolarisation, (B) the threshold potential and (C) the maximum diastolic potential. Each of these (shown by dotted lines) may be altered by disease states leading to abnormal automaticity.

suppression by the sinus node, or the development of pacemaker activity in cells that do not form part of the cardiac conduction system.

Triggered activity

Triggered activity describes impulse formation dependent upon afterdepolarisations. Early afterdepolarisations (EADs) occur during phase 2 or 3 of the cardiac action potential whereas delayed afterdepolarisations (DADs) occur during phase 4 (Fig. 22.5). In both cases, afterdepolarisation may

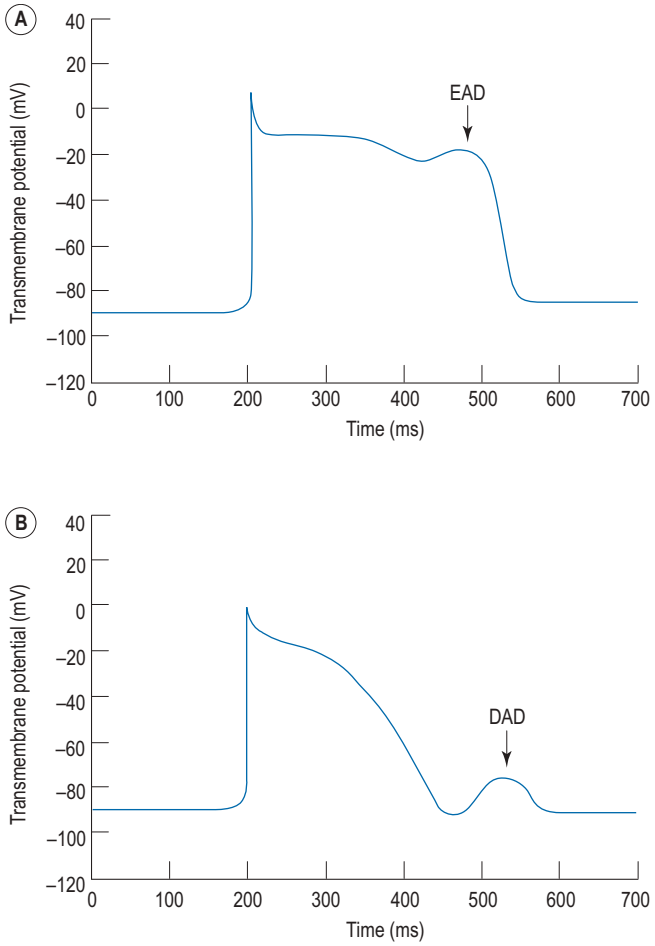

Fig. 22.5 Triggered activity. (A) An early afterdepolarisation (EAD) occurring at the start of phase 3 of the cardiac action potential. (B) A delayed afterdepolarisation (DAD) occurring after repolarisation, during phase 4. Either EADs or DADs may reach the threshold potential for generation of a further action potential.

reach the threshold potential required for generation of a new action potential.

EADs are characteristic of the congenital and acquired long QT syndromes. The prolonged APD promotes reactivation of the inward calcium current I_{Ca} which may directly cause EADs during phase 2. Furthermore, action potential prolongation and ß-adrenoreceptor stimulation promote calcium overload in the sarcoplasmic reticulum. This in turn leads to the spontaneous release of calcium in bursts by the sarcoplasmic reticulum. The resultant increase in intracellular calcium concentration activates the transmembrane Na^+/Ca^{2+} exchanger which moves one calcium ion out of the myocyte in exchange for three sodium ions and, therefore, results in an EAD during phase 3. In the long QT syndromes, an EAD may initiate a form of polymorphic ventricular tachycardia (VT) known as Torsade de Pointes. EADs are more prominent at slow heart rates.

DADs are seen during reperfusion following ischaemia, heart failure, digitalis toxicity and in catecholaminergic polymorphic VT. They occur because of spontaneous release of calcium in bursts by the sarcoplasmic reticulum, activating the

Na^+/Ca^{2+} exchanger as described for EADs and resulting in a DAD during phase 4. A DAD may result in a single extrastimulus ('ectopic beat') or in repetitive firing, that is, tachycardia. DADs are more prominent at rapid heart rates and during sympathetic nervous stimulation of ß-adrenoreceptors.

Abnormal impulse propagation

Re-entry

Many clinically important arrhythmias are due to re-entry, in which an activation wavefront rotates continuously around a circuit. Re-entry depends upon a trigger in the form of a premature beat, and a substrate, that is, the re-entry circuit itself. A precise set of electrophysiological conditions must be met in order for re-entry to occur (Fig. 22.6): (i) there must be a central non-conducting obstacle around which the re-entry circuit develops, (ii) a premature beat must encounter unidirectional conduction block in one limb (a) of the re-entry circuit, (iii) conduction must proceed slowly enough down the other limb (b) of the re-entry circuit that electrical excitability has returned in the original limb (a), allowing the activation wavefront to propagate in a retrograde direction along that limb, and (iv) the circulating activation wavefront must continue to encounter electrically excitable tissue. This is a function of the length of the re-entry circuit, the conduction velocity of the activation wavefront and the effective refractory period of the myocardium throughout the circuit. Class I antiarrhythmic drugs block sodium channels and, therefore, reduce the amplitude and rate of rise of the cardiac action potential and in so doing, reduce the conduction velocity of an activation wavefront. Class I antiarrhythmic drugs may exert their major antiarrhythmic effect by abolishing conduction altogether in areas of diseased myocardium forming part of a re-entry circuit in which conduction is already critically depressed. Class III antiarrhythmic drugs prolong cardiac APD and hence the refractory period. If previously activated cells in a re-entry circuit (the 'tail') remain refractory when the re-entrant wavefront (the 'head') returns to that area, conduction will fail and re-entry will be abolished. Drug-induced prolongation of the refractory period may, therefore, terminate and/or prevent re-entrant arrhythmias.

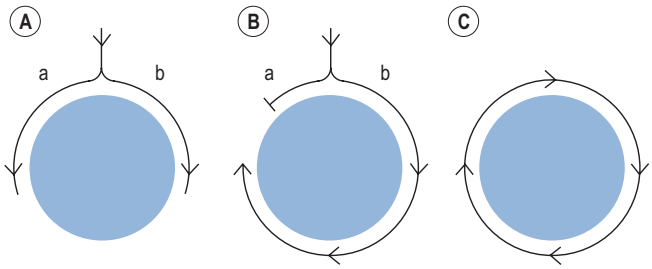

Fig. 22.6 Re-entry. During sinus rhythm, (A) an activation wavefront encounters a zone of fixed conduction block but can propagate anterogradely on either side of this zone, down limbs a and b of a potential re-entry circuit. A premature beat (B) encounters unidirectional conduction block in limb a but propagates anterogradely down limb b and re-enters limb a retrogradely. If limb a is now capable of retrograde conduction, the re-entry circuit is completed and re-entry continues (C) as long as the activation wavefront continually meets electrically excitable tissue.

Clinical problems

Patients with a cardiac arrhythmia may present with a number of symptoms:

- The most common symptom is palpitation, an awareness of an abnormal heartbeat, although some patients with clearly documented arrhythmia have no palpitation. Arrhythmias start suddenly and, therefore, if the patient clearly describes palpitation of sudden onset ('like flicking a switch'), this is a useful pointer to an arrhythmia rather than heightened awareness of sinus tachycardia, which has a less sudden onset.
- The heart is designed to work most efficiently in sinus rhythm. Any arrhythmia compromises cardiac function. Classical symptoms that arise due to reduced cardiac output include reduced exercise capacity, breathlessness and fatigue.
- Angina may accompany tachycardia, even in the absence of coronary artery disease. Tachycardia increases the metabolic rate of cardiac muscle and hence its demand for blood flow. Myocardial perfusion occurs predominantly during diastole and during tachycardia proportionately less time is spent in diastole and so myocardial demand for blood can exceed supply, resulting in angina.
- A sudden drop in cardiac output may accompany either bradycardia or tachycardia, causing episodes of dizziness (presyncope), loss of consciousness (syncope) or, in extreme cases, sudden death from cardiac arrest.
- Atrial tachyarrhythmias such as atrial flutter and atrial fibrillation may be complicated by the development of intracardiac thrombus, usually within the left atrial appendage. This thrombus may embolise to any part of the body but the most common clinical presentation is with a transient ischaemic attack or stroke.

Arrhythmias may aggravate heart failure in two ways: (i) the haemodynamic effect of the arrhythmia may precipitate heart failure or aggravate existing heart failure and (ii) prolonged tachycardia of any type may lead to tachycardia-induced cardiomyopathy.

Diagnosis

A detailed history should be obtained, covering all of the symptoms listed above. A characteristic of cardiac arrhythmias is their random onset. Symptoms occurring under specific circumstances are less likely to be due to arrhythmia, but there are exceptions including certain uncommon types of VT, some cases of supraventricular tachycardia (SVT) due to an accessory pathway and vasovagal syncope (faints). Other key features of the history include:

- A history of cardiac disease
- Other diagnosed medical conditions

- A full drug history, including over-the-counter medicines and recreational drugs including alcohol
- A family history of heart disease and of sudden unexpected death.

Physical examination is essential but often normal between episodes of arrhythmia. Mandatory investigation includes a 12-lead ECG and an echocardiogram to detect structural heart disease. Other investigations for structural and ischaemic heart disease may be indicated at this stage with the aim of detecting any underlying structural heart disease. If the history does not include sinister features such as syncope or a family history of sudden unexpected death at a young age, and the resting 12-lead ECG and echocardiogram are normal, then the patient can be reassured that they are extremely unlikely to have a serious heart rhythm disturbance. The extent of further investigation will be dictated by how troublesome the symptoms are.

The most certain way of reaching a firm diagnosis is a 12-lead ECG recorded during the patient's symptoms demonstrating arrhythmia. As many arrhythmias occur intermittently, some form of ECG monitoring is often necessary. This may include a continuous ambulatory ECG (Holter) recording for up to 7 days at a time if the symptoms occur frequently or, for less frequent symptoms an event recorder, which may store ECG strips automatically if it detects an arrhythmia or if activated by the patient during their symptoms. An insertable loop recorder may be implanted subcutaneously and is an ECG event recorder with a battery life of about 3 years, making it a useful tool for the diagnosis of infrequent arrhythmias.

Management

Pathological tachycardia is conventionally defined as a resting heart rate over 100 beats/min and can be classified according to whether it arises in or involves the atria (supraventricular tachycardias) or the ventricle (ventricular tachyarrhythmias).

Supraventricular tachycardias

These are tachycardias arising from or involving the atria.

Inappropriate sinus tachycardia

Although uncommon, inappropriate sinus tachycardia, that is, sinus tachycardia with no identifiable underlying cause, is one of the more difficult arrhythmias to treat. The presenting symptom is usually palpitation and the typical patient is a young, predominantly female, adult with no history of heart disease or other physical illness. The 12-lead ECG shows sinus tachycardia and ambulatory ECG monitoring demonstrates sinus tachycardia but with diurnal variation in heart rate. Echocardiography is required to exclude structural heart disease, and thyroid function and urinary catecholamine excretion should be measured to detect thyrotoxicosis and phaechromocytoma, respectively, as rare underlying causes of sinus tachycardia. If treatment is required on symptomatic grounds, ß-blockers or verapamil are first line therapy. Ivabradine, a selective 'funny channel' blocker, has been used in resistant cases but is not currently licensed for this indication. Catheter ablation of the sinus node has been performed in highly symptomatic drug-resistant inappropriate sinus tachycardia but with limited success and risks including symptomatic sinus bradycardia and phrenic nerve palsy.

Atrial flutter

Atrial flutter is a right atrial tachycardia with a re-entry circuit around the tricuspid valve annulus. The atrial rate is typically 300 min^{-1}. The long refractory period of the AV node protects the ventricles from 1:1 conduction: In the presence of a healthy AV node and the absence of AV node-modifying drugs, there is usually 2:1 AV conduction resulting in a regular narrow-complex tachycardia with a ventricular rate of 150 min^{-1}.

Atrial flutter confers a risk of thromboembolism similar to that of AF and this risk should be managed in the same way. Emergency management of atrial flutter is dictated by the clinical presentation but may include d.c. cardioversion or ventricular rate control with drugs which increase the refractory period of the AV node such as ß-blockers, verapamil, diltiazem or digoxin. ß-Blockers, verapamil and digoxin may be given intravenously. As the re-entry circuit is confined to the right atrium and does not involve the AV node, adenosine will not terminate atrial flutter but will produce transient AV block, allowing the characteristic flutter waves to be seen on the ECG (Fig. 22.7).

There is a limited role for antiarrhythmic drugs, whether used acutely to achieve chemical cardioversion or in the longer term to maintain sinus rhythm. Class Ic antiarrhythmic drugs such as flecainide should be used only in conjunction with AV node-modifying drugs such as ß-blockers, verapamil, diltiazem or digoxin because they may otherwise cause slowing of the atrial flutter circuit and 1:1 conduction though the AV node which may be life-threatening. Sotalol and amiodarone have been used to restore and maintain sinus rhythm and have the advantage of controlling the ventricular rate where rhythm control is incomplete. Catheter ablation of atrial flutter is highly effective and safe and is increasingly used in preference to long-term drug treatment.

Focal atrial tachycardia

As its name implies, this relatively uncommon arrhythmia results from the repetitive discharge of a focal source within the atria or surrounding venous structures. The tachycardia mechanism may be caused by abnormal automaticity, triggered activity or microreentry. Management is as described for atrial flutter with three exceptions: (i) some focal atrial tachycardias terminate with adenosine, (ii) the potential for class Ic antiarrhythmic drugs to slow tachycardia and result in 1:1 AV conduction is lower than for atrial flutter, and (iii) catheter ablation of focal atrial tachycardia may be more challenging than that of atrial flutter, but is curative in a majority of cases.

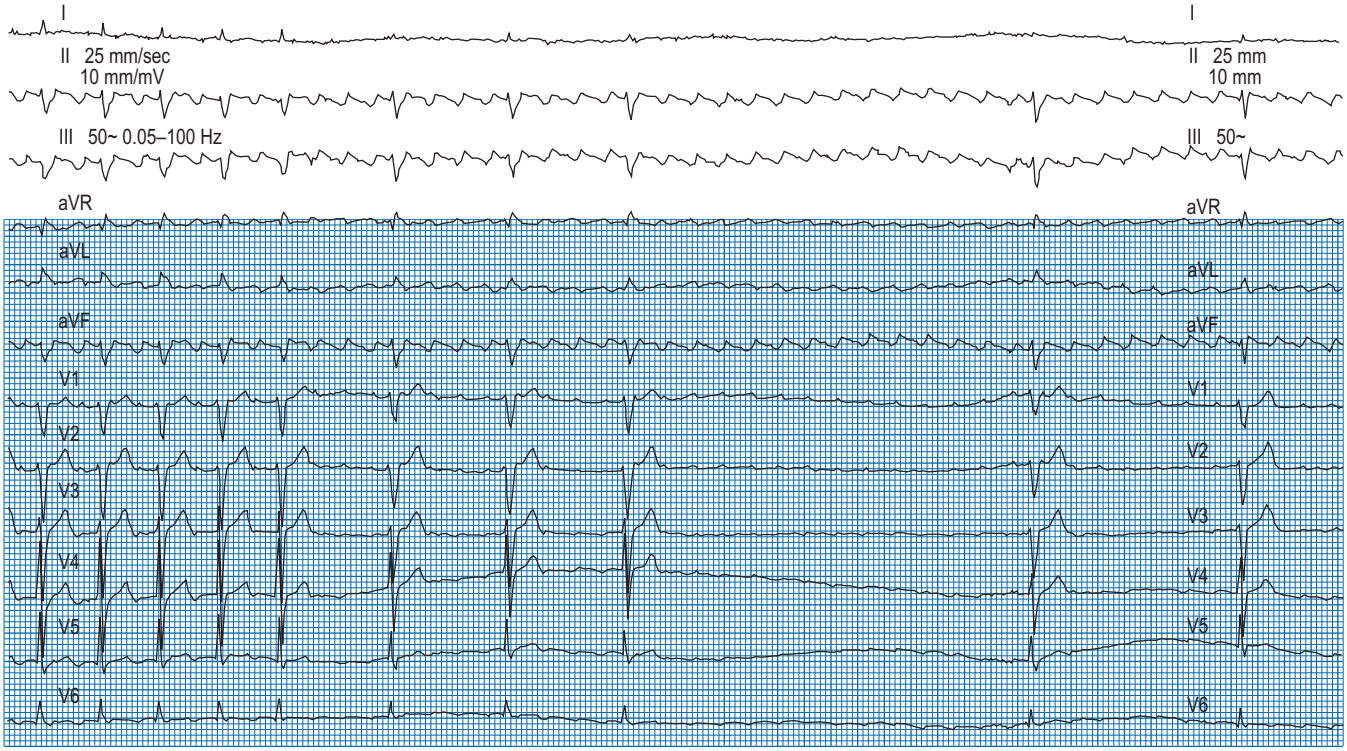

Fig. 22.7 A 12-lead electrocardiogram (ECG) recorded during the administration of intravenous adenosine. The initial rhythm is atrial flutter with 2:1 conduction from atria to ventricles. The QRS complexes obscure the atrial activity on the ECG. Adenosine does not terminate the atrial flutter but causes temporary atrioventricular block revealing the characteristic 'sawtooth' ECG morphology of typical atrial flutter.

Junctional re-entry tachycardia

The term 'supraventricular tachycardia' (SVT) is widely used to describe junctional re-entry tachycardias but is a misnomer because it implies any tachycardia arising from the atria. Junctional re-entry tachycardia is a more specific term and may be preferable.

Two mechanisms account for most junctional re-entry tachycardias: both involve a macroreentry circuit (Fig. 22.8). AV nodal re-entry tachycardia (AVNRT) rotates around a circuit including the AV node itself and the so-called AV nodal fast and slow pathways, which feed into the AV node. Atrioventricular re-entry tachycardia (AVRT) comprises a re-entry circuit involving the atrial myocardium, the AV node, the ventricular myocardium and an accessory pathway, a congenital abnormality providing a second electrical connection between the atria and ventricles in addition to the His bundle, thus forming a potential re-entry circuit.

Many accessory pathways conduct only retrogradedly from the ventricles to the atrium. In these cases, the ECG during sinus rhythm appears normal and the accessory pathway is described as 'concealed'. Other accessory pathways conduct anterogradely and retrogradely. In these cases, the ECG during sinus rhythm is abnormal and is described as having a Wolff–Parkinson–White pattern (Fig. 22.9). This abnormality is characterised by a short PR interval as the conduction velocity of an accessory pathway is usually faster than that of the AV node, and a delta wave, a slurred onset to the QRS complex which occurs because an accessory pathway inserts into ventricular myocardium which conducts more slowly than the His–Purkinje system.

Junctional re-entry tachycardias are characterised by a history of discrete episodes of rapid regular palpitation that start and stop suddenly and occur without warning and apparently at random. The peak age range at which symptoms begin is from the mid-teens to the mid-thirties and the condition is more common in women. There are no symptoms between episodes, and cardiac examination and investigation at these times are usually normal. The diagnosis is usually made on the basis of the history, ideally confirmed by an ECG recorded during an episode showing a regular narrow-complex tachycardia with no discernible P waves or P waves occurring in a 1:1 relationship with the QRS complexes.

Acute treatment of junctional re-entry tachycardia aims to terminate the tachycardia by causing transient conduction block in the AV node, an obligatory part of the re-entry circuit. Vagotonic manoeuvres such as carotid sinus massage, a Valsalva manoeuvre or eliciting the diving reflex by immersion of the face in ice-cold water may all result in a brief vagal discharge sufficient to block conduction in the AV node, terminating tachycardia. The same effect may be achieved with intravenous adenosine given as a rapid bolus injection in doses up to 12 mg. Intravenous verapamil 5 mg also as a rapid bolus injection is a good alternative where adenosine is contraindicated.

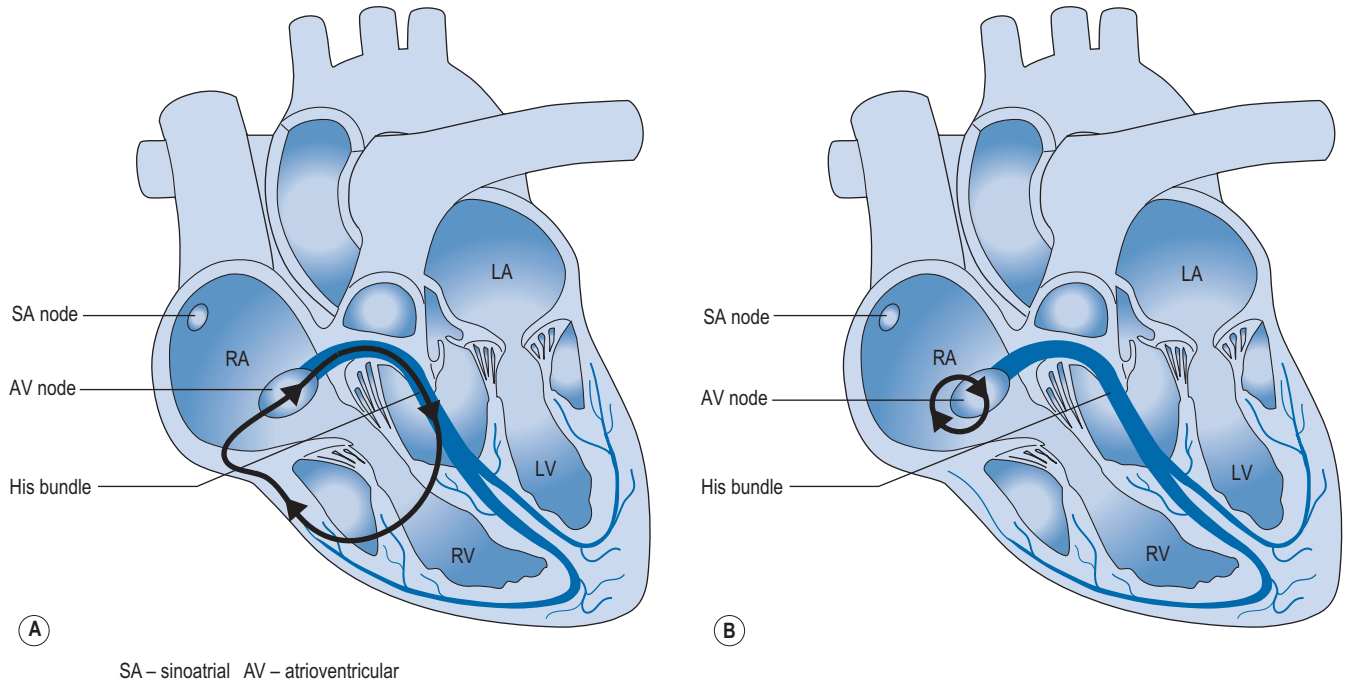

Fig. 22.8 The re-entry circuits of (A) AV nodal re-entry tachycardia (AVNRT) and (B) atrioventricular re-entry tachycardia (AVRT). (A) The AVNRT circuit comprises 'fast' and 'slow' pathways feeding into the AV node itself. The slow pathway is the target of catheter ablation. The AVRT circuit comprises atrial myocardium, the AV node and His bundle, ventricular myocardium and an accessory pathway, a small strand of muscle providing a second abnormal connection between atrium and ventricle, thus forming a potential re-entry circuit. The accessory pathway itself is the target of catheter ablation. SA, sinoatrial; AV, atrioventricular.

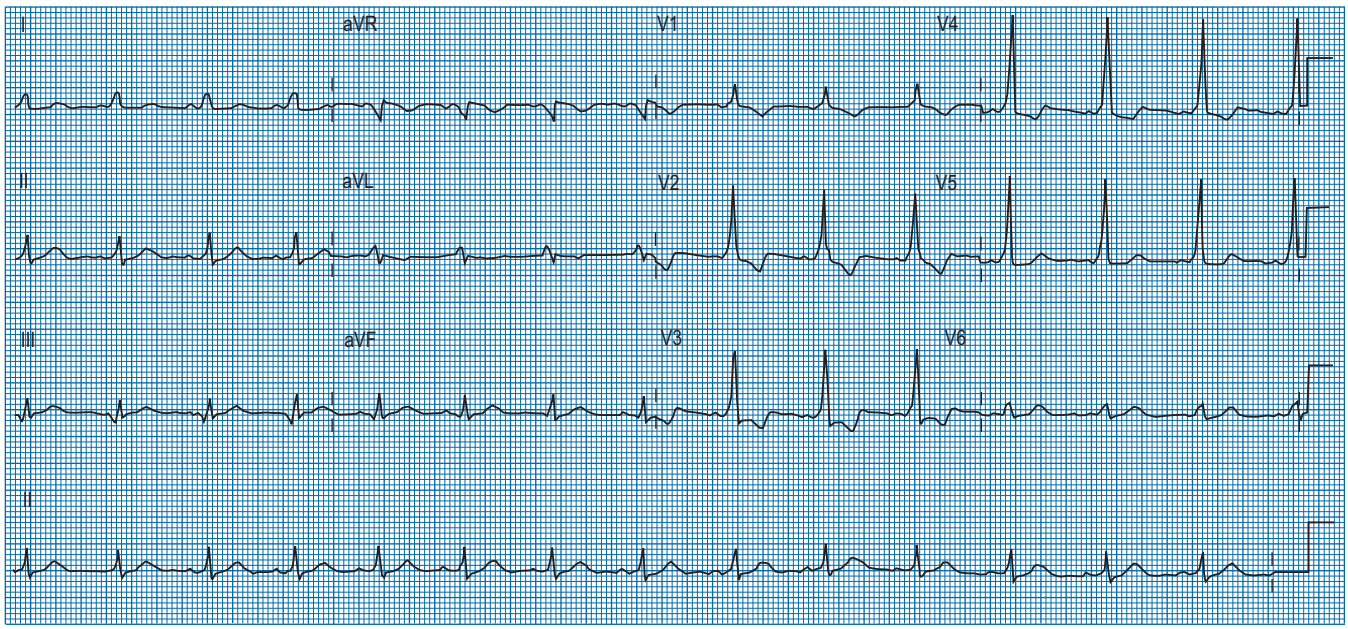

Fig. 22.9 An electrocardiogram showing a Wolff–Parkinson–White pattern. The PR interval is short and the QRS complex is abnormally broad, with a slurred upstroke or delta wave.

Junctional re-entry tachycardia is often recurrent. There is a limited role for prophylactic drug treatment as this is generally not a dangerous condition affecting young and otherwise healthy people. Among other factors, the efficacy, toxicity and acceptability of what may be long-term drug treatment require careful consideration. Options for prophylactic drug treatment include ß-blockers, verapamil, flecainide and sotalol. Particular importance should be given to discussion about the management of junctional re-entry tachycardia during pregnancy. Catheter ablation is curative in one sitting in a majority of cases.

Atrial fibrillation

AF is the most common sustained arrhythmia, affecting about 1% of the population. AF is rare before the age of 50 but its prevalence approximately doubles with each decade thereafter such that about 10% of those over 80 are affected. AF is characterised by extremely rapid and uncoordinated electrical activity in the atria and variable conduction through the AV node, resulting in irregular and usually rapid ventricular contraction.

The clinical importance of AF results from:

(i) Symptoms including palpitation, reduced exercise capacity, breathlessness and fatigue
(ii) Increased risk of thomboembolic stroke
(iii) Exacerbation of heart failure through its direct haemodynamic effect and by causing tachycardia-induced cardiomyopathy
(iv) Increased all-cause mortality (odds ratio 1.5 for men and 1.9 for women)

AF may be classified as:

Paroxysmal: self-limiting episodes of AF lasting no more than 7 days

Persistent: AF lasting more than 7 days or requiring cardioversion

Longstanding persistent: continuous AF for more than 1 year

Permanent: where a decision has been made not to attempt cure of persistent AF.

Stroke risk. All patients presenting with AF (or atrial flutter) should undergo assessment of their risk of stroke. Although various risk stratification schemes exist, they are exemplified by the $CHADS_2$ score, which assigns one point each for Congestive cardiac failure, Hypertension, Age >75 years, and Diabetes mellitus and two points for if there is a history of previous Stroke. Surprisingly, the frequency of AF episodes does not seem to influence stroke risk. The risk of stroke is directly proportional to the $CHADS_2$ score. Meta-analysis of numerous trials of stroke prevention in AF has suggested a relative risk reduction for stroke of 64% with warfarin and 22% with aspirin (Fig. 22.10).

Warfarin is more difficult to take than aspirin because of the need for monitoring of the international normalised ratio (INR) and because of the potential for dietary and drug interactions with warfarin. Warfarin also increases the risk of serious bleeding. The absolute benefit of warfarin over aspirin for the prevention of stroke in AF is proportional to the $CHADS_2$ score and the point at which the benefit of warfarin is considered to outweigh the risk is an annual untreated stroke risk of 4%. For this reason, current guidelines recommend stroke prophylaxis with warfarin for those with a $CHADS_2$ score of ≥2, warfarin or aspirin for a $CHADS_2$ score of 1 and aspirin for those with a $CHADS_2$ score of 0.

While $CHADS_2$ is the most common guideline, in patients with AF and a $CHADS_2$ score of 1, a lower incidence of stroke and/or death from all causes has been found among patients treated with vitamin K antagonists (VKAs) when compared with no antithrombotic therapy. In contrast, prescription of an antiplatelet agent was not associated with a lower risk of events compared with no antithrombotic therapy.

Identification of the 'low risk' category clearly needed to be improved, so patients can be truly identified as low risk.

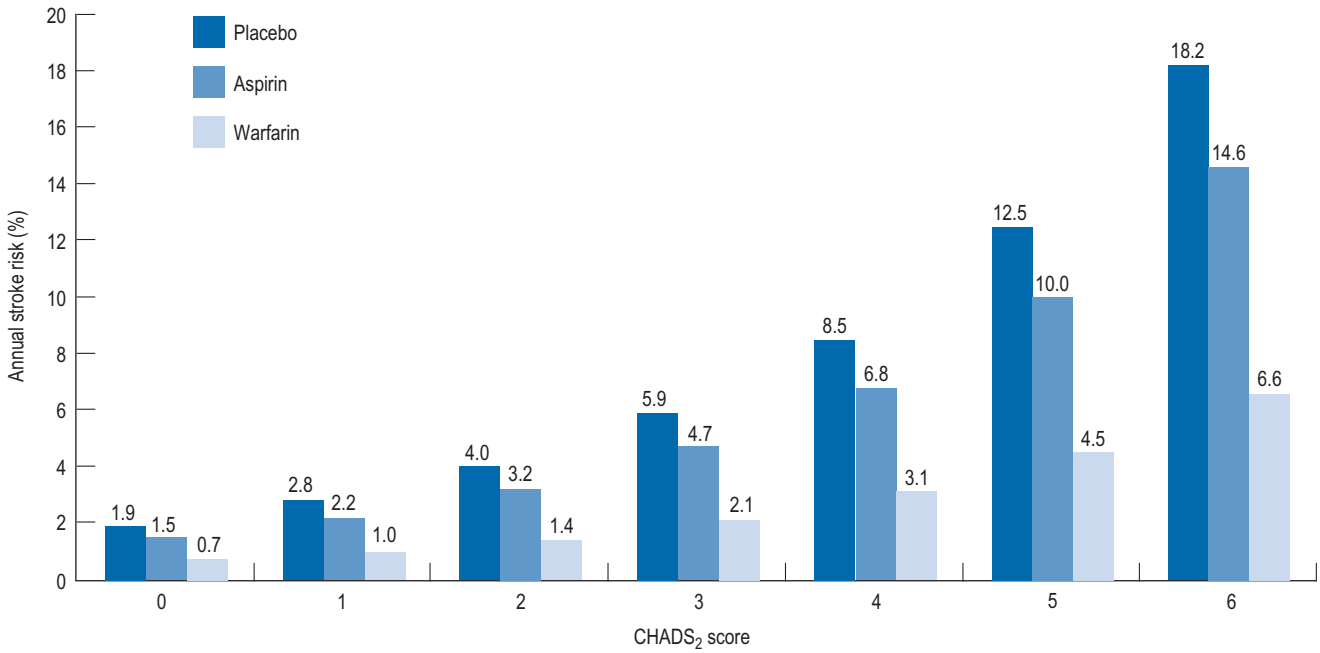

Fig. 22.10 Annual stroke risk is directly related to the $CHADS_2$ score (black bars). Aspirin reduces stroke risk by approximately 22% (dark blue bars) and warfarin by approximately 64% (light blue bars). This figure shows that, although the *relative* stroke risk reduction is higher with warfarin than with aspirin whatever the $CHADS_2$ score, the *absolute* difference is directly related to the $CHADS_2$ score. Warfarin is inconvenient to take and increases the risk of serious bleeding and, therefore, a clear benefit from taking warfarin rather than aspirin is apparent only for those with $CHADS_2$ scores of ≥2.

This can be achieved by using CHA2DS2–VASc [Cardiac failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled)–Vascular disease (prior myocardial infarction, peripheral artery disease, complex aortic plaque), Age 65–74 and Sex category (female =1, male = 0)]. This schema improves on $CHADS_2$ as it classifies a low proportion of subjects into the 'moderate risk' category, and helps better determine the truly 'low risk' patients who have very low event rates and no need for anticoagulation.

There is no evidence that any form of treatment for AF, other than warfarin or aspirin, reduces the risk of stroke regardless of how apparently successful it is in maintaining sinus rhythm. Current guidelines, therefore, recommend indefinite stroke prophylaxis with warfarin or aspirin on the basis of the risk stratification.

It is often difficult to maintain INR levels within the therapeutic range of 2.0–3.0. There is evidence that the INR may be outside of this range up to half of the time. A subtherapeutic INR substantially increases risk of stroke or arterial thromboembolism. Conversely, a high INR increases the risk of bleeding. The approximate annual frequency of major and minor bleeding with warfarin is 3% and 10%, respectively. Patients' and physicians' concern about the use of warfarin has resulted in its under-utilisation, particularly among elderly people, who are at the greatest risk of stroke. These difficulties have led to a search for alternative agents. The most advanced of these achieve their anticoagulant effect by inhibiting a single activated clotting factor, either thrombin (factor IIA) or factor XA. These drugs have a more predictable pharmacological profile that negates the need for frequent monitoring and may represent a step forward in the care of patients with AF. These agents are expected to offer advantages of enhanced or similar efficacy compared with warfarin without an increased risk of major bleeding.

Emergency management. AF associated with unstable angina, heart failure or hypotension requires emergency treatment. In most cases, the treatment of choice is d.c. cardioversion. Concerns about thromboembolism as the heart returns to sinus rhythm are valid but should not delay emergency treatment. Immediate d.c. cardioversion is appropriate when the onset of AF is clearly identified as within 48 h of presentation or when the patient is already taking warfarin and has had a therapeutic INR for at least 4 weeks. If facilities permit, a trans-oesophageal echocardiogram may be performed in patients not already on warfarin in order to exclude intracardiac thrombus. Heparin should then be given immediately and continued until the INR is within the therapeutic range. Anticoagulant therapy should be continued for at least 3 months following cardioversion. Long-term stroke prophylaxis is guided thereafter by the $CHADS_2$ score. If d.c. cardioversion is deemed inappropriate, rapid ventricular rate control may be achieved with intravenous ß-blockers, verapamil or digoxin.

Long-term management. There has been considerable debate about the pros and cons of a rate-control strategy, focusing on achieving adequate control of the ventricular rate with drugs modifying the AV node versus a rhythm-control strategy, in which an attempt is made to restore and maintain sinus rhythm with antiarrhythmic drugs ± d.c. cardioversion. These strategies have been compared in several large-scale prospective randomised trials, which have failed to demonstrate an advantage to a rhythm-control strategy. Sinus rhythm has been associated with a 47% reduction in all-cause mortality, although this benefit was offset by a 49% increase in mortality associated with antiarrhythmic drugs (AFFIRM investigators, 2004). In that study, a wide variety of antiarrhythmic drugs were used at the discretion of the investigator. These included several class I antiarrhythmic drugs, sotalol and amiodarone. A rhythm-control strategy may be more appropriate in (i) younger patients, (ii) those with paroxysmal AF, (iii) AF associated with heart failure and (iv) patients who remain symptomatic despite adequate ventricular rate control.

Ventricular rate control. The mainstay of a ventricular rate-control strategy is the use of drugs which prolong the AV nodal refractory period, thus reducing the ventricular rate. Digoxin may control the ventricular rate at rest but is less successful at controlling the rate during exertion. ß-Blockers or calcium channel blockers (verapamil or diltiazem) are generally effective both at rest and on exertion, although a combination of these drugs is occasionally necessary. Where ventricular rate control cannot be achieved with drugs, catheter ablation of the AV node in combination with permanent pacemaker implantation can provide excellent symptom relief. The adverse effects of right ventricular apical pacing may offset some of the benefit of a slower ventricular rate and regular rhythm and, therefore, biventricular pacing may be more appropriate in this situation.

Rhythm control. Rhythm control can be considered in terms of either restoration or maintenance of sinus rhythm. The most rapid and effective means of restoring sinus rhythm is d.c. cardioversion. Where AF is of short duration, well tolerated and not associated with structural heart disease, class IC antiarrhythmic drugs such as flecainide and class III drugs such as amiodarone may be used intravenously in order to achieve chemical cardioversion. Stroke risk should be managed in the same way as described for the emergency management of AF.

Although sinus rhythm can be restored in most patients through d.c. cardioversion or antiarrhythmic drugs, alone or in combination, most patients will revert to AF without further treatment. The SAFE-T trial examined 665 patients with AF of at least 72 h duration. Sinus rhythm was restored with antiarrhythmic drugs (sotalol or amiodarone) or placebo, supplemented where necessary by d.c. cardioversion (Singh et al., 2005). Patients were then maintained on placebo, sotalol or amiodarone. By 2 years, that probability of remaining in sinus rhythm was 10% (placebo), 30% (sotalol) and 50% (amiodarone). Another similar study (Roy et al., 2000) demonstrated equivalent efficacy of sotalol and the class Ic antiarrhythmic propafenone in the maintenance of sinus rhythm (40% at 2 years) and confirmed the superiority of amiodarone (60%). Most heart rhythm specialists consider that the toxicity of amiodarone precludes its long-term use for the management of AF. Dronedarone, it was hoped, would provide efficacy similar to amiodarone but it has been shown to be less effective, although it has far fewer side effects.

Modern strategies for curative catheter ablation of AF followed the discovery in 1998 that paroxysmal AF is due, in most cases, to rapid firing by the musculature surrounding the pulmonary veins close to their junctions with the left atrium. The cornerstone of most current ablation strategies for paroxysmal AF is complete electrical isolation of all four pulmonary veins from the left atrium, using either radiofrequency ablation (cautery) or cryoablation to ablate in rings around the pairs of ipsilateral veins. Catheter ablation can cure a majority of paroxysmal AF but needs to be repeated in 30–40% of patients and carries risk including stroke (3/1000) and pericardial effusion (1–2/100). Catheter ablation has been shown in small randomised studies to be superior to antiarrhythmic drug therapy in maintaining sinus rhythm and improving symptoms and quality of life. Catheter ablation has also been shown in non-randomised studies to improve left ventricular ejection fraction and heart failure symptoms. No benefit has been demonstrated in terms of reduced stroke risk or mortality. The natural history of AF is for episodes of AF to increase in frequency and duration until persistent AF supervenes. This progression appears to occur as a result of atrial remodelling, a complex and incompletely understood process involving electrical and structural changes in the whole atrial myocardium predisposing to the development of AF independent of the pulmonary veins. Catheter ablation strategies for persistent AF are more complex than those for paroxysmal AF with a correspondingly higher rate of repeat procedures and a lower overall success rate. For all of these reasons, drug therapy remains the first line treatment of AF with catheter ablation reserved for patients with symptomatic AF that cannot be managed satisfactorily with drugs and whose symptoms trouble them enough to wish to undergo ablation.

Ventricular tachyarrhythmias

Ventricular tachycardia

VT is a rapid heart rhythm originating in the ventricles. VT may present with palpitation, chest pain, breathlessness, presyncope, syncope or sudden cardiac death (death occurring suddenly and unexpectedly within 1 h of the onset of symptoms from a presumed cardiac cause). It is clinically useful to subdivide VT in the following ways:

VT complicating structural heart disease. Most VT occurs in patients with significant structural heart disease. Most of these are associated with a healed myocardial infarction but other important causes include hypertensive and valvular heart disease and a variety of cardiomyopathies including dilated, hypertrophic or arrhythmogenic right ventricular cardiomyopathy. VT of this type is usually due to re-entry. Scarring of ventricular myocardium creates the central obstacle around which potential re-entry circuits develop forming the VT 'substrate'. In this setting, a single ventricular premature beat, the VT 'trigger', may induce VT. The importance of VT complicating structural heart disease is that there is a high chance of the VT recurring and patients are at substantially increased risk of sudden cardiac death.

'Normal heart' VT. These uncommon VTs occur in the context of a structurally normal heart and a normal ECG in sinus rhythm and are exemplified by right ventricular outflow tract (RVOT) tachycardia and fascicular tachycardia. The importance of recognising these VTs is that unlike VT associated with structural heart disease, they are associated with a normal prognosis, may be managed successfully with drugs (ß-blockers, verapamil or flecainide for RVOT tachycardia, verapamil for fascicular tachycardia) and are curable by catheter ablation.

Ventricular fibrillation

Ventricular fibrillation (VF) comprises rapid and totally disorganised electrical activity in the ventricles such that effective contraction ceases and results in sudden death unless sinus rhythm is restored either spontaneously or by defibrillation. Acute myocardial ischaemia and infarction are probably responsible for most VF, although virtually any structural heart disease may also be complicated by VF. Other cases occur in the context of a group of conditions known as channelopathies:

Channelopathies. This is a group of inherited conditions characterised by abnormal function of the protein channels present in the cardiac myocyte cell membrane that regulate the flow of ions responsible for generating the resting transmembrane potential and the action potential. These include the long QT syndromes, short QT syndrome, early repolarisation syndrome, Brugada syndrome and catecholaminergic polymorphic VT. A detailed description of these conditions is beyond the scope of this chapter but there are certain key points:

- With the exception of catecholaminergic polymorphic VT, each is associated with characteristic abnormalities of the resting ECG in sinus rhythm.
- Each may be complicated by ventricular tachyarrhythmias and sudden cardiac death.
- ß-Blockers reduce the likelihood of arrhythmia in long QT syndromes and catecholaminergic polymorphic VT.
- Many drugs lengthen the QT interval (Box 22.1) and are contraindicated in patients with long QT syndromes.

Box 22.1 Drugs associated with prolonged QT intervals (adapted from Crouch et al., 2003)

Inhalational agents: halothane, isoflurane
Macrolide antibiotics: erythromycin, clarithromycin
Halofantrine
Lithium
Fosphenytoin
Mizolastine
Phenothiazines
Pentamidine
Sertindole
Antihistamines: terfenadine, astemizole, mizolastine
Antipsychotics: haloperidol, droperidol, pimozole
Tricyclic antidepressants: amitriptyline, imipramine
Class IA or III antiarrhythmics

A list of drugs known to prolong the QT interval can be found at http://www.azcert.org.

- Class I antiarrhythmic drugs and a variety of other drugs are contraindicated in Brugada syndrome. A list of drugs to avoid in the Brugada syndrome can be found at http://www.azcert.org.
- Most patients with these conditions who experience syncope, cardiac arrest or who develop spontaneous ventricular arrhythmias will be considered for an implantable cardioverter-defibrillator (ICD).

Emergency management of ventricular arrhythmias. VF and pulseless VT should be managed according to Resuscitation Council (UK) guidelines for advanced life support, which are updated periodically and can be found at http://www.resus.org.uk.

VT associated with a pulse is also the subject of guidelines by the Resuscitation Council (UK). If the patient is hypotensive in a low cardiac output state or has heart failure, the correct treatment is prompt d.c. cardioversion. If none of these features is present, chemical cardioversion may be attempted with intravenous amiodarone 300 mg over 20–60 min followed by 900 mg over the next 24 h. Amiodarone must be given via a central vein because it can cause thrombophlebitis when given peripherally and limb threatening soft tissue damage if extravasation occurs.

Ongoing management of ventricular arrhythmias. Once stabilised, patients presenting with VT or VF should remain in hospital and their management should be discussed at an early stage with a specialist cardiac electrophysiology service. Investigations should be performed to establish the nature and extent of underlying heart disease, with emphasis on detecting structural heart disease, coronary artery disease, inducible myocardial ischaemia and consideration of channelopathies in those with structurally normal hearts.

Most patients with ischaemic heart disease should be treated with aspirin, statins, angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists and ß-blockers. ß-Blockers and ACE inhibitors reduce somewhat the risk of sudden cardiac death. Although these patients remain at high risk of sudden cardiac death due to recurrent ventricular tachyarrhythmias, there is no role for the routine use of antiarrhythmic drugs. In patients with complex ventricular ectopy and impaired left ventricular systolic function following acute myocardial infarction, class IC antiarrhythmic drugs including flecainide were shown in the CAST study (Echt et al., 1991) to increase mortality while in other high-risk groups amiodarone has been shown to have no effect on all-cause mortality (Cairns et al., 1997; Julian et al., 1997). All patients should be considered for an ICD. These devices have been shown to improve prognosis following:

- Cardiac arrest due to VT or VF in the absence of a reversible underlying cause
- VT associated with syncope or significant haemodynamic compromise
- VT with a left ventricular ejection fraction of less than 35%.

Although ICDs treat further episodes of VT and VF, they do not prevent these arrhythmias from recurring and resulting in device therapies including shocks that are psychologically traumatic and lead to premature battery depletion. In the case of frequently recurring ventricular arrhythmias, patients should be on the maximum tolerated dose of a ß-blocker and there is a role for antiarrhythmic drugs including amiodarone and mexiletine. Catheter ablation of VT is an important adjunctive treatment in this situation.

Bradycardia

Bradycardia is conventionally defined as a resting heart rate below 60 min^{-1} when awake or 50 min^{-1} when asleep. Bradycardia can be classified as sinus bradycardia, where the sinus node discharges too slowly, or AV block ('heart block'), where conduction between the atria and ventricles is impaired. AV block may be subdivided into three classes:

First degree. Every P wave conducts to the ventricles but takes longer than normal to do so. The PR interval on the ECG is prolonged to greater than 200 ms (one large square on a standard ECG).

Second degree. Some but not all P waves conduct to the ventricles. Progressive PR interval prolongation followed by a non-conducted P wave is referred to as Mobitz type I or Wenckebach heart block and implies block occurring in the AV node. Mobitz type II heart block is the term used when a non-conducted P wave is not preceded by progressive PR interval prolongation and implies block occurring in the conducting system below the level of the AV node.

Third degree ('complete heart block'). No P waves conduct to the ventricles.

Bradycardia may be due to intrinsic cardiac disease or secondary to non-cardiac disease or drugs. In many cases, bradycardia due to intrinsic cardiac disease is idiopathic, that is, occurs without other identifiable heart disease. Bradycardia may also complicate acute myocardial infarction or virtually any form of structural heart disease and is also common following cardiac surgery. Non-cardiac causes of bradycardia include vasovagal syncope (faints), hypothyroidism, hyperkalaemia, hypothermia and raised intracranial pressure. Complete heart block may occur as a complication of Lyme disease (tick-borne borreliosis). Drugs commonly associated with bradycardia include ß-blockers, verapamil, diltiazem, digoxin and antiarrhythmic drugs of any class.

The management of bradycardia is as follows:

- Treat underlying medical conditions
- Consider stopping or reducing the dose of causative drugs
- Consider temporary or permanent pacemaker implantation. Permanent pacemaker implantation for sinus bradycardia is indicated for symptom relief whereas in the case of second and third degree AV block permanent pacemaker implantation is indicated on both symptomatic and prognostic grounds.

In an emergency situation, drugs may be used in an attempt to support the heart rate until trans-venous pacing can be established. The most useful drugs in this situation are atropine in 500 µcg boluses up to a total of 3 mg, adrenaline infused at a rate of 2–10 µcg/min or isoprenaline 1–10 µcg/min, titrated

against heart rate. External pacing is another useful measure until transvenous pacing can be established. More detailed guidance on the emergency management of bradycardia may be viewed at http://www.resus.org.uk.

Drug therapy

Antiarrhythmic drug therapy is used to control the frequency and severity of arrythmias, with the aim of maintaining sinus rhythm where possible. Although antiarrhythmic drug treatment has been the mainstay of arrhythmia treatment, many of these drugs have limited efficacy and important toxicity. Many arrhythmias are now curable by catheter ablation. Implantable devices such as permanent pacemakers and ICDs have assumed an increasingly important role in the treatment of arrhythmias and, in many cases, antiarrhythmic drugs have an adjunctive role. Antiarrhythmic drugs can be grouped according to their electrophysiological effects at a cellular level, using the Vaughan–Williams classification. Alternatively, antiarrhythmic drugs may be classified according to their main sites of action within the heart.

Vaughan–Williams Classification

All antiarrhythmic drugs act by altering the movement of electrolytes across the myocardial cell membrane. The Vaughan–Williams classification groups drugs according to their ability to block the movement of one or more of these ions across the myocardial cell membrane. Most drugs have several modes of action, and their effectiveness as antiarrhythmic agents depends upon the summation of these effects. The effect of the different drug classes on the various phases of the action potential in His–Purkinje fibres are shown in Table 22.1. The choice of which drug to use is based upon the origin of the arrhythmia, regardless of its pattern. However, the preference of one class over another may vary, depending on a clinician's experience with particular drugs, on the presentation of the arrhythmia and on patient characteristics. Such factors also govern the choice of drug within a class. The drug chosen should have the dosing schedule and adverse effect profile that best suit the patient or inconvenience them least (see Tables 22.2–22.4). Thus, for example, a patient with glaucoma or prostatism should not be given disopyramide which possesses marked anticholinergic properties, and a patient with obstructive airways disease should preferably not be prescribed a ß-blocker (class II), though if considered essential they could have a cardioselective agent.

The pharmacokinetic profiles of selected antiarrhythmics are presented in Table 22.5.

Table 22.1 Effect of different drug classes on phases of action potential in His–Purkinje fibres

Phase	Dominant ion movement	Drug class	Effect
0	Sodium inward	IA IB IC	Block ++ Block + Block +++
2	Calcium inward	IV	Block
3	Potassium outward	III	Marked slowing
4	Sodium inward, potassium outward	I, II, IV	Slows

Class I

Class I drugs act by blocking the fast sodium channels that are responsible for the rapid depolarisation phase of the cardiac action potential, thus reducing the rate of depolarisation (the slope of phase 0) and the amplitude of the action potential. The conduction velocity of an activation wavefront is determined partly by the slope and amplitude of the cardiac action potential and partly by the resistance to current flow through the myocardium. The effect of sodium channel blockade is a decrease in conduction velocity. Certain re-entrant arrhythmias such as VT complicating previous myocardial infarction depend upon slow conduction in part of the re-entrant circuit. Class I antiarrhythmic drugs may critically slow or even abolish conduction in these areas, thus terminating and/or preventing re-entry.

The action potential in the sinoatrial and AV nodes does not depend on fast sodium channels for depolarisation; instead, phase 0 depolarisation is carried by calcium channels. Class I antiarrhythmic drugs, therefore, have no direct effect on nodal tissue.

In addition to their effect on depolarisation, class I antiarrhythmic drugs may also alter the APD and hence the

Table 22.2 Electrophysiological effects of some antiarrhythmics

Class	Antiarrhythmic agents	Effects on duration of QRS	Effects on duration of QT	Sinus rate
IA	Quinidine, procainamide, disopyramide	+	+	+
IB	Lidocaine (lignocaine), mexiletine, phenytoin	0/–	–	0
IC	Flecainide, propafenone	++	0	––
II	Atenolol, metoprolol, sotalol, esmolol	0	++	––
III	Amiodarone, bretylium, sotalol	0	+++	–
IV	Verapamil, diltiazem, adenosine	0	0	––

+, increased; –, decreased; 0, no change.

Table 22.3 Adverse effects of antiarrhythmic drugs (class I)

Drug	Cardiac	Non-cardiac	Caution or avoid in
Disopyramide	Torsade de Pointes Myodepressant	Anticholinergic (urinary retention, constipation, dry mouth, blurred vision)	Glaucoma, prostatism, hypotension
Procainamide		Lupus, nausea, diarrhoea	Myasthenia gravis, slow acetylators (increased risk of lupus)
Quinidine	Torsade de Pointes Vasodilation (i.v.)	Diarrhoea, nausea, tinnitus, headache, deafness, confusion, visual disturbances, blood dyscrasias	Myasthenia gravis
Lidocaine (lignocaine)		Convulsions in overdose, paraesthesiae	Liver failure (reduce dose)
Mexiletine		Nausea, paraesthesiae	Second or third degree heart block
Flecainide	Proarrhythmic Myodepressant	Paraesthesiae, tremor	Not recommended if any cardiac dysfunction
Propafenone	Proarrhythmic Myodepressant	Gastro-intestinal disturbances	Not recommended if any cardiac dysfunction

Table 22.4 Adverse effects of antiarrhythmic drugs (classes II–IV)

Drug	Cardiac	Non-cardiac	Caution or avoid in
ß-blockers (general)	Myodepressant Heart block	Bronchoconstriction ($ß_2$) Vasoconstriction Hallucinations/vivid dreams (greater with more lipophilic agents) Decreased renal blood flow Changes in serum lipid profile Drowsiness, fatigue	Asthma, COPD, Raynaud's disease, diabetes mellitus, depression
Dofetilide	Torsade de Pointes		Combination with disopyramide or amiodarone or drugs in Table 22.1
Amiodarone	Torsade de Pointes	Hyper-/hypothyroidism, pneumonitis, myopathy, neuropathy, hepatitis, corneal deposits, photosensitivity	Thyroid disease, liver dysfunction, lung disease (e.g. pneumonectomy)
Bretylium	Hypotension	Initial sympathomimetic response, nausea	
Verapamil	Heart block	Constipation, headaches, flushing, ankle oedema, light-headedness	Myasthenia gravis
Adenosine	Heart block	Bronchoconstriction, flushing, chest pain	Asthma, COPD, combination with dipyridamole Decompensated heart failure, patients with a history of convulsions/seizures or recent heart transplant (<1 year)

effective refractory period (ERP) via an effect on potassium channels responsible for action potential repolarisation. Class I antiarrhyhmic drugs are subdivided into three groups according to their effect on APD: class IA drugs increase the APD, class IB drugs shorten the APD, and class IC drugs have no effect on APD. These effects may be assessed by measurement of the QT interval on the ECG, which reflects average ventricular APD.

The properties of class I antiarrhythmic drugs may be summarised as follows:

Table 22.5 Pharmacokinetics of selected antiarrhythmics

	Oral absorption	% protein binding	Elimination, metabolism, half-life (therapeutic range if recommended to be measured)
Amiodarone	Slow, variable	>95	Extensive metabolism, very variable rate, $t_{1/2}$ 2 days initially increasing to 40–60 days
Bretylium	Intravenous/intramuscular only	Unbound	Renal, $t_{1/2}$ 5–10 h
Digoxin	Variable, 70%	25	70% renal, variable, $t_{1/2}$ 36 h (0.8–2 ng/mL)
Diltiazem	40% absorbed	80	Hepatic, $t_{1/2}$ 3 h
Disopyramide	Rapid, >80%	30–90	50% renal, 15% bile, active metabolite, $t_{1/2}$ 4–10 h
Flecainide	Complete, slow	40	30% renal, $t_{1/2}$ 20 h
Lidocaine	Intravenous/intramuscular only	60–80	10% renal, rapid hepatic metabolism to CNS-toxic products, $t_{1/2}$ 8–100 min increases with duration of dosing
Mexiletine	>90%	60–70	10% renal, $t_{1/2}$ 10–12 h, hepatic metabolites mostly inactive
Procainamide	Rapid, >75%	15–20	50% renal, 25–40% converted to *N*-acetylprocainamide (active, $t_{1/2}$ 6 h), procainamide $t_{1/2}$ 2.5–4.5 h
Propafenone	Complete, rapid	>95	Extensive first-pass metabolism, capacity-limited, $t_{1/2}$ 2–12 h
Quinidine	Rapid, >80%	80–90	Mixed renal and hepatic, $t_{1/2}$ 6 h
Verapamil	Rapid, >90%	90	Hepatic, $t_{1/2}$ 4–12 h, marked first-pass effect

All values quoted are subject to marked interindividual variability. Most therapeutic ranges are poorly defined. Oral absorption does not account for drug lost by first-pass hepatic metabolism. Rapid absorption indicates a peak plasma concentration in less than 2 h.
$t_{1/2}$ elimination half-life at normal renal function.

Sodium channel blockade
IC > IA > IB
Effect on APD and ERP
IA prolong
IB shorten
IC no effect

Increasing the APD, and hence the effective refractory period, may terminate and prevent re-entry tachycardias by prolonging the duration that tissue is refractory and prevent re-entrant wavefronts from re-exciting the tissue. Although contributing to the antiarrhythmic effects of these drugs, APD prolongation is also responsible for one of their important adverse effects, Torsade de Pointes.

Class IA antiarrhythmic drugs have additional anticholinergic actions and oppose vagal activity. This can lead to both sinus tachycardia and a shortened refractory period of the AV node, as both the sinus and AV nodes are densely innervated and tonically inhibited by the vagus nerve. One consequence of this effect on the AV node is a more rapid ventricular rate during AF, necessitating co-treatment with drugs such as digoxin, ß-blockers or calcium channel blockers.

Class IA agents

Class IA antiarrhythmic drugs have been used for the treatment of a variety of atrial and ventricular arrhythmias but are now rarely used because of their proarrhythmic (Torsade de Pointes) and non-cardiac side effects and potential for drug interactions.

Quinidine was one of the earliest antiarrhythmic drugs developed. Quinidine, an alkaloid derived from the cinchona tree bark, had a significant role in the treatment of many arrhythmias. After concerns about increased risk of ventricular arrhythmia and death with quinidine emerged, the use of quinidine fell dramatically in favour of newer antiarrhythmic medications.

Disopyramide has been used to treat a wide variety of supraventricular and ventricular arrhythmias. The drug is given orally and excreted by the kidneys, with a half-life of 6–8 h, necessitating frequent dosing. Disopyramide has strong affinity for muscarinic cholinergic receptors (40 times that of quinidine) and commonly causes anticholinergic side effects such as blurred vision, dry mouth, constipation and urinary retention. Disopyramide may precipitate acute glaucoma in predisposed individuals. Disopyramide also causes sympathetic inhibition

resulting in vasodilation. Other adverse effects occur less frequently than with quinidine (e.g. gastro-intestinal, QRS prolongation, Torsade de Pointes and hypotension) and there is no interaction with digoxin.

Procainamide has been used in an initial attempt at the pharmacologic cardioversion of AF of recent onset. Procainamide may be given orally or intravenously. Procainamide is metabolised to *n*-acetyl procainamide. Both have antiarrhythmic activity and are excreted mainly by the kidneys. The half-life of procainamide is short (3–4 h), necessitating frequent dosing. The half-life of *n*-acetyl procainamide is considerably longer than that of procainamide. The risk of a lupus-like syndrome comprising a rash, fever and arthralgia (likeliest in slow acetylators) is about one in three of those patients treated for longer than 6 months. Hypotension due to an inhibitory effect on sympathetic ganglia, QRS and QT interval prolongation are common adverse effects with intravenous administration.

Class IB agents

As a group, class IB agents inhibit the fast sodium current (typical class I effect) while shortening the APD in non-diseased tissue. The former has the more powerful effect, while the latter might actually predispose to re-entrant arrhythmias, but ensures that QT prolongation does not occur. Class IB agents act selectively on diseased or ischaemic tissue, where they are thought to promote conduction block in slowly conducting tissue critical to the maintenance of re-entry, thereby interrupting re-entry circuits.

Lidocaine was previously the standard intravenous agent for the suppression of serious ventricular arrhythmias associated with acute myocardial infarction and following cardiac surgery but has now been almost completely superseded by ß-blockers. Lidocaine acts preferentially on ischaemic myocardium and is more effective in the presence of a high external potassium concentration. Therefore, hypokalaemia must be corrected for maximum efficacy. The kinetics of lidocaine is such that it is rapidly de-ethylated by the liver precluding oral administration. The two critical factors governing lidocaine metabolism, and hence its efficacy, are liver blood flow (decreased in old age and by heart failure and ß-blockade) and drugs that induce or inhibit the enzyme of the cytochrome P450 system. Lidocaine is rapidly distributed within minutes after an initial intravenous loading dose, requiring the need for a continuous infusion or repetitive dosing to maintain therapeutic blood levels. Lidocaine has no value in treating supraventricular tachyarrhythmias.

Mexiletine may be administered intravenously or orally to control VT. Frequent gastro-intestinal and central nervous system (CNS) side effects (dizziness, light-headedness, tremor, nervousness, difficulty with coordination) limit the dose and possible therapeutic benefit.

Class IC agents

The major electrophysioloical effects of these agents are that they are powerful inhibitors of the fast sodium channel causing a marked depression of the upstroke of the cardiac action potential. In addition, they may variably prolong the APD by delaying inactivation of the slow sodium channel and inhibition of the rapid component of the repolarising delayed rectifier current (I_{kr}) which may explain the prolongation of the QRS complex and QT interval. Class IC agents are potent antiarrhythmics used largely in the control of paroxysmal supraventricular and ventricular tachyarrhythmias resistant to other drugs, although they have acquired a particularly bad reputation as a result of the proarrhythmic effects seen in CAST (Cardiac Arrhythmia Supression Trial) and the CASH (Cardiac Arrest Study Hamburg) studies. Faster heart rates, increased sympathetic activity, and diseased or ischaemic myocardium all contribute to the proarrhythmic effects of these drugs. This has led to these drugs being contraindicated in patients with structural heart disease as poor systolic function exaggerates the proarrhythmic effects. However, flecainide is effective for the treatment of both supraventricular and ventricular arrhythmias in patients without structural heart disease and is moderately successful for maintenance of sinus rhythm after cardioversion of AF. Propafenone has mild ß-blocking properties, especially in higher doses so should be avoided in patients with reversible obstructive airways disease.

Class II agents: ß-Adrenoreceptor antagonists (ß-blockers)

$ß_1$- and $ß_2$-adrenoreceptors are present in the cell membranes of myocytes throughout the heart. Activation of ß-adrenoreceptors by norepinephrine released from postganglionic sympathetic neurones and circulating norepinephrine and epinephrine increases the rate of discharge of the sinus node (positive chronotropy), increases the conduction velocity and shortens the refractory period of the AV node (positive dromotropy) and increases the force of contraction (contractility) of myocytes (positive inotropy).

ß-Adrenoreceptors are coupled to G proteins, which activate adenylyl cyclase to form cAMP from ATP. Increased cAMP directly activates the pacemaker current I_f to increase the rate of diastolic depolarisation and hence to increase the sinus rate. cAMP also activates a cAMP-dependent protein kinase (PK-A) that phosphorylates L-type calcium channels, which causes increased calcium entry into the cell. Increased calcium entry during the plateau phase of the action potential leads to enhanced release of calcium by the sarcoplasmic reticulum and hence an increase in contractility. Intracellular calcium overload predisposes to the development of early or late afterdepolarisations which may result in arrhythmias due to triggered activity.

ß-Blockers prevent the normal ligand (norepinephrine or epinephrine) from binding to the ß-adrenoreceptor by competing for the binding site. The antiarrhythmic properties of ß-blockers are probably the result of several mechanisms: (i) reducing the likelihood of arrhythmias due to triggered activity, (ii) opposing the increased sympathetic activity in patients with sustained VT and in patients with acute myocardial infarction and (iii) indirectly preventing arrhythmia via their antihypertensive and anti-ischaemic effect.

ß-Blockers licensed for the treatment of arrhythmias include propranolol, acebutol, atenolol, esmolol, metoprolol and sotalol. The antiarrhythmic activity of the various ß-blockers is reasonably uniform, the critical property being $ß_1$-adrenoreceptor blockade. Atenolol, metoprolol propranolol and esmolol are available for intravenous use. Esmolol, a selective $ß_1$-adrenoreceptor antagonist, has a half-life of 9 min with full recovery from its ß-blockade properties within 30 min. Esmolol is quickly metabolised in red blood cells, independent of renal and hepatic function, and due to its short half-life, can be useful in situations where there are relative contraindications or concerns about the use of a ß-blocker. Sotalol has some class III activity as well as class II effects and bretylium is considered to have class II activity in addition to class III.

The use of ß-blockers is somewhat constrained by their adverse effects. $ß_2$-Adrenoreceptors on bronchial smooth muscle are tonically activated by circulating catecholamines to cause bronchodilation. ß-Blockers can, therefore, cause bronchoconstriction and are contraindicated in patients with asthma and should be used with caution in chronic obstructive pulmonary disease. $ß_2$-Adrenoreceptors are also found on vascular smooth muscle and are tonically activated by circulating catecholamines to cause vasodilatation. ß-Blockers may, therefore, cause vasoconstriction and exacerbate the symptoms of peripheral vascular disease.

Cardiac adverse effects of ß-blockers include sinus bradycardia, exacerbation of AV conduction block, reduced exercise capacity and exacerbation of acute heart failure. In patients with chronic, stable heart failure, however, due to mild to moderate LV systolic dysfunction and already treated by ACE inhibitors and diuretics, ß-blockers improve both symptoms and prognosis. Other adverse effects of ß-blockers include nightmares and impotence.

ß-Blockers vary in their lipid solubility. Agents such as propranolol and carvedilol are highly lipid-soluble whilst others such as atenolol and nadolol are more hydrophilic. Lipid solubility determines the degree of drug penetration into the CNS and the utility of haemodialysis or haemofiltration. High lipid solubility is associated with a larger volume of distribution and better CNS penetration. Lipophilic ß-blockers are primarily metabolised by the liver. Conversely, hydrophilic ß-blockers have a small volume of distribution and are eliminated essentially unchanged by the kidneys; this property allows hydrophilic ß-blockers to be removed by haemodialysis.

Class III agents

Class III antiarrhythmic drugs prolong cardiac APD by inhibiting repolarising outward potassium currents I_{Kr} and/or I_{Ks}. This action prolongs the effective refractory period, reducing the likelihood of arrhythmias due to re-entry. Prolongation of cardiac APD is reflected by QT interval prolongation on the ECG. Primary indications for class III agents are AF, atrial flutter and ventricular tachyarrhythmias.

Class III drugs include amiodarone, sotalol and bretylium. Amiodarone has additional class I, II and IV activity while sotalol has marked class II activity. An important limitation of class III agents is that action potential prolongation may be complicated by Torsade de Pointes. The development of Torsade de Pointes is attributed to a combination of triggered activity as a result of EADs and increased transmural dispersion of repolarisation within the ventricles as action potential prolongation is not uniform across the ventricular wall. Hypokalaemia, hypomagnesaemia or bradycardia increase the likelihood of Torsade de Pointes and, therefore, sotalol, with marked class II activity, may be uniquely arrhythmogenic.

Amiodarone. Amiodarone is a potent antiarrhythmic drug that is effective in treating a wide variety of atrial and ventricular arrhythmias but its use is constrained by complex pharmacokinetics and concern about toxicity. Many heart rhythm specialists would consider that the side effect profile of amiodarone precludes its use for the long-term treatment of atrial arrhythmias. Amiodarone may be extremely effective in the emergency treatment of VT and ventricular fibrillation, especially where recurrent. Amiodarone may also reduce the likelihood of recurrent ventricular arrhythmias when taken on a long-term basis but confers no prognostic benefit and should be considered as an adjunct to treatment with an ICD.

When rapid control of an arrhythmia is needed, the intravenous route is preferred, with 300 mg given over 30 min to an hour followed by 900 mg over 23–24 h, administered through a central vein. Higher loading doses may cause hypotension. A concurrent oral loading regimen of up to 2400 mg daily in two to four divided doses is usually given for 7–14 days and then reduced to a maintenance dose of 200 mg daily or less.

During the early stages of therapy with amiodarone (whether intravenous or oral), the kinetics of the drug are different from those after chronic administration. Amiodarone is highly lipid soluble and so has a very large volume of distribution. As the slowly equilibrating tissue stores are penetrated to a minimal extent during the early days of therapy, the effective elimination half-life ($t_{1/2}$) is initially dependent upon a more rapidly exchanging compartment, with a $t_{1/2}$ of 10–17 h, substantially shorter than the $t_{1/2}$ seen during chronic administration. The short $t_{1/2}$ becomes important during the acute phase and any intravenous to oral changeover period because the absorption of oral amiodarone is very slow, taking up to 15 h. The combination of a relatively fast elimination and a poor rate of absorption could lead to a significant fall in serum amiodarone levels if intravenous therapy is stopped abruptly when oral therapy is initiated, with the period of maximum risk being the first 24 h of oral therapy. It is, therefore, advisable to phase out intravenous therapy gradually and allow an intravenous/oral overlap period of at least 24 h. Once amiodarone has reached saturation, amiodarone is eliminated very slowly, with a half-life of about 25–110 days. Due to amiodarone's long terminal half-life, there is a potential for drug interactions to occur several weeks (or even months) after treatment with it has been stopped. Common interactions include antibacterials, other antiarrhythmics, lipid-regulating drugs and digoxin.

Amiodarone has been associated with toxicity involving the lungs, thyroid gland, liver, eyes, skin, and peripheral nerves. The incidence of most adverse effects is related to total

amiodarone exposure (i.e. dosage and duration of treatment). Therefore, practitioners must consider carefully the risk–benefit ratio of the use of amiodarone in each patient, use the lowest possible dose of amiodarone, monitor for adverse effects and, if possible, discontinue treatment if adverse effects occur.

Corneal microdeposits (reversible on withdrawal of treatment) develop in nearly all adult patients given prolonged amiodarone; these rarely interfere with vision, but drivers may be dazzled by headlights at night. However, if vision is impaired or if optic neuritis or optic neuropathy occur, amiodarone must be stopped to prevent blindness. Long-term administration of amiodarone is associated with a blue-grey discoloration of the skin. This is more commonly seen in individuals with lighter skin tones. The discoloration may revert upon cessation of the drug. However, the skin color may not return completely to normal.

Individuals taking amiodarone may become more sensitive to the harmful effects of UV-A light. Using sunblock that also blocks UV-A rays appears to prevent this side effect. Amiodarone contains iodine and can cause disorders of thyroid function. Both hypothyroidism and hyperthyroidism may occur. Clinical assessment alone is unreliable and laboratory tests should be performed before treatment and every 6 months including tri-iodothyronine (T3), T4 and thyroid stimulating hormone (TSH). A raised T3 and T4 with a very low or undetectable TSH concentration suggests the development of thyrotoxicosis. Amiodarone-associated thyrotoxicosis may be refractory to treatment and amiodarone should usually be withdrawn, at least temporarily, to help achieve control, although treatment with carbimazole is often required. Hypothyroidism can be treated safely with replacement therapy without the need to withdraw amiodarone if amiodarone is considered essential. Amiodarone is also associated with hepatotoxicity and treatment should be discontinued if severe liver function abnormalities or clinical signs of liver disease develop.

The most serious adverse effect of amiodarone therapy is pulmonary toxicity, typically acute pneumonitis or more insidious pulmonary fibrosis. In early studies, the frequency of pulmonary toxicity during amiodarone therapy was 2–17%. More recent studies have shown a lower incidence in patients receiving dosages of 300 mg/day or less. Although acute pneumonitis may respond to corticosteroids, pulmonary fibrosis is largely irreversible.

Class IV agents

The plateau phase of the cardiac action potential results from the inward movement of Ca^{2+} ions balanced by the outward movement of K^+ ions. Class IV agents (calcium channel blockers) block the inward movement of calcium ions during phase 2 by binding to L-type calcium channels on cardiac myocytes. The effect of class IV antiarrhythmic drugs is most marked in the sinoatrial and AV nodes, in which depolarisation is dependent upon calcium channels. Class IV antiarrhythmic drugs, therefore, cause sinus bradycardia (negative chronotropic effect), and, by reducing the conduction velocity and prolonging the AV nodal effective refractory period, reduce the ventricular rate during atrial tachyarrhythmias such as AF and flutter (negative dromotropic effect). By reducing intracellular calcium concentration class IV antiarrhythmic drugs also exert a negative inotropic effect. Only the non-dihydropyridine calcium channel blockers (verapamil and diltiazem) have direct cardiac effects.

Verapamil possesses a chiral carbon and is marketed as a racemic mixture of R- and S-stereoisomers. In humans, both isomers share qualitatively similar negative chronotropic and dromotropic effects on the sinoatrial and AV nodes, respectively, but the S-stereoisomer is 10–20 times more potent than the R with respect to these effects. Hence, the S-stereoisomer determines the negative chronotropic and dromotropic effects of verapamil, while the R-stereoisomer is of minor importance.

Verapamil also undergoes extensive stereoselective first-pass hepatic metabolism. S-verapamil is more rapidly metabolised than R-verapamil after oral administration, resulting in a lower bioavailability of the S-stereoisomer and a proportionally higher concentration of the R-stereoisomer in the systemic circulation (20% and 50%, respectively). However, because C_{max} is higher with the immediate-release formulation and S-verapamil is 10–20 times more potent than R-verapamil, it is unsurprising that this difference is also clinically significant. With the immediate-release formulation, a plot of PR-interval change versus time has the same shape as the concentration–time curve. The extended-release formulation does not have the same concentration–time effect relationship. This has been attributed to the difference in oral input rates, to the concentration-related saturable first-pass hepatic metabolism, or both.

Since the formulation of verapamil may play a role in the drug's complex pharmacokinetics and efficacy, one formulation of verapamil cannot be safely substituted for another. Immediate release preparations are preferred to maximise bioavailability of the S-stereoisomer.

Class IV antiarrhythmic drugs should be avoided in sick sinus syndrome or second- or third-degree heart block unless the patient has a permanent pacemaker. Combined therapy with a calcium channel blocker and ß-blocker should be instituted with caution because of the risk of excessive AV block, and should be used where only where monotherapy is insufficient to control ventricular rate during atrial flutter or fibrillation. Verapamil causes greater arterial vasoodilation than diltiazem and may be especially useful in patients with hypertension or angina. Both agents have a negative inotropic effect and are thus contraindicated in heart failure. Adverse effects are mostly predictable and include ankle oedema, flushing, dizziness, light-headedness and headache. Constipation is common in patients receiving verapamil whilst a rash is common with diltiazem.

Adenosine

The potassium channel opener adenosine and its pro-drug adenosine triphosphate (ATP) act as indirect calcium antagonists and resemble verapamil in their antiarrhythmic activity.

In cardiac tissue, adenosine binds to adenosine type 1 (A_1) receptors, which are coupled to Gi proteins. Activation of this pathway opens transmembrane potassium channels, which hyperpolarises the cell. Activation of the Gi protein also decreases cAMP, which inhibits L-type calcium channels and, therefore, calcium entry into the cell. In cardiac pacemaker cells located in the sinoatrial node, adenosine acting through A_1 receptors inhibits the pacemaker current (I_f), which decreases the slope of phase 4 of the pacemaker action potential thereby decreasing its spontaneous firing rate (negative chronotropy). Inhibition of L-type calcium channels also decreases conduction velocity of the AV node (negative dromotropy). Finally, adenosine, by acting on presynaptic purinergic receptors located on sympathetic nerve terminals, inhibits the release of norepinephrine.

The ultra-short duration of action (<10 s) of intravenous adenosine makes it very suitable as a diagnostic aid and for interrupting supraventricular arrhythmias in which the AV node is part of the re-entry pathway. Adenosine is, however, a bronchoconstrictor and causes dyspnoea, flushing, chest pain and further transient arrhythmias in a high proportion of patients, and its metabolism is inhibited by dipyridamole, a vasodilator drug that blocks adenosine uptake by cells, thereby reducing the metabolism of adenosine.

Digoxin

Digitalis compounds are potent inhibitors of transmembrane Na^+/K^+-ATPase. This ion transport system moves sodium ions out of the cell in exchange for potassium ions. The consequent rise in the intracellular sodium concentration increases the activity of a transmembrane Na^+/Ca^+ exchanger in cardiac myocytes as well as many other cells, which moves sodium out of the cell in exchange for calcium. The resulting increased intracellular calcium concentration stimulates calcium release from the sarcoplasmic reticulum which increases contractility (positive inotropic effect).

Digoxin also acts on the autonomic nervous system to increase vagal tone and reduce sympathetic nervous activity, reducing conduction velocity and increasing the effective refractory period of the AV node. Digoxin, therefore, reduces the ventricular rate during persistent atrial flutter and AF and may be particularly useful in patients with these arrhythmias in the context of congestive cardiac failure. Digoxin has limited efficacy in controlling the ventricular rate in situations where the sympathetic nervous system predominates such as during exercise. It is, therefore, only useful as monotherapy in sedentary patients. ß-Blockers and calcium channel blockers are more useful for controlling the ventricular rate on exertion as well as at rest.

Digoxin is no longer indicated for the treatment of paroxysmal AF as it has no direct antiarrhythmic effect and neither terminates an episode of AF nor reduces the likelihood of further episodes of AF occurring. Furthermore, digoxin has limited efficacy for ventricular rate control at the start of an episode of AF where sympathetic nervous system activity is often high.

The positive inotropic effect of digoxin has long been used in the treatment of patients with systolic heart failure and sinus rhythm. As evidence emerged that other positive inotropic agents such as milrinone increase mortality in heart failure the role of digoxin was reexamined. Perhaps the largest and best designed of these trials, the Digitalis Investigation Group (1997) trial, established that digoxin had no effect on all-cause mortality in patients with stable congestive cardiac failure, a left ventricular ejection fraction of under 45% and sinus rhythm but significantly reduced a combined endpoint of CHF mortality and hospitalisation due to heart failure. With a large body of evidence attesting to the morbidity and mortality benefits of ACE inhibitors, ß-blockers and spironolactone the role of digoxin has diminished. Digoxin may still be useful in patients who remain symptomatic despite comprehensive therapy with these drugs.

The long half-life of digoxin (about 36 h) warrants special consideration when treating arrhythmias as several days of constant dosing would be required to reach steady-state. Therefore, loading doses of up to 1.5 mg may be used rapidly to increase digoxin serum levels. Digoxin is given once daily thereafter, usually in 125 or 250 µcg doses and has a narrow therapeutic window with the ideal blood concentration regarded as 1–2 µcg/L. Since digoxin is excreted predominantly by the kidney (70% renal elimination in normal renal function), renal function is the most important determinant of the daily digoxin dosage. Importantly, in severe renal insufficiency, there is also a decrease in the volume of distribution of digoxin and, therefore, lower loading doses should be used.

Both the therapeutic and toxic effects of digoxin are potentiated by hypokalaemia and hypercalcaemia. There are also numerous drug interactions (Table 22.6), some of which are pharmacokinetic and some of which are pharmacological.

The occurrence of adverse drug reactions is common, owing to the narrow therapeutic index of digoxin. Adverse effects are concentration-dependent, and are rare when serum digoxin concentration is less than 0.8 µcg/L. Common adverse effects

Table 22.6 Interactions involving digoxin

Effect	Offending agent or condition
Serum level increased by	Amiodarone, verapamil, diltiazem, quinidine, propafenone, clarithromycin, broad-spectrum antibiotics (erythromycin, tetracyclines), decreased renal blood flow (ß-blockers, NSAIDs), renal failure, heart failure
Serum level decreased by	Colestyramine, sulfasalazine, neomycin, rifampicin, antacids, improved renal blood flow (vasodilators), levothyroxine (thyroxine)
Therapeutic effect increased by	Hypokalaemia, hypercalcaemia, hypomagnesaemia, antiarrhythmic classes IA, II, IV, diuretics that cause hypokalaemia, corticosteroids, myxoedema, hypoxia (acute or chronic), acute myocardial ischaemia or myocarditis
Therapeutic effect decreased by	Hyperkalaemia, hypocalcaemia, thyrotoxicosis

include loss of appetite, nausea, vomiting and diarrhoea as gastro-intestinal motility increases. Other common effects are blurred vision, visual disturbances (yellow-green halos and problems with colour perception), confusion and drowsiness. The often described adverse effect of digoxin, xanthopsia, the disturbance of colour vision (mostly yellow and green colour) is rarely seen.

Patient care

Patients with arrhythmias may experience considerable anxiety about the possibility that they will have a serious arrhythmia at any moment and may, therefore, require considerable reassurance with regular follow-up. The patient's family and friends may need to be advised on what to do in the event of an acute arrhythmia. An individual's anxiety may not be helped by the fact that most antiarrhythmic drugs work in only a proportion of patients and several treatment options may be tried before the most appropriate one is identified.

Patients should give informed consent for all interventions, and prescribers must be prepared for a patient to have a different view on the use of a medicine compared to their own. This was illustrated in a study of patients' and prescribers' attitudes to the use of aspirin and warfarin for stroke prevention in AF. Not only did prescribers differ markedly on the balance of risks between stroke prevention and bleeding caused by treatment but patients feared a stroke more than doctors. Prescribers should seek and respect patients' views on such treatment choices, rather than assume all patients are the same or that they will always agree with their own views.

Examples of some common therapeutic problems that may occur during the management of arrhythmias are set out in Table 22.7.

Table 22.7 Common therapeutic problems in the management of arrhythmias

Problem	Comment
All antiarrhythmics are proarrhythmic	Prevention is better than cure. Minimise the requirement for drugs by careful attention to precipitating factors. Consider use of pacemakers or non-pharmacological therapies if appropriate
Nausea and vomiting with blurred vision and visual discolouration on digoxin	Symptoms and signs of digoxin toxicity noting digoxin has a narrow therapeutic range. Poor renal function may have also contributed
ß-Blockers are generally contraindicated in bronchial and peripheral vascular disease	Consider verapamil or diltiazem
Calcium channel blockers-induced constipation	If it occurs, give regular osmotic laxatives
Torsade de Pointes may be precipitated by taking other medication with amiodarone or disopyramide	Patients should remind members of health care team that they are taking antiarrhythmic drugs, as well as consider electrolyte disturbance such as hypokalaemia
Patients experiencing myopathy	Healthcare professionals involved in screening prescriptions for antiarrhythmics should be aware of the clinically relevant interactions and how to manage these. Patients who are taking statins will need regular monitoring for signs of myopathy, particularly those on high-intensity statin therapy
Severe asthmatic patient admitted with SVT	Adenosine is contraindicated due to the risk of bronchospasm. Verapamil is a suitable alternative
Amiodarone is commonly associated with an increased tendency to sunburn	Warn all patients to stay covered up when outdoors, use sun block or stay indoors
Acutely treated patient with AF cardioverted initially with i.v. amiodarone, but on converting to oral therapy, converted back to AF	While amiodarone has a long terminal half-life once saturated, amiodarone has a very large volume of distribution and since tissue stores are penetrated to a minimal extent during the early days of therapy, the effective elimination half-life ($t_{1/2}$) is initially dependent upon a more rapidly exchanging compartment, with a $t_{1/2}$ of 10–17 h, substantially shorter than the $t_{1/2}$ seen during chronic administration. The shorter $t_{1/2}$ becomes important during the acute phase and any intravenous to oral changeover period because the absorption of oral amiodarone is very slow, taking up to 15 h. The combination of a relatively fast elimination and a poor rate of absorption could lead to a significant fall in serum amiodarone levels if intravenous therapy is stopped abruptly when oral therapy is initiated, with the period of maximum risk being the first 24 h of oral therapy. It is, therefore, advisable to phase out intravenous therapy gradually and allow an intravenous/oral overlap period of at least 24 h

SVT, supraventricular tachycardia; AF, atrial fibrillation.

Case studies

Case 22.1

A 25-year-old female presents to the hospital emergency department with a 2-h history of palpitation and chest tightness. She has experienced several similar episodes in the past, all of which have started abruptly at rest, and consisted of rapid, regular palpitations. Previous episodes have all stopped after a few minutes and between events she has been entirely well. She has no history of heart disease or other ongoing medical problems and is on no regular drug treatment. She drinks alcohol within recommended weekly limits and takes no other recreational drugs. On examination she is anxious, has a slightly cool periphery, her pulse is 190 bpm and regular and blood pressure is 130/90 mmHg. The remainder of the examination is unremarkable. A 12-lead ECG demonstrates a regular narrow-complex tachycardia with no discernible P waves.

Question

What is the most likely diagnosis and how should she be managed?

Answer

The patient has the signs and symptoms of SVT. Non-pharmacological means of restoring sinus rhythm include carotid sinus massage, subjecting the patient to the Valsalva manoeuvre or eliciting the diving reflex by immersion of the face in ice-cold water. Either approach should result in a brief vagal discharge sufficient to block conduction in the AV node and terminate the tachycardia. If these manoeuvres are unsuccessful, intravenous adenosine can be given in doses of up to 12 mg as a rapid bolus injection followed quickly by a saline flush. Intravenous verapamil 5 mg may also be administered as a rapid bolus injection and is a good alternative where adenosine is contraindicated.

Case 22.2

Mr DS was admitted to hospital for an emergency laparotomy for a perforated gut. He has a history of paroxysmal atrial fibrillation (AF) for which he is on long-term amiodarone 200 mg once daily.

Following the laparotomy he has new onset AF which the medical team would like to treat pharmacologically. His only other current medication is thromboprophylaxis with enoxaparin 20 mg once daily.

Questions

1. What treatment plan would you initially suggest?
2. What long-term monitoring would be appropriate for Mr DS?

Answers

1. If Mr DS has any electrolyte abnormalities these should be corrected. If he remains in AF he should be prescribed amiodarone by IV infusion, as the long-term maintenance dose is clearly no longer adequate following the laparotomy.

The reduced dose of enoxaparin should be noted. This is because Mr DS is a post surgical patient and at high risk of bleeding.

Mr DS cardioverts back to sinus rhythm following a bolus dose of 300 mg amiodarone. The plan is to maintain him on amiodarone long term.

2. Given that Mr DS is to continue amiodarone long term the following monitoring would be appropriate:

Chest X-ray: pulmonary	Baseline and if symptoms present
Thyroid panel	Baseline and every 3–6 months
Liver panel	Baseline and every 3–6 months
Eye examination	Baseline and every 12 months
ECG	Baseline and as required
Clinical evaluation	Baseline and every 3 months

Case 22.3

Mr SB is 77 years of age who attends the hospital emergency department with worsening shortness of breath. His previous medical history includes a myocardial infarction 10 years ago which left him with left ventricular dysfunction (ejection fraction < 40%). He also has hypertension. His current medication includes:

Bisoprolol 5 mg daily
Ramipril 5 mg daily
Aspirin 75 mg daily
Furosemide 80 mg each morning.

His heart rate is 65 bpm and irregular, and he has a blood pressure of 160/85 mmHg. Mr SB's ECG shows atrial fibrillation (AF). It was decided to control his AF with bisoprolol with no alteration of dose.

Questions

1. What drug is most appropriate for stroke prevention in Mr SB?
2. The junior doctor asks you whether warfarin should be initiated along with aspirin or in place of it.

Answers

1. All patients presenting with AF (or atrial flutter) should undergo assessment of their risk of stroke. Although various risk stratification schemes exist, the $CHADS_2$ score is widely used. For Mr SB the following is determined:

Congestive cardiac failure 1
Hypertension 1
Age >75 years 1
Diabetes mellitus 0
Stroke 0

Given Mr SB has a $CHADS_2$ score of 3 this suggests an annual stroke risk of 5.9% if no therapy is prescribed. This risk will reduce to 4.7% if he is prescribed aspirin, or 2.1% if he is prescribed warfarin. Assuming no contraindications or concerns, warfarin should be prescribed.

2. In patients with stable vascular disease, such as those with no acute ischaemic events or PCI/stent procedure in the preceding year, warfarin monotherapy should be used. Concomitant antiplatelet therapy should not be prescribed. Published data support the use of warfarin for secondary prevention in patients with coronary artery disease. Warfarin is at least as effective as aspirin. It should be noted that any combination of an antiplatelet agent with a vitamin K antagonist such as warfarin will significantly increase the risk of a major bleed.

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23 Thrombosis

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Key points

Venous thromboembolism (VTE)

- VTE has an incidence of 2–5%.
- Combinations of sluggish blood flow and hypercoagulability are the commonest causes of VTE. Vascular injury is also a recognised causative factor.
- Treatment of VTE involves the use of anticoagulants and, in severe cases, thrombolytic drugs.
- Anticoagulant therapy usually involves an immediate-acting agent such as heparin followed by maintenance treatment with warfarin.
- Unfractionated heparins increase the rate of interaction of thrombin with antithrombin III 1000-fold and prevent the production of fibrin from fibrinogen.
- Low molecular weight heparins inactivate factor Xa, have a longer half-life and produce a more predictable response than unfractionated heparins.
- Warfarin is the most widely used coumarin because of potency, reliable bioavailability and an intermediate half-life of elimination (36 h).
- Warfarin consists of an equal mixture of two enantiomers, (*R*)- and (*S*)-warfarins, that have different anticoagulant potencies and routes of metabolism.

Arterial thromboembolism

- Arterial thromboembolism is normally associated with vascular injury and hypercoagulability.
- Acute myocardial infarction is the commonest form of arterial thrombosis.
- Arterial thromboembolism affecting the cerebral circulation results in either transient ischaemic attacks (TIAs) or, in severe cases, cerebral infarction (stroke).

Thrombosis is the development of a 'thrombus' consisting of platelets, fibrin, red cells and white cells in the arterial or venous circulation. If part of this thrombus in the venous circulation breaks off and enters the right heart, it may be lodged in the pulmonary arterial circulation, causing pulmonary embolism (PE). In the left-sided circulation, an embolus may result in peripheral arterial occlusion, either in the lower limbs or in the cerebral circulation (where it may cause thromboembolic stroke). Since the pathophysiology of each of these conditions differs, they will be discussed separately under the headings 'Venous thromboembolism' (VTE) and 'Arterial thromboembolism'.

Venous thromboembolism

Epidemiology

VTE is common, with an incidence of 2–5%. PE is now the commonest cause of maternal death, and deep vein thrombosis may result in not only PE but also subsequent morbidity as a result of the post-phlebitic limb. Thromboembolism appears to increase in prevalence over the age of 50 years, and the diagnosis is more often missed in this age group.

Aetiology

VTE occurs primarily due to a combination of stagnation of blood flow and hypercoagulability. Vascular injury is also a recognised causative factor but is not necessary for the development of venous thrombosis. In VTE, the structure of the thrombus is different from that in arterial thromboembolism. In the former, platelets seem to be uniformly distributed through a mesh of fibrin and other blood cell components, whereas in arterial thromboembolism the white platelet 'head' is more prominent and it appears to play a much more important initiatory role in thrombus.

Sluggishness of blood flow may be related to bed rest, surgery or reduced cardiac output, for example in heart failure. Factors increasing the risk of hypercoagulability include surgery, pregnancy, oestrogen administration, malignancy, myocardial infarction and several acquired or inherited disorders of coagulation (for further detail of genetic factors, see Rosendaal and Reitsma, 2009).

Protein C deficiency

Protein C deficiency is inherited by an autosomal dominant transmission. Such patients are at increased risk not only of VTE but also of warfarin skin necrosis. This occurs because protein C (and its closely related co-factor, protein S) is a vitamin K-dependent antithrombotic factor that can be further suppressed by the administration of warfarin. Thrombosis in the small vessels of the skin may occur if large loading (induction) doses of warfarin are given to such patients when the suppression of the antithrombotic effects of these factors occurs before the antithrombotic effects of blockade of vitamin K-dependent clotting factor (II, VII, IX and X) production has occurred. Although the prevalence of protein C deficiency is 0.2%, only one subject in 70 (i.e. 0.0003%) will be

symptomatic, and the condition accounts for around 4% of patients presenting with thromboembolic disease before the age of 45 years.

Protein S deficiency

Protein S deficiency is probably even rarer than protein C deficiency, but the familial form, inherited in an autosomal dominant fashion, is a high-risk state, accounting for possibly 5–8% of cases of thromboembolism in patients less than 45 years old.

Factor V Leiden

The presence of factor V Leiden, a point mutation in the factor V gene, causes the activated factor V molecule to be resistant to deactivation by activated protein C (APC). This defect may have a prevalence of 5% in Caucasian populations, and higher in patients with thromboembolic disease, and may in itself be of little consequence until there is another risk factor, such as immobility and use of the contraceptive pill. In these circumstances, the combination of risks may be responsible for the increased predisposition to thromboembolism in a high proportion of affected individuals.

Antithrombin III deficiency

Antithrombin III deficiency is a rare autosomal dominantly inherited abnormality associated with a reduced plasma concentration of this protein. The defect may not result in clinical problems until pregnancy or until patients enter their fourth decade, when venous and (to a lesser extent) arterial thrombosis becomes more common. Nevertheless, it has been estimated to be responsible for between 2% and 5% of thromboembolism occurring before age 45.

Lupus anticoagulant

Lupus anticoagulant, an antibody against phospholipid, is so named because it increases the clotting time in blood when measured by some standard coagulation tests. Patients affected are more prone to thromboembolism. This factor is found in 10% of patients with systemic lupus erythematosus (SLE) where it is associated with a threefold increase in thromboembolic risk; it is also found in the primary antiphospholipid syndrome (PAPS), where it may signify an increased risk of venous and arterial thrombosis and of recurrent miscarriage.

Prothrombin 20210 mutation

A mutation in part of the prothrombin gene (prothrombin 20210A) results in increased prothrombin concentrations and an increased risk of venous thrombosis. Carriers have a two- to threefold increased risk of venous thrombosis, and the variant is found with similar frequency as factor V Leiden in Caucasian populations.

Fibrinogen gamma 10034T

Approximately 6% of individuals carry this variant gene, which increases thrombotic risk approximately twofold.

Oestrogens

Oestrogens increase the circulating concentrations of clotting factors I, II, VII, VIII, IX and X and reduce fibrinolytic activity. They also depress the concentrations of antithrombin III, which is protective against thrombosis. This effect is dose-related, and venous thrombosis was more often seen with the high (50 μcg) oestrogen-containing contraceptive pill than with the present lower dose preparations. Hormonal replacement therapy, pregnancy and the puerperium (up to 6 weeks after delivery) are also recognised risk factors for VTE.

Malignancy

VTE is also commoner in malignancy (the risk may be up to fivefold greater). Although first described in association with carcinoma of the pancreas, all solid tumours seem to be associated with this problem. This may be related to the expression of tissue factor or factor X activators, but several other mechanisms may also be responsible. Cancer treatment also appears to be a risk factor.

Surgery

The increased risk of VTE in surgery is related in part to stagnation of venous blood in the calves during the operation and also to tissue trauma, since it appears to be more common in operations that involve marked tissue damage, such as orthopaedic surgery. This may in turn be related to release of tissue thromboplastin and to reduced fibrinolytic activity. The most important risk factors associated with clinical thromboembolism after surgery are age, varicose veins with associated phlebitis and obesity (body mass index > 30 kg/m^2), prolonged immobility or continuous travel of greater than 3 h approximately 4 weeks before or after surgery.

Other risk factors

There are several other patient-related risk factors for VTE. Age over 60 years is an important factor. Critical care admission, dehydration, and one or more significant medical comorbidities such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases and inflammatory conditions are all important risk factors for VTE. A full list can be found in the relevant National Institute for Health and Clinical Excellence (2010) guideline.

Clinical manifestations

In 90% of patients, deep vein thrombosis occurs in the veins of the lower limbs and pelvis. In up to half of cases, this may not result in local symptoms or signs, and the onset of PE may be the first evidence of the presence of VTE. In other cases, patients classically present with pain involving the calf

or thigh associated with swelling, redness of the overlying skin and increased warmth. In a large deep venous thrombosis that prevents venous return, the leg may become discolored and oedematous. Massive venous thrombus can occasionally result in gangrene, although this occurs very rarely now that effective drug therapies are available.

PE may occur in the absence of clinical signs of venous thrombosis. It may be very difficult to diagnose because of the non-specificity of symptoms and signs. Clinical diagnosis is often made because of the presence of associated risk factors. Obstruction with a large embolus of a major pulmonary artery may result in acute massive PE, presenting with sudden shortness of breath and dull central chest pain, together with marked haemodynamic disturbance, for example severe hypotension and right ventricular failure, sometimes resulting in death due to acute circulatory failure unless rapidly treated.

Acute submassive pulmonary embolus occurs when less than 50% of the pulmonary circulation is occluded by embolus, and the embolus normally lodges in a more distal branch of the pulmonary artery. It may result in some shortness of breath but if the lung normally supplied by that branch of the pulmonary artery becomes necrotic, pulmonary infarction results with pleuritic pain and haemoptysis (coughing up blood), and there may be a pleural 'rub' (a sound like Velcro® being torn apart when the patient breathes in) as a result of inflammation of the lung. Patients may, rarely, develop recurrent thromboembolism. This may not result in immediate symptoms or signs but the patient may present with increasing breathlessness and signs of pulmonary hypertension (right ventricular hypertrophy) and, if untreated, progressive respiratory failure.

Investigations

Deep vein thrombosis

Although several conditions may mimic deep vein thrombus, such as a Baker's cyst, which involves rupture of the posterior aspect of the synovial capsule of the knee, deep vein thrombosis is the commonest cause of pain, swelling and tenderness of the leg. The clinical diagnosis of venous thrombosis is relatively unreliable, and venography is the most specific diagnostic test.

Venography. Venography involves injection of radio-opaque contrast medium, normally into a vein on the top of the foot, and subsequent radiography of the venous system.

Ultrasound. Ultrasound is a non-invasive alternative to venography that does not involve exposure to ionizing radiation or potentially allergenic contrast media. It is now the initial investigation of choice in clinically suspected deep vein thrombosis, although it is less sensitive for below-knee and isolated pelvic deep vein thrombosis.

Magnetic resonance imaging (MRI). MRI is also non-invasive and avoids radiation exposure. When used with direct thrombus imaging (DTI), which detects methaemoglobin in the clot, MRI DTI is sensitive and specific, even with below-knee and isolated pelvic deep vein thrombosis. However, it is not widely clinically available and ultrasound remains the primary initial investigation.

Pulmonary embolism

Pulmonary arteriography. The diagnosis of PE is most often made using one of two techniques: pulmonary arteriography or ventilation–perfusion scanning. Pulmonary arteriography is the most specific test. This requires catheterisation of the right side of the heart and an injection of contrast medium into the pulmonary artery. Adequate facilities and experienced personnel are, therefore, required and it is now generally reserved for those situations where massive or submassive PE is suspected but non-invasive tests have given indeterminate results.

Ventilation–perfusion scanning. Ventilation–perfusion scanning involves the injection of a radiolabelled substance into the vein and measurement of perfusion via the pulmonary circulation, using a scintillation counter. This is often combined with a ventilation scan in which radiolabelled gas, normally xenon, is inhaled by the patient. PE classically results in an area of under- or non-perfusion of a part of the lung that, nevertheless, because the airways are patent, ventilates normally. This pattern is called ventilation–perfusion mismatch and is a specific sign of PE.

Spiral computed tomography. Computed tomography angiography (CT angiography) using helical or spiral CT (sCT) is now being increasingly used in some centres and has a high accuracy rate. Although subsegmental emboli can be missed, visualisation of smaller arterial branches, and therefore detection of small emboli, may improve with the availability of multidetector scanners. Not only does sCT enable direct visualisation of emboli, but also visualisation of the lung parenchyma and mediastinum may help in the differential diagnosis in non-embolic cases. MRI is also being developed for the diagnosis of PE and early results are promising.

Other findings. Other findings occur in PE, such as changes in the chest radiograph, for example a raised right hemidiaphragm as a result of loss of lung volume (PE more commonly affects the right than the left lung). Hypoxia is also seen, and the larger the pulmonary embolus the worse this is. The electrocardiogram may show signs of right ventricular strain. The echocardiogram may show right ventricular overload and dysfunction in massive PE. However, all these changes are relatively non-specific and do not obviate the need for the specific tests mentioned above.

Treatment

The aim of treatment of venous thrombosis is to allow normal circulation in the limbs and, wherever possible, to prevent damage to the valves of the veins, thus reducing the risk of the swollen post-phlebitic limb. Second, it is important to try to prevent associated PE and also recurrence of either venous thrombosis or PE in the risk period after the initial episode.

In acute massive PE, the initial priority is to correct the circulatory defect that has caused the haemodynamic upset, and in these circumstances, rapid removal of the obstruction using thrombolytic drugs or surgical removal of the embolus may be necessary. In acute submassive PE, the goal of treatment is to prevent further episodes, particularly of the more serious acute massive PE. In both deep vein thrombosis and PE,

a search must be made for underlying risk factors, such as carcinoma, which may occur in up to 10% of patients, and particularly in those with repeated episodes of VTE.

The treatment of VTE consists of the use of anticoagulants and, in severe cases, thrombolytic drugs. Anticoagulant therapy involves the use of immediate-acting agents (particularly heparin) and oral anticoagulants, the commonest of which is warfarin. Not only do these treat the acute event, but they also prevent recurrence and may be necessary for some time after the initial event, depending on the persistence of risk factors for recurrent thromboembolism.

Prophylaxis

Prevention of initial episodes of VTE in those at risk is clearly of great importance. It was estimated that around 25,000 people in the UK die from preventable hospital-acquired VTE annually, including patients admitted to hospital for medical care as well as surgery. There is also widespread evidence of inconsistent use of prophylactic measures for VTE in hospital patients, including mechanical as well as pharmacological means of VTE prophylaxis. Some of the medicines described below contribute to those pharmacological measures. Guidelines on this are available (National Institute for Health and Clinical Excellence, 2010).

Heparins

Conventional or unfractionated heparin (UFH) is a heterogeneous mixture of large mucopolysaccharide molecules ranging widely in molecular weight between 3000 and 30,000, with immediate anticoagulant properties. It acts by increasing the rate of the interaction of thrombin with antithrombin III by a factor of 1000. It, thus, prevents the production of fibrin (factor I) from fibrinogen. Heparin also has effects on the inhibition of production of activated clotting factors IX, X, XI and XII, and these effects occur at concentrations lower than its effects on thrombin.

Unlike UFH, low molecular weight heparins (LMWHs) contain polysaccharide chains ranging in molecular weight between 4000 and 6000. Whereas UFH produces its anticoagulant effect by inhibiting both thrombin and factor Xa, LMWHs predominantly inactivate only factor Xa. In addition, unlike UFH, they inactivate platelet-bound factor Xa and resist inhibition by platelet factor 4 (PF4), which is released during coagulation. Bemiparin, dalteparin, enoxaparin, reviparin and tinzaparin are LMWHs with similar efficacy and adverse effects.

Because UFH and LMWHs all consist of high molecular weight molecules that are highly ionised (heparin is the strongest organic acid found naturally in the body), they are not absorbed via the gastro-intestinal tract and must be given by intravenous infusion or deep subcutaneous (never intramuscular) injection. UFH is highly protein-bound and it appears to be restricted to the intravascular space, with a consequently low volume of distribution. It does not cross the placenta and does not appear in breast milk. Its pharmacokinetics are complex, but it appears to have a dose-dependent increase in half-life. The half-life is normally about 60 min, but is shorter in patients with PE. It is removed from the body by metabolism, possibly in the reticuloendothelial cells of the liver, and by renal excretion. The latter seems to be more important after high doses of the compound.

LMWHs have a number of potentially desirable pharmacokinetic features compared with UFH. They are predominantly excreted renally and have longer and more predictable half-lives than UFH and so have a more predictable dose response than UFH. They can, therefore, be given once or, at the most, twice daily in a fixed dose, sometimes based on the patient's body weight, without the need for laboratory monitoring, except for patients given treatment doses and at high risk of bleeding.

The major adverse effect of all heparins is haemorrhage, which is commoner in patients with severe heart or liver disease, renal disease, general debility and in women aged over 60 years. The risk of haemorrhage is increased in those with prolonged clotting times and in those given heparin by intermittent intravenous bolus rather than by continuous intravenous administration. UFH is monitored by derivatives of the activated partial thromboplastin time (APTT), for example the kaolin–cephalin clotting time (KCCT); in those patients with a KCCT three times greater than control, there is an eightfold increase in the risk of haemorrhage. The therapeutic range for the KCCT during UFH therapy, therefore, appears to be between 1.5 and 2.5 times the control values. Rapid reversal of the effect of heparin can be achieved using protamine sulphate, but this is rarely necessary because of the short duration of action of heparin. LMWHs may produce fewer haemorrhagic complications, and monitoring of effect is not routinely required. At doses normally used for treatment, they do not significantly affect coagulation tests and routine monitoring is not necessary (British Committee for Standards in Haematology, 2006a).

Heparins, particularly UFH, may also cause thrombocytopenia (low platelet count). This may occur in two forms. The first occurs 3–5 days after treatment and does not normally result in complications. The second type of thrombocytopenia occurs after about 6 days of treatment and often results in much more profound decreases in platelet count and an increased risk of thromboembolism. LMWHs are thought to be less likely to cause thrombocytopenia but this complication has been reported, including in individuals who had previously developed thrombocytopenia after UFH. For these reasons, patients should have a platelet count on the day of starting UFH and the alternate-day platelet counts should be performed from days 4 to 14 thereafter. For patients on LMWH, the platelet counts should be performed at 2–4 day intervals from day 4 to 14 (British Committee for Standards in Haematology, 2006b). If the platelet count falls by 50% and/or the patient develops new thrombosis or skin allergy during this period, heparin-induced thrombocytopenia (HIT) should be considered, and if strongly suspected or confirmed, heparin should be stopped and an alternative agent such as a heparinoid or hirudin commenced.

Heparin-induced osteoporosis is rare but may occur when the drug is used during pregnancy, and may be dose-related.

The exact mechanism is unknown. Other adverse effects of heparin are alopecia, urticaria and anaphylaxis, but these are also rare.

It has been shown that there is a non-linear relationship between the dose of UFH infused and the KCCT. This means that disproportionate adjustments in dose are required depending on the KCCT if under- or over-dosing is to be avoided (Box 23.1). Since the half-life of UFH is 1 h, it would take 5 h (five half-lives of the drug) to reach a steady state. A loading dose is, therefore, administered to reduce the time to achieve adequate anticoagulation. UFH in full dose can also be given by repeated subcutaneous injection, and in these circumstances the calcium salt appears to be less painful than the sodium salt. Opinions differ as to whether the subcutaneous or intravenous route is preferable. The subcutaneous route may take longer to reach effective plasma heparin concentrations but avoids the need for infusion devices.

Heparin is normally used in the immediate stages of venous thrombosis and PE until the effects of warfarin become apparent. In the past, it has been continued for 7–10 days, but recent evidence indicates that around 5 days of therapy may be sufficient in many instances. This shorter treatment may also reduce the risk of the rare but potentially very serious complications of severe HIT, which normally occurs after the sixth day. LMWH should be administered for at least 5 days or until the INR has been in the therapeutic range for two successive days, whichever is the longer. They have largely replaced UFH, since they can be given subcutaneously (without a loading dose), and without routine monitoring. A full blood count should be ordered after 5 days on LMWH and throughout the duration of LMWH treatment to monitor for heparin-related thrombocytopenia. Patients with previous exposure to heparin within the past 100 days should also have a platelet count performed before the second dose of heparin is administered (Winter et al., 2005).

Box 23.1 Guidelines to control unfractionated heparin (UFH) treatment

Loading dose
5000 iu over 5 min

Infusion
Start at 1400 iu/h (e.g. 8400 iu in 100 mL of normal saline over 6 h). Check after 6 h. Adjust dose according to ratio of the KCCT to the control value using the values below

KCCT ratio	*Infusion rate change*
>7.0	Discontinue for 30 min to 1 h and reduce by >500 iu/h
>5.0	Reduce by 500 iu/h
4.1–5.0	Reduce by 300 iu/h
3.1–4.0	Reduce by 100 iu/h
2.6–3.0	Reduce by 50 iu/h
1.5–2.5	No change
1.2–1.4	Increase by 200 iu/h
<1.2	Increase by 400 iu/h

After each dose change, wait 10 h before next KCCT estimation unless KCCT >5, when more frequent (e.g. 4-hourly) estimation is advisable. Developed using Diogen (Bell and Alton); local validation may be necessary.

Source: Modified from Fennerty et al. (1986) and reproduced in British Committee for Standards in Haematology (1998).

KCCT, Kaolin–cephalin clotting time.

Heparinoids

Danaparoid is a heparinoid that is licensed for prophylaxis of deep vein thrombosis in patients undergoing general or orthopaedic surgery. It is a mixture of the low molecular weight sulphated glycosaminoglycuronans: heparin sulphate, dermatan sulphate and a small amount of chondroitin sulphate. It acts by inhibiting factor Xa and, like LMWHs, is given by subcutaneous injection. It normally has a low cross-reactivity rate with heparin-associated antiplatelet antibodies and if this is not present can be used in the treatment of individuals who develop HIT but still need ongoing anticoagulation. It is administered intravenously, with monitoring of anti-Xa activity only required in those at high risk of bleeding, for example renal insufficiency. It should be avoided in severe renal insufficiency and severe hepatic insufficiency.

Hirudins

Lepirudin, a recombinant hirudin, is licensed for anticoagulation in patients with type II (immune) HIT who require parenteral antithrombotic treatment. The dose of lepirudin is adjusted according to the APTT, and it is given intravenously by infusion. Haemorrhage is greater in those with poor renal function. Severe anaphylaxis occurs rarely in association with lepirudin treatment and is more common in previously exposed patients (British Committee for Standards in Haematology, 2006b). Bivaluridin is an analogue of hirudin, but acts as a direct thrombin inhibitor. It is licensed for anticoagulation in patients undergoing percutaneous coronary intervention (PCI). It has to be administered parenterally and the activated clotting time (ACT) is used to assess its activity. Haemorrhage is also an important adverse effect of this agent.

Fondaparinux

Fondiparinux sodium is a synthetic pentasaccharide that binds to antithrombin III, thus inhibiting factor Xa but without effect on factor IIa. Therefore, at doses normally used for treatment, it does not significantly affect coagulation tests and routine monitoring of these is not necessary. It has to be given parenterally. It is used for prophylaxis of VTE in high-risk situations and for treatment of acute deep vein thrombosis and treatment of acute PE, except in haemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy. It also has an indication for the treatment of unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI) and for treatment of ST-segment elevation myocardial infarction (STEMI). Haemorrhage is the most important adverse effect.

Oral anticoagulants

Warfarin. Although not the only coumarin anticoagulant available, warfarin is by far the most widely used drug in this group because of its potency, duration of action and more reliable bioavailability. Acenocoumarol (nicoumalone) has a much shorter duration of action and phenindione may be associated with a higher incidence of non-haemorrhagic adverse effects. When given by mouth, warfarin is completely and rapidly absorbed, although food decreases the rate (but not the extent) of absorption. It is extremely highly plasma protein-bound (99%) and, therefore, has a small volume of distribution (7–14 L). It consists of an equal mixture of two enantiomers, (*R*)- and (*S*)-warfarins. They have different anticoagulant potencies and routes of metabolism.

Both enantiomers of warfarin act by inducing a functional deficiency of vitamin K and thereby prevent the normal carboxylation of the glutamic acid residues of the amino-terminal ends of clotting factors II, VII, IX and X. This renders the clotting factors unable to cross-link with calcium and thereby bind to phospholipid-containing membranes. Warfarin prevents the reduction of vitamin K epoxide to vitamin K by epoxide reductase. (*S*)-warfarin appears to be at least five times more potent in this regard than (*R*)-warfarin. Since warfarin does not have any effect on already carboxylated clotting factors, the delay in onset of the anticoagulant effect of warfarin is dependent on the rate of clearance of the fully carboxylated factors already synthesised. In this regard, the half-life of removal of factor VII is approximately 6 h, that of factor IX 24 h, factor X 36 h and factor II 50 h. Some of the variability in response to warfarin may be related to genetic variations in the gene encoding the vitamin K epoxide reductase multiprotein complex (*VKORC1* gene).

The effect of warfarin is monitored using the one-stage prothrombin time, for example the international normalised ratio (INR). This test is sensitive chiefly to factors VII, II and X (and to a lesser extent factor V, which is not a vitamin K-dependent clotting factor). However, factor VII, to which the INR is sensitive, is the most important factor in the extrinsic pathway of clotting. The optimum therapeutic range for the INR differs for different clinical indications since the lowest INR consistent with therapeutic efficacy is the best in reducing the risk of haemorrhage. Examples of therapeutic ranges recommended for certain indications are given in Table 23.1 (British Committee for Standards in Haematology, 1998, 2006c).

Warfarin is metabolised by the liver via the cytochrome P450 system. Only very small amounts of the drug appear unchanged in the urine. The average clearance is 4.5 L/day and the half-life ranges from 20 to 60 h (mean 40 h). It, thus, takes approximately 1 week (around five half-lives) for the steady state to be reached after warfarin has been administered. The enantiomers of warfarin are metabolised stereo-specifically, (*R*)-warfarin being mainly reduced at the acetyl side chain into secondary warfarin alcohols while (*S*)-warfarin is predominantly metabolised at the coumarin ring to hydroxywarfarin. The clearance of warfarin may be reduced in liver disease as well as during the administration of a variety of drugs known to inhibit either the (*S*) or (*R*), or both, enantiomers. These are shown in Table 23.2 which is not exhaustive. The number of possible interactions and the potential severity of their outcome mean that it is essential not to prescribe any medicine concomitantly with warfarin until a thorough check on all possible interactions has been undertaken. The British National Formulary contains comprehensive tables listing possible interactions between warfarin and other medicines.

Renal function is thought to have little effect on the pharmacokinetics of, or anticoagulant response to, warfarin. Some of the variability in warfarin dose requirement is related to genetic polymorphisms of the cytochrome (CYP2C9) mediating the rate of hepatic metabolism of (*S*)-warfarin. Individuals with the variant isoform (either heterozygotes or in particular homozygotes) metabolise this more active enantiomer more slowly and so require lower doses.

The major adverse effect of warfarin is haemorrhage, which often occurs at a predisposing abnormality such as an ulcer and a tumour. The risk of bleeding is increased by excessive anticoagulation, although this may not need to be present for severe haemorrhage to occur. Close monitoring of the degree of anticoagulation of warfarin is, therefore, important, and guidelines for reversal of excessive anticoagulation are shown in Table 23.3.

It is also important to reduce the duration of therapy of the drug to the minimum effective period to reduce the period of risk.

Skin reactions to warfarin may also occur but are rare. The most serious skin reaction is warfarin-induced skin necrosis, which may occur over areas of adipose tissue such as the breasts, buttocks or thighs, especially in women, and which is related to relative deficiency of protein C or S. This is important because these deficiencies result in an increased risk of thrombosis, and therefore warfarin may more often be used in such subjects. Preventing excessive anticoagulation in the initial stages of induction of therapy may reduce the severity of the reaction. A dosing schedule which helps to achieve this is shown in Table 23.4.

Warfarin may also be teratogenic, producing in some instances a condition called chondrodysplasia punctata. This is associated with 'punched-out' lesions at sites of ossification, particularly of the long bones but also of the facial bones, and may be associated with absence of the spleen. Although it has been associated predominantly with warfarin anticoagulation during the first trimester of pregnancy, other abnormalities, including cranial nerve palsies, hydrocephalus and microcephaly, have been reported at later stages of pregnancy if the child is exposed.

Although other coumarin anticoagulants are available, in the vast majority of cases these have not been shown to have any clear benefits over warfarin. They may be used occasionally where a patient does not tolerate warfarin. The necessary duration of anticoagulation in venous thrombosis and pulmonary embolus is still uncertain. On the basis of the available evidence, therapy may be required for approximately 6 months after the first deep vein thrombosis or pulmonary embolus. It may be possible to reduce the duration of therapy in patients who have

Table 23.1 Recommended target INRs for different conditions and grade of recommendation

Indication	Target INR	Grade of recommendation
Pulmonary embolus	2.5	A
Proximal deep vein thrombosis	2.5	A
Calf vein thrombus	2.5	A
Recurrence of venous thromboembolism when no longer on warfarin therapy	2.5	A
Recurrence of venous thromboembolism while on warfarin therapy	3.5	C
Symptomatic inherited thrombophilia	2.5	A
Antiphospholipid syndrome	3.5	A
Non-rheumatic atrial fibrillation	2.5	A
Atrial fibrillation due to rheumatic heart disease, congenital heart disease, thyrotoxicosis	2.5	C
Cardioversion	2.5	B
Mural thrombus	2.5	B
Cardiomyopathy	2.5	C
Mechanical prosthetic heart valve (caged ball or caged disk), aortic or mitral[a]	3.5	B
Mechanical prosthetic heart valve (tilting disc or bileaflet), mitral[a]	3.0	B
Mechanical prosthetic heart valve (tilting disc), aortic[a]	3.0	B
Mechanical prosthetic heart valve (bileaflet), aortic[a]	2.0	B
Bioprosthetic valve	2.0 (if anticoagulated)	A
Ischaemic stroke without atrial fibrillation	Not indicated	C
Retinal vessel occlusion	Not indicated	C
Peripheral arterial thrombosis and grafts	Not indicated	A
Arterial grafts	2.5 (if anticoagulated)	
Coronary artery thrombosis	2.5 (if anticoagulated)	
Coronary artery graft	Not indicated	A
Coronary angioplasty and stents	Not indicated	A

Source: British Committee for Standards in Haematology (1998, 2006c).
INR, international normalised ratio; A, at least one randomised controlled trial (RCT); B, well-conducted clinical trials but no RCT; C, expert opinion but no studies.
[a]If the valve type is not known, a target INR of 3.0 is recommended for valves in the aortic position and 3.5 in the mitral position.

had a postoperative episode since it is likely that the risk factor has been reversed (unless immobility continues). In patients with a second episode, therapy may be required for even longer and in patients with more than two episodes, life-long treatment may be necessary to reduce the risk of recurrence (British Committee for Standards in Haematology, 1998).

Dabigatran. Dabigatran is an orally active inhibitor of both free and clot-bound thrombin (Wittkowsky, 2010). It has a rapid onset of action and does not require laboratory monitoring. Dabigatran etexilate is a pro-drug which is hydrolysed to active dabigatran in the liver. Since 80% of activated dabigatran is excreted unchanged through the kidneys, it

Table 23.2 Some clinically important drug interactions with warfarin

Interacting drug	Effect of interaction on anticoagulant effect	Probable mechanism(s)
Colestyramine Colestipol	Reduced anticoagulant effect	Impaired absorption and increased elimination of warfarin. N.B. Long-term treatment may cause impaired vitamin K absorption and enhance anticoagulant effect
Barbiturates Carbamazepine Griseofulvin Phenytoin (see also below) Primidone Rifampicin Rifabutin St John's wort	Reduced anticoagulant effect	Induction of warfarin metabolism
Amiodarone Azapropazone Chloramphenicol Cimetidine Ciprofloxacin Clarithromycin Dextropopoxyphene Erythromycin Fluconazole Fluvastatin Itraconazole Ketoconazole Mefenamic acid Metronidazole Miconazole Nalidixic acid Norfloxacin Ofloxacin Phenylbutazone Sulfinpyrazone Sulphonamides (e.g. in co-trimoxazole) Voriconazole Zafirlukast	Increased anticoagulant effect	Inhibition of warfarin metabolism
Anabolic steroids Bezafibrate Danazol Gemfibrozil Levothyroxine Phenytoin (see also above) Salicylates/aspirin (high dose) Stanozolol Tamoxifen Testosterone	Increased anticoagulant effect	Pharmacodynamic potentiation of anticoagulant effect
Cranberry juice	Increased anticoagulant effect	Mechanism unknown
NSAIDs (including aspirin at all doses) Clopidogrel	Increased risk of bleeding	Additive effects on coagulation and haemostasis
Oral contraceptives, oestrogens and progestogens	Reduced anticoagulant effect	Pharmacodynamic antagonism of anticoagulant effect
Vitamin K (e.g. in some enteral feeds)		

Table 23.3 Recommendations for management of bleeding and excessive anticoagulation in patients receiving warfarin

Cause	Recommendation
3.0<INR<6.0 (target INR 2.5) 4.0<INR<6.0 (target INR 3.5)	1. Reduce warfarin dose or stop 2. Restart warfarin when INR <5.0
6.0<INR<8.0, no bleeding or minor bleeding	1. Stop warfarin 2. Restart when INR <5.0
INR>8.0, no bleeding or minor bleeding	1. Stop warfarin 2. Restart warfarin when INR <5.0 3. If other risk factors for bleeding give 0.5–2.5 mg of vitamin K (oral)
Major bleeding	1. Stop warfarin 2. Give prothrombin complex concentrate 50 units/kg or FFP 15 mL/kg 3. Give 5 mg of vitamin (oral or i.v.)

Source: British Committee for Standards in Haematology (1998).
INR, international normalised ratio; FFP, fresh frozen plasma.

Table 23.4 Suggested warfarin induction schedule

Day	INR	Warfarin dose (mg)
First	<1.4	10
Second	<1.8	10
	1.8	1
	>1.8	0.5
Third	<2.0	10
	2.0–2.1	5
	2.2–2.3	4.5
	2.4–2.5	4
	2.6–2.7	3.5
	2.8–2.9	3
	3.0–3.1	2.5
	3.2–3.3	2
	3.4	1.5
	3.5	1
	3.6–4.0	0.5
	>4.0	0 (predicted maintenance dose)
Fourth	<1.4	>8
	1.4	8
	1.5	7.5
	1.6–1.7	7
	1.8	6.5
	1.9	6
	2.0–2.1	5.5
	2.2–2.3	5
	2.4–2.6	4.5
	2.7–3.0	4
	3.1–3.5	3.5
	3.6–4.0	3
	4.1–4.5	Miss out next day's dose then give 2 mg
	>4.5	Miss out 2 days' doses then give 1 mg

Source: Modified from Fennerty et al. (1984).
INR, international normalised ratio.

should be avoided in patients with severe renal impairment (creatinine clearance < 30 mL/min) and the dose should be reduced in moderate renal impairment (creatinine clearance 30–50 mL/min). Dabigatran is a substrate for the transport protein p-glycoprotein (p-GP), which facilitates renal elimination of certain drugs. Amiodarone, an inhibitor of p-GP, reduces the clearance of dabigatran and so doses should be reduced in patients who are on concurrent treatment with amiodarone. In patients who are on strong p-GP inhibitors such as verapamil and clarithomycin, dabigatran should be used with caution and it should not be used together with quinidine. Drugs such as rifampicin and St John's Wort, which are potent p-GP inducers, may potentially reduce its efficacy. Dabigatran can be used for prophylaxis of VTE in adults after total hip replacement or total knee replacement surgery (National Institute for Health and Clinical Excellence, 2008). Haemorrhage is the major adverse effect.

Rivaroxaban. Rivaroxaban is an orally active inhibitor of both the 'free' and prothombinase complex-bound forms of activated factor X (Xa) (Wittkowsky, 2010). Two thirds of the dose is metabolised, principally by CYP450 enzymes and the remaining third is excreted unchanged in the urine. Like dabigatran, rivaroxaban also appears to be a p-GP substrate and it should be used with caution when prescribed concomitantly with p-GP inhibitors and potent p-GP inducers. It should also be used with caution in patients with creatinine clearance less than 30 mL/min (severe renal impairment) and is contraindicated in those with creatinine clearance less than 15 mL/min. Several CYP3A4 inhibitors and inducers have been shown to affect its metabolism. Some CYP3A4 inhibitors significantly increase the AUC of rivaroxaban, particularly ketoconazole and other azole-antimycotics such as itraconazole, voriconazole and posaconazole and also HIV protease inhibitors such as ritonavir. Therefore, the use of rivaroxaban is not recommended in patients receiving concomitant systemic treatment with these agents. The CYP3A4 inducer rifampicin (and possibly other inducers of this cytochrome) reduces the AUC for rivaroxaban. It is recommended as an option for prophylaxis of VTE in adults after hip or knee replacement surgery (National Institute for Health and Clinical Excellence, 2009). It also does not require laboratory monitoring. Haemorrhage is the major adverse effect.

Fibrinolytic drugs

Thrombolytic therapy is used in life-threatening acute massive pulmonary embolus. It has been used in deep vein thrombosis, particularly in those patients where a large amount of clot exists and venous valvular damage is likely. However, fibrinolytic drugs are potentially more dangerous than anticoagulant drugs, and evidence is not available in situations other than acute massive embolism to show a sustained benefit from their use.

Streptokinase. Streptokinase was the first agent available in this class. It was produced from streptococci and is a large protein that binds to and activates plasminogen, thus encouraging the breakdown of formed fibrin to fibrinogen degradation products. It also acts on the circulating fibrinogen to produce

a degree of systemic anticoagulation. Since it is a large protein molecule, it cannot be administered orally and has to be given by intravenous infusion. The half-life of removal from the body is 30 min. It is cleared chiefly by the reticuloendothelial system in the liver.

Its major adverse effect is to increase the risk of haemorrhage but it may also be antigenic and produce an anaphylactic reaction. It may also cause hypotension during infusion and in some patients, particularly those who have been administered the drug within the previous 12 months, a relative resistance to the drug may occur. Thrombolytic therapy is contraindicated in patients who have had major surgery or with active bleeding sites in the gastro-intestinal or genitourinary tract, those who have a history of stroke, renal or liver disease, and those with hypertension. It should also be avoided during pregnancy and the postpartum period.

Alteplase. Tissue plasminogen activator (rt-PA) or alteplase was developed using recombinant DNA technology. Although this agent is much more expensive than streptokinase, it can be used in those situations where streptokinase may be less effective because of development of antibodies, for example within 1 year of previous streptokinase use or where allergy to streptokinase has previously occurred. Because it produces a lesser degree of systemic anticoagulation (it is more active against plasminogen associated with the clot), immediate use of heparin subsequently is necessary to prevent recurrence of thrombosis. Alteplase is also used for acute ischaemic stroke, where its prompt use may improve outcome in carefully selected individuals (National Institute for Health and Clinical Excellence, 2007). At the time of writing, it is the only thrombolytic licensed for this indication (see arterial thromboembolism).

Reteplase and tenectaplase. Reteplase, and more recently tenecteplase, are also fibrin-specific agents and so heparin is required to prevent rebound thrombosis. They are indicated for the treatment of acute myocardial infarction. In this clinical situation, reteplase is administered as an intravenous bolus, followed by a second bolus 30 min later (double bolus), and tenecteplase is given as a single intravenous bolus. They, therefore, have the advantage of convenience of administration compared with alteplase, and are the preferred option in pre-hospital settings, particularly when administered by paramedics (National Institute for Health and Clinical Excellence, 2002a).

Urokinase. Urokinase, like alteplase and streptokinase, can be used for the treatment of deep vein thrombosis and PE. It is also licensed to restore patency in intravenous catheters and cannulas blocked by fibrin thrombi.

Patient care

The patient on oral anticoagulants should be given full information on what to do in case of problems and what circumstances and drugs to avoid. An anticoagulant card with previous INR values and doses should also be provided. The patient should be told of the colour code for the different strengths of warfarin tablet and advised to carry their treatment card at all times. The likely duration of anticoagulant therapy should be made clear to the patient to avoid unnecessary and potentially dangerous prolongations of treatment. Patients who have received a fibrinolytic agent should also carry a card identifying the drug given and the date of administration.

Arterial thromboembolism

Acute myocardial infarction is the commonest clinical presentation of acute arterial thrombosis. Stroke is commonly caused by atherothromboembolism from the great vessels or embolism arising from the heart (approximately 80% of strokes). These two conditions are discussed elsewhere. Peripheral arterial thrombosis or thromboembolism may also occur, most often in the lower limb. Antiplatelet drugs are often used for prophylaxis, but surgical embolectomy and/or fibrinolytic therapy may be needed for treatment of acute thrombotic or thromboembolic events to avoid consequent ischaemic damage.

Aetiology

Arterial thromboembolism is normally associated with vascular injury and hypercoagulability. Vascular injury is most often due to atheroma, itself aggravated by smoking, hypertension, hyperlipidaemia or diabetes mellitus. Although the exact mechanism is not clear, it is thought that platelet aggregation may be induced by the sheer stresses caused by stenosis of an atherosclerotic vessel. This thrombotic material may embolise to cause occlusion further downstream. Hypercoagulability is also a risk factor. It may be associated with increased plasma fibrinogen levels and an increase in circulating cellular components, for example polycythaemia or thrombocythaemia. As mentioned earlier, the thrombus formed in the artery contains a much larger proportion of platelets, possibly reflecting the fact that other blood components that are not as readily adherent may be dissipated by the higher flow rates in the arterial circulation. Oestrogens, by the mechanisms described earlier, are likely to increase the risk of arterial as well as venous thrombosis. Hyperlipidaemia may also increase the risk of hypercoagulability as well as enhancing thrombotic risk through its role in the progression of atheroma and vascular injury.

Treatment and prevention

Aspirin

Aspirin (acetylsalicylic acid) is a potent inhibitor of the enzyme cyclo-oxygenase, which catalyses the production of prostaglandins. It reduces the production of pro-aggregatory prostaglandin, thromboxane A_2 in the platelet, an effect that lasts for the life of the platelet.

Aspirin is well absorbed after oral administration. It is rapidly metabolised by esterases in the blood and liver (so that its half-life is only 15–20 min) to salicylic acid and other metabolites that are excreted in the urine. In the doses used

in prophylaxis against thromboembolism, aspirin is largely metabolised by the liver but in overdose, urinary excretion of salicylate becomes a limiting factor in drug elimination.

The major adverse effect of aspirin is gastro-intestinal irritation and bleeding. This problem is much more common with higher doses of aspirin (300 mg or more) that were once used in the prevention of arterial thromboembolism but are less common with the doses (e.g. 75 mg) now recommended. There is evidence that concomitant use of ulcer-healing drugs, particularly proton pump inhibitors, can reduce the risk of non-steroidal anti-inflammatory drug (NSAID)-induced peptic ulceration in patients susceptible to the problem, but haemorrhagic risk may not be significantly reduced. There is also little evidence that buffered or enteric-coated preparations of aspirin are safer in this respect. However, the vast majority of patients tolerate low-dose aspirin well, and it is normally given as a single oral dose of soluble aspirin. Aspirin may also, rarely, induce asthma, particularly in patients with co-existing reversible airway obstruction. Other patients have a form of aspirin hypersensitivity that may result in urticaria and/or angioedema. In this situation, there may be cross-reactivity with other NSAIDs.

Haemorrhagic stroke is a rare but a very serious complication of therapy with aspirin (and with other antiplatelet agents). Recent evidence examining risks and benefits of aspirin has resulted in the recommendation that while long-term use of aspirin, in a dose of 75 mg daily, is of benefit for all patients with established cardiovascular disease, use of aspirin in primary prevention, in those with or without diabetes, is of unproven overall benefit. It must not be given to children or young people under 16 years of age because of the risk of the rare but life-threatening possibility of Reye's Syndrome (which may cause liver and renal failure).

Clopidogrel

Clopidogrel is a pro-drug that is metabolised in part to an active thiol derivative. The latter inhibits platelet aggregation by rapidly and irreversibly inhibiting the binding of adenosine diphosphate (ADP) to its platelet receptor, thus preventing the ADP-mediated activation of the glycoprotein IIb/IIIa receptor for the life of the platelet. It is an orally active pro-drug and is given once daily for the reduction of atherosclerotic events in those with pre-existing atherosclerotic disease. In this respect, it may be a useful alternative to aspirin in aspirin-allergic subjects but haemorrhage occurs with the same frequency as aspirin, and thrombocytopenia (sometimes severe) may be commoner than with aspirin therapy. Activation to its active metabolite may be subject to a genetic polymorphism of CYP450 2C19 and may also be reduced by the proton pump inhibitor, omeprazole or esomeprazole; so use of alternative gastroprotective agents may need to be considered if required.

Clopidogrel is also licensed for combination use with low-dose aspirin in the management of acute coronary syndrome without ST-segment elevation, when it is given for up to 12 months after the initial event (National Institute for Health and Clinical Excellence, 2004, 2005). Most benefit is obtained in the first 3 months and there is no evidence of benefit of clopidogrel after 12 months in this indication. In combination with low-dose aspirin, clopidogrel is also licensed for acute myocardial infarction with ST-segment elevation. It is recommended for at least 4 weeks in this indication, but the optimum treatment duration has not been established. Finally clopdogrel is sometimes used (with aspirin) in stenting procedures and this sometimes results in long-term use.

Prasugrel

Prasugrel inhibits platelet activation and aggregation. Its active metabolite binds to the $P2Y_{12}$ class of ADP receptors on platelets. It is recommended for use in combination with aspirin as an option for the prevention of atherothrombotic events in patients with acute coronary syndromes undergoing PCI, only when immediate primary PCI is necessary for STEMI, *or* stent thrombosis occurred during treatment with clopidogrel, or the patient has diabetes mellitus (National Institute for Health and Clinical Excellence, 2009).

Dipyridamole

Dipyridamole is used by mouth as an adjunct to oral anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves. Modified-release preparations are licensed (alone or preferably in combination with low-dose aspirin) for secondary prevention of ischaemic stroke and TIAs (see treatment of stroke). There is evidence that the combination of modified-release dipyridamole and low-dose aspirin may reduce the risk of recurrent stroke and other cardiovascular events compared to aspirin alone. It is a phosphodiesterase inhibitor and, thus, elevates concentrations of cyclic AMP. It may also block the uptake of adenosine by erythrocytes and other cells. Adverse effects include headache (to which tolerance may gradually develop) gastro-intestinal problems, flushing and hypotension.

Glycoprotein IIb/IIIa inhibitors

Glycoprotein IIb/IIIa inhibitors prevent platelet aggregation by blocking the binding of fibrinogen to receptors on platelets.

Abciximab. Abciximab is a monoclonal antibody which binds to coronary glycoprotein IIb/IIIa receptors and to other related sites. It is licensed as an adjunct to heparin and aspirin for the prevention of ischaemic complications in high-risk patients undergoing percutaneous transluminal coronary intervention. Abciximab should be used once only to avoid further risk of thrombocytopenia.

Eptifibatide and tirofiban. Eptifibatide and tirofiban also inhibit glycoprotein IIb/IIIa receptors; they are licensed for use with heparin and aspirin to prevent early myocardial infarction in patients with unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI).

Abciximab, eptifibatide and tirofiban all have to be administered parenterally and should be used by specialist clinicians only (National Institute for Health and Clinical Excellence, 2002b).

Patient care

Aspirin is normally well tolerated at the doses used for stroke prevention. However, it should not be given to patients with a history of gastro-intestinal ulceration. Since it may induce bronchospasm in susceptible individuals, it should be used cautiously in such circumstances. It is best tolerated if taken once daily as soluble aspirin after food.

Case studies

Case 23.1

A 75-year-old patient receiving warfarin to prevent deep vein thrombosis and previously well controlled comes to the clinic with an INR of 12, despite taking the same dose of drug. There is no evidence of bleeding.

Question

What should be done?

Answer

Since the patient's INR is >8 (even if there is no bleeding), the national guidelines recommend that warfarin be stopped. The patient should then be given phytomenadione (vitamin K_1) 2.5–5 mg by mouth using the intravenous preparation orally [unlicensed use], or 0.5–1 mg by slow intravenous injection (if complete reversal required 5–10 mg by slow intravenous injection). The dose of phytomenadione should be repeated if the INR is still too high after 24 h. The warfarin can be restarted when the INR is <5.0. However, a single dose often helps the INR to return to close to the target level at 24 h without causing warfarin resistance subsequently. A search for clinical conditions or drugs which might cause warfarin sensitivity should also be made. Measurement of plasma warfarin concentration may help in difficult cases.

Case 23.2

A patient receiving heparin for 7 days for extensive VTE develops arterial thrombosis.

Question

What would you suspect in this situation and what should be done?

Answer

The rare but serious HIT may be responsible. The platelet count should be measured immediately and if HIT is strongly suspected or confirmed, the heparin should be discontinued immediately. An alternative anticoagulant should be started in full dosage whilst specific confirmatory tests are being performed unless there are significant contraindications. Danaparoid and lepirudin may be considered as alternative anticoagulants in these circumstances.

Case 23.3

A patient admitted to an acute hospital with suspected myocardial infarction says that he had a myocardial infarction 4 years ago and was treated with a drug to 'dissolve the clot in the coronary artery'. The chest pain started 4 h earlier and his electrocardiogram shows ST-segment elevation in the anterior leads.

Question

What relevance may his previous treatment and present history and findings have to his management on this occasion?

Answer

Thrombolytic drugs are indicated for any patient with acute myocardial infarction, provided the likely benefits outweigh the possible risks. Trials have shown that the benefit is greatest in those with ECG changes that include ST-segment elevation, especially in those with anterior infarction, and in patients with bundle branch block. The patient has received a thrombolytic, possibly streptokinase, in the past. He should be asked if he was given a card with the identity of the therapy to carry with him. If the prior treatment was with streptokinase or anistreplase (no longer available), prolonged persistence of antibodies to streptokinase may reduce the effectiveness of subsequent treatment. Therefore, streptokinase should not be used again beyond 4 days of first administration of streptokinase (or anistreplase) and urgent consideration should be given to the use of an alternative thrombolytic agent such as alteplase, reteplase and tenecteplase.

Case 23.4

A 64-year-old male patient is to be prescribed aspirin therapy following an acute myocardial infarction.

Question

What questions should you ask the patient before starting treatment with aspirin?

Answer

The patient should be asked if he has had aspirin before and, if so, whether he tolerated it. Caution is necessary in patients with a previous history of gastro-intestinal ulceration, with uncontrolled hypertension; active peptic ulceration is also a contraindication. Other contraindications include severe hepatic impairment and severe renal failure. It may induce bronchospasm or angioedema in susceptible individuals, for example in asthmatics, and caution should be exercised in these circumstances.

Case 23.5

A 56-year-old woman on warfarin therapy for atrial fibrillation with mitral stenosis appears to become resistant to warfarin after previously good control on 5 mg daily. Her INR does not rise above 1.4 even when her warfarin dose is increased to 20 mg daily.

Question

What can be done to find the cause of the resistance?

Answer

The patient should be asked about any new medications which might have been introduced recently, including over-the-counter and herbal preparations. Some proprietary medicines may contain vitamin K which could cause resistance by pharmacodynamic mechanisms. Other medicines, including the herbal medicine St John's wort, might induce warfarin metabolism and result in resistance as a result of a pharmacokinetic interaction (see Table 23.2). One other cause of apparent resistance to warfarin is poor adherence and this should, therefore, be considered. Supervised administration of the dose and/or measurement of plasma warfarin concentrations may be of value if the latter is suspected.

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24 Dyslipidaemia

R. Walker and H. Williams

Key points

- Elevated concentrations of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) increase the risk of cardiovascular disease (CVD), while high-density lipoprotein cholesterol (HDL-C) confers protection.
- Two-thirds of the UK adult population have a serum TC above 5 mmol/L. The average TC concentration is 5.6 mmol/L.
- Dyslipidaemia may develop secondary to disorders such as diabetes mellitus, hypothyroidism, chronic renal failure, nephrotic syndrome, obesity, high alcohol intake and some drugs.
- Androgens, β-blockers, ciclosporin, oral contraceptives, diuretics, glucocorticoids and vitamin A derivatives are examples of drugs that can have an adverse effect on the lipid profile.
- There are five main classes of lipid-lowering agents: statins, fibrates, resins, nicotinic acid derivatives and absorption blockers.
- Statins are generally the drugs of choice in the treatment of primary prevention and secondary prevention of CVD.
- The aim of treatment in primary prevention (>20% risk of cardiovascular disease over 10 years) is to reduce overall cardiovascular risk by treatment with simvastatin 40 mg/day or a suitable alternate generic agent. No target treatment levels for TC or LDL cholesterol are recommended in primary prevention.
- In secondary prevention, treatment should be started with simvastatin 40 mg/day or a suitable alternate generic agent. If serum TC remains above 4 mmol/L or LDL-C remains above 2 mmol/L, the dose of statin can be increased, but this may increase the likelihood of side effects.

Disorders of lipoprotein metabolism together with high fat diets, obesity and physical inactivity have all contributed to the current epidemic of atherosclerotic disease seen in developed countries. Disorders of lipoprotein metabolism that result in elevated serum concentrations of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) increase the risk of an individual developing cardiovascular disease (CVD). In contrast, high-density lipoprotein cholesterol (HDL-C) confers protection against CVD, with the risk reducing as HDL-C increases. It is, therefore, clear that the term hyperlipidaemia, which was formerly used to describe disorders of lipoprotein metabolism, is inappropriate. It is more appropriate to use the term dyslipidaemia, which encompasses both abnormally high levels of specific lipoproteins, for example, LDL-C, and abnormally low levels of other lipoproteins, for example, HDL-C, as well as disorders in the composition of the various lipoprotein particles. It is particularly appropriate when considering the individual at risk of CVD with a normal or high TC and low HDL-C (total cholesterol:HDL-C ratio).

Epidemiology

Lipid and lipoprotein concentrations vary among different populations, with countries consuming a Western type of diet generally having higher TC and LDL-C levels than those where regular consumption of saturated fat is low.

The ideal serum lipid profile is unknown and varies between different populations, even across Europe, and also within a given population. For practical purposes the values presented in Table 24.1 represent the target levels for TC and LDL-C in the UK for adults receiving treatment for secondary prevention of CVD. For completeness, the values for triglycerides and HDL-C are also presented, although the benefit of achieving the stated targets is less clear.

Despite a 50% reduction in the death rate from CVD over the past 25 years, it remains the leading cause of premature

Table 24.1 Optimal serum lipid profile

Total cholesterol (TC)[a]	<4.0 mmol/L
LDL cholesterol (LDL-C)[a]	<2.0 mmol/L
Triglycerides[b]	<1.7 mmol/L
HDL cholesterol (HDL-C)	>1.0 mmol/L in men
	>1.2 mmol/L in women

[a]Target levels in individuals with established atherosclerotic disease, coronary heart disease, stroke, peripheral arterial disease, diabetes mellitus or where there is a cardiovascular disease risk >20% over 10 years. In these identified individuals, the aim is to achieve the value stated in the table or a 25% reduction in total cholesterol and a 30% reduction in LDL-C from their baseline levels should these set target levels lower than those stated in the table.
[b]Fasting levels.

death and morbidity in the UK (British Heart Foundation, 2008), and the higher the levels of TC in an individual the greater the chance of developing CVD. At the individual level there appears no level below which a further reduction of TC or LDL-C is not associated with a lower risk of CVD. The death rate from CVD is threefold higher in males than females, but because women live longer and are at increased risk of stroke after the age of 75 years their lifetime risk of disease is greater (National Institute of Health and Clinical Excellence, 2008a).

TC levels tend to increase with age such that 80% of British men aged 45–64 years have a level that exceeds 5 mmol/L and the population average is 5.6 mmol/L. In contrast, in rural China and Japan, the average is 4 mmol/L.

Population-based approaches to vascular screening have the potential to provide significant health gain for society as most deaths from CVD occur in individuals who are not yet identified as at increased risk. Moreover, a small reduction in average population levels of TC and LDL-C can potentially prevent many deaths. In England, a scheme was introduced in 2009 for everyone between 40 and 74 years of age to receive a free health check to include measurement of TC and the TC:HDL-C ratio. The intention was that individuals would be given the necessary information about their health to make changes to lifestyle and avoid preventable disease.

Lipid transport and lipoprotein metabolism

The clinically important lipids in the blood (unesterified and esterified cholesterol and triglycerides) are not readily soluble in serum and are rendered miscible by incorporation into lipoproteins. There are six main classes of lipoproteins: chylomicrons, chylomicron remnants, very low-density lipoproteins (VLDL-C), intermediate-density lipoproteins (IDL-C), low-density lipoproteins (LDL-C) and high-density lipoproteins (HDL-C).

The protein components of lipoproteins are known as apoproteins (apo), of which apoproteins A-I, E, C and B are perhaps the most important. Apoprotein B exists in two forms: B-48, which is present in chylomicrons and associated with the transport of ingested lipids, and B-100, which is found in endogenously secreted VLDL-C and associated with the transport of lipids from the liver (Fig. 24.1).

When dietary cholesterol and triglycerides are absorbed from the intestine they are transported in the intestinal lymphatics as chylomicrons. These are the largest of the lipoprotein particles of which triglycerides normally constitute approximately 80% of the lipid core. The chylomicrons pass through blood capillaries in adipose tissue and skeletal muscle where the enzyme lipoprotein lipase is located, bound to the endothelium. Lipoprotein lipase is activated by apoprotein C-II on the surface of the chylomicron. The lipase catalyses the breakdown of the triglyceride in the chylomicron to free fatty acid and glycerol, which then enter adipose tissue and muscle. The cholesterol-rich chylomicron remnant is taken up by receptors on hepatocyte membranes, and in this way dietary cholesterol is delivered to the liver and cleared from the circulation.

VLDL-C is formed in the liver and transports triglycerides, which again make up approximately 80% of its lipid core, to the periphery. The triglyceride content of VLDL-C is removed by lipoprotein lipase in a similar manner to that described for chylomicrons above, and forms IDL-C particles. The core of IDL-C particles is roughly 50% triglyceride and 50% cholesterol esters, acquired from HDL-C under the influence of the enzyme lecithin-cholesterol acyltransferase (LCAT). Approximately 50% of the body's IDL particles are cleared from serum by the liver. The other 50% of IDL-C are further hydrolysed and modified to lose triglyceride and apoprotein E1 and become LDL-C particles. LDL-C is the major cholesterol-carrying particle in serum.

LDL-C provides cholesterol, an essential component of cell membranes, bile acid and a precursor of steroid hormones to those cells that require it. LDL-C is also the main lipoprotein involved in atherogenesis, although it only appears to take on this role after it has been modified by oxidation. For reasons that are not totally clear, the arterial endothelium becomes permeable to the lipoprotein. Monocytes migrate through the permeable endothelium and engulf the lipoprotein, resulting in the formation of lipid-laden macrophages that have a key role in the subsequent development of atherosclerosis. The aim of treatment in dyslipidaemia is normally to reduce concentrations of LDL-C (and consequently atherogenesis) and thus reduce TC at the same time.

While VLDL-C and LDL-C are considered the 'bad' lipoproteins, HDL-C is often considered to be the 'good' antiatherogenic lipoprotein. In general, about 65% of TC is carried in LDL-C and about 25% in HDL.

High-density lipoprotein

HDL-C is formed from the unesterified cholesterol and phospholipid removed from peripheral tissues and the surface of triglyceride-rich proteins. The major structural protein is apoA-I. HDL-C mediates the return of lipoprotein and cholesterol from peripheral tissues to the liver for excretion in a process known as reverse cholesterol transport.

Reverse cholesterol transport pathway

The reverse cholesterol transport pathway (Fig. 24.2) controls the formation, conversion, transformation and degradation of HDL-C and is the target site for a number of new, novel drugs and has recently been described (Chapman et al., 2010).

The reverse cholesterol transport system involves lipoprotein-mediated transport of cholesterol from peripheral, extra-hepatic tissues and arterial tissue (potentially including cholesterol-loaded foam cell macrophages of the atherosclerotic plaque) to the liver for excretion, either in the form of biliary cholesterol or bile acids. The ATP-binding cassette transporters, ABCA1 and ABCG1, and the scavenger receptor B1, are all implicated in cellular cholesterol efflux mechanisms to specific apoA-1/HDL acceptors. The progressive action of lecithin:cholesterol

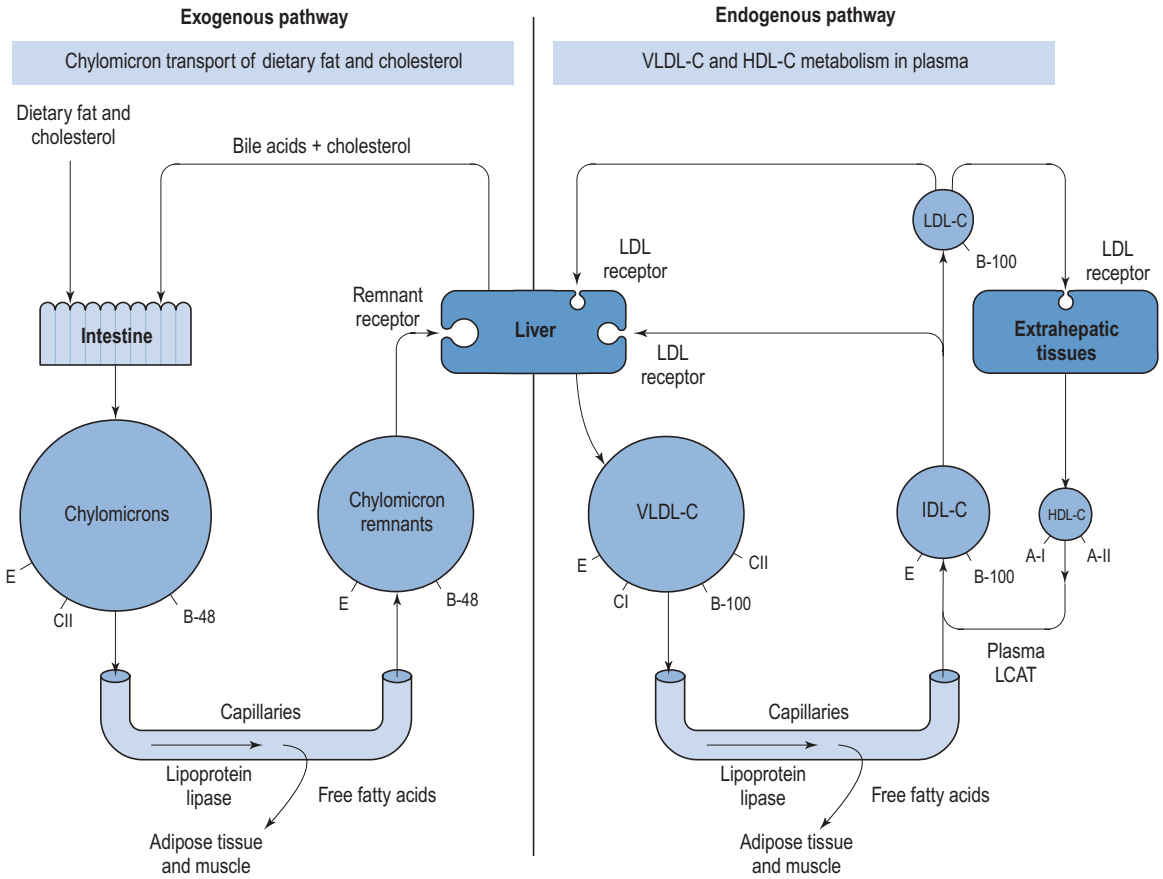


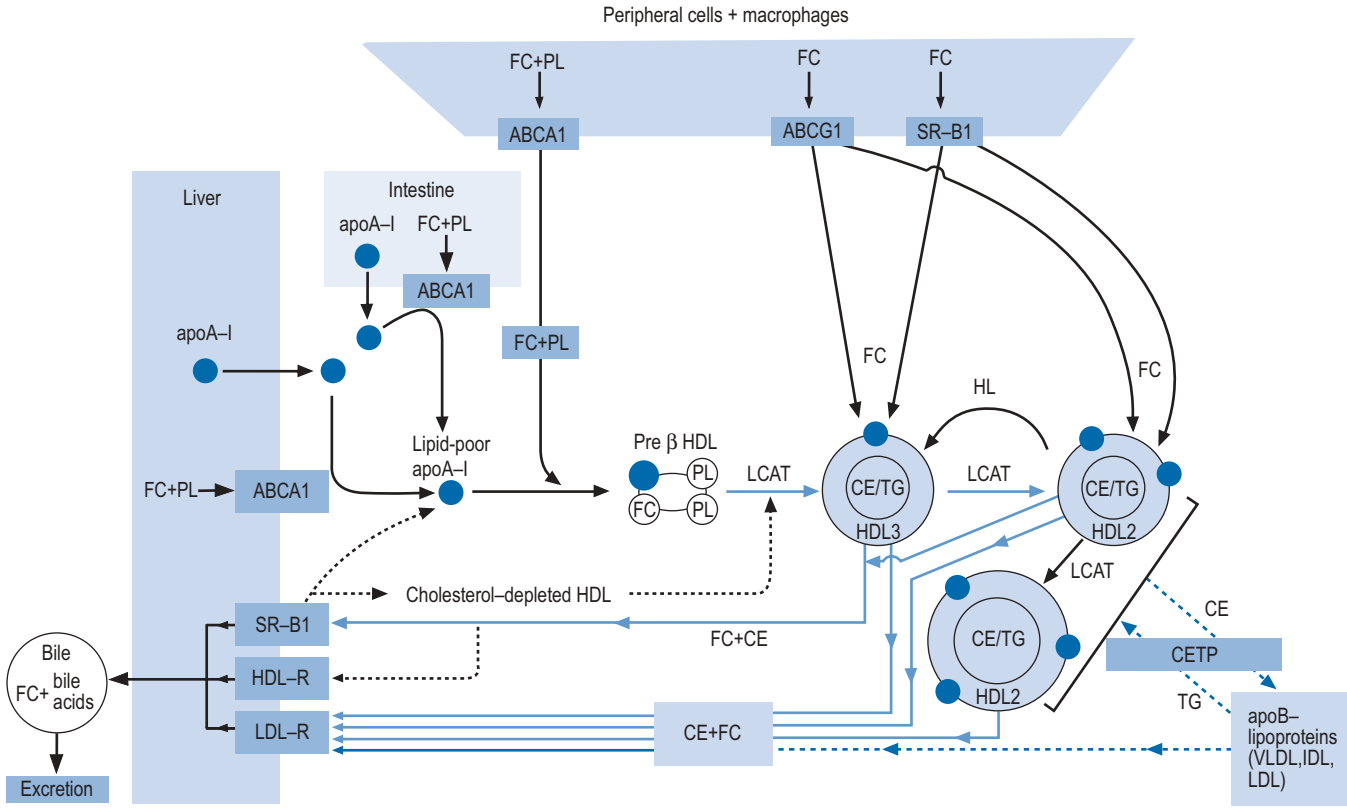
Fig. 24.1 Schematic representation of lipoprotein metabolism in plasma. Dietary cholesterol and fat are transported in the exogenous pathway. Cholesterol produced in the liver is transported in the endogenous pathway.

acyl transferase on free cholesterol in lipid-poor, apolipoprotein A-I-containing nascent high-density lipoproteins, including pre-β-HDL, gives rise to the formation of a spectrum of mature, spherical high-density lipoproteins with a neutral lipid core of cholesteryl ester and triglyceride. Mature high-density lipoproteins consist of two major subclasses, large cholesteryl ester-rich HDL_2 and small cholesteryl ester-poor, protein-rich HDL_3 particles; the latter represent the intravascular precursors of HDL_2. The reverse cholesterol transport system involves two key pathways: (a) the direct pathway (blue lines), in which the cholesteryl ester content (and potentially some free cholesterol) of mature high-density lipoprotein particles is taken up primarily by a selective uptake process involving the hepatic scavenger receptor B1 and (b) an indirect pathway (dotted blue lines) in which cholesteryl ester originating in HDL is deviated to potentially atherogenic VLDL, IDL and LDL particles by cholesteryl ester transfer protein. Both the cholesteryl ester and free cholesterol content of these particles are taken up by the liver, predominantly via the LDL receptor which binds their apoB100 component. This latter pathway may represent up to 70% of cholesteryl ester delivered to the liver per day. The hepatic LDL receptor is also responsible for the direct uptake of high-density lipoprotein particles containing apoE; apoE may be present as a component of both HDL_2 and HDL_3 particles, and may be derived either by transfer from triglyceride-rich lipoproteins, or from tissue sources (principally liver and monocyte-macrophages). Whereas HDL uptake by the LDL receptor results primarily in lysosomal-mediated degradation of both lipids and apolipoproteins, interaction of HDL with scavenger receptor B1 regenerates lipid-poor apoA-I and cholesterol-depleted HDL, both of which may re-enter the HDL/apoA-I cycle.

From the above it is evident that HDL-C plays a major role in maintaining cholesterol homeostasis in the body. As a consequence it is considered desirable to maintain both levels of the protective HDL-C and the integrity of the reverse cholesterol transport pathway. Low levels of HDL-C are found in 17% of men and 5% of women and may be a risk factor for atherogenesis that is comparable in importance to elevated levels of LDL-C. Drugs that reduce HDL-C levels are considered to have an undesirable effect on lipid metabolism and increase the risk of developing CVD.

Triglycerides

The role of hypertriglyceridaemia as an independent risk factor for coronary heart disease (CHD) is unclear because triglyceride levels are confounded by an association with low HDL-C, hypertension, diabetes and obesity, and a synergistic effect with LDL-C and/or low HDL-C. An isolated elevation of triglyceride may be the consequence of a primary disorder of lipid metabolism, it may be secondary to the use of medicines or it may be a component of the metabolic syndrome or type 2



ABC A1 = ATP binding cassette transporter A1; ABC G1 = ATP binding casssette transporter G1; CE = cholesterol ester; CETP = cholesteryl ester transfer protein; FC = free cholesterol; HDL–R = holo HDL receptor; HL = hepatic lipase; LCAT = lecithin cholesterol acyltransferase; LPL = lipoprotein lipase; PL = phospholipids; SR–B1 = hepatic scavenger receptor B1; TG = triglycerides

Fig. 24.2 Pathways of reverse cholesterol transport in man (Chapman et al., 2010 with kind permission from Oxford University Press, Oxford).

diabetes mellitus. Many individuals have a mixed dyslipidaemia that includes elevated levels of triglycerides and LDL-C, but reduction of LDL-C normally remains the primary focus of treatment. A recent analysis, in over 73,000 individuals, of a genetic variant which regulates triglyceride concentrations has demonstrated a causal association between triglycerides and CHD (Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration, 2010).

Aetiology

Primary dyslipidaemia

Up to 60% of the variability in cholesterol fasting lipids may be genetically determined, although expression is often influenced by interaction with environmental factors. The common familial (genetic) disorders can be classified as:

- the primary hypercholesterolaemias such as familial hypercholesterolaemias in which LDL-C is raised
- the primary mixed (combined) hyperlipidaemias in which both LDL-C and triglycerides are raised
- the primary hypertriglyceridaemias such as type III hyperlipoproteinaemia, familial lipoprotein lipase deficiency and familial apoC-II deficiency.

Familial hypercholesterolaemia

Heterozygous familial hypercholesterolaemia (often referred to as FH) is an inherited metabolic disease that affects approximately 1 in 500 of the population. In the UK, this represents about 110,000 individuals. Familial hypercholesterolaemia is caused by a range of mutations, which vary from family to family, in genes for the pathway that clear LDL-C from the blood. The most common mutation affects the LDL receptor gene. Given the key role of LDL receptors in the catabolism of LDL-C, patients with FH may have serum levels of LDL-C two to three times higher than the general population. It is important to identify and treat these individuals from birth, otherwise they will be exposed to high concentrations of LDL-C and will suffer the consequences. Familial hypercholesterolaemia is transmitted as a dominant gene, with siblings and children of a parent with FH having a 50% risk of inheriting it. It is important to suspect FH in people that present with TC >7.5 mmol/L, particularly where there is

evidence of premature CV disease within the family. Guidance on diagnosis, identifying affected relatives and management are available but it is important to seek specialist advice for this group of high-risk patients (National Institute of Health and Clinical Excellence, 2008b).

In patients with heterozygous FH, CVD presents about 20 years earlier than in the general population, with some individuals, particularly men, dying from atherosclerotic heart disease often before the age of 40 years. The adult heterozygote typically exhibits the signs of cholesterol deposition such as corneal arcus (crescentic deposition of lipids in the cornea), tendon xanthoma (yellow papules or nodules of lipids deposited in tendons) and xanthelasma (yellow plaques or nodules of lipids deposited on eyelids) in their third decade.

In contrast to the heterozygous form, homozygous FH is extremely rare (1 per million) and associated with an absence of LDL receptors and almost absolute inability to clear LDL-C. In these individuals, involvement of the aorta is evident by puberty and usually accompanied by cutaneous and tendon xanthomas. Myocardial infarction has been reported in homozygous children as early as 1.5–3 years of age. Up to the 1980s, sudden death from acute coronary insufficiency before the age of 20 years was normal.

Familial combined hyperlipidaemia

Familial combined hyperlipidaemia has an incidence of 1 in 200 and is associated with excessive synthesis of VLDL-C. In addition to increases in triglyceride and LDL-C levels, patients also typically have raised levels of apoB and elevated levels of small, dense LDL particles. It is associated with an increased risk of atherosclerosis and occurs in approximately 15% of patients who present with CHD before the age of 60 years.

Familial type III hyperlipoproteinaemia

Familial type III hyperlipoproteinaemia has an incidence of 1 in 5000. It is characterised by the accumulation of chylomicron and VLDL remnants that fail to get cleared at a normal rate by hepatic receptors due to the presence of less active polymorphic forms of apoE. Triglycerides and TC are both elevated and accompanied by corneal arcus, xanthelasma, tuberoeruptive xanthomas (groups of flat or yellowish raised nodules on the skin over joints, especially the elbows and knees) and palmar striae (yellow raised streaks across the palms of the hand). The disorder predisposes to premature atherosclerosis.

Familial lipoprotein lipase deficiency

Familial lipoprotein lipase deficiency is characterised by marked hypertriglyceridaemia and chylomicronaemia, and usually presents in childhood. It has an incidence of 1 per million and is due to a deficiency of the extrahepatic enzyme lipoprotein lipase, which results in a failure of lipolysis and the accumulation of chylomicrons in plasma. The affected patient presents with recurrent episodes of abdominal pain, eruptive xanthomas, lipaemia retinalis (retinal deposition of lipid) and enlarged spleen. This disorder is not associated with an increased susceptibility to atherosclerosis; the major complication is acute pancreatitis.

Familial apolipoprotein C-II deficiency

In the heterozygous state, familial apoC-II deficiency is associated with reduced levels of apoC-II, the activator of lipoprotein lipase. Typically, levels of apoC-II are 50–80% of normal. This level of activity can maintain normal lipid levels. In the rare homozygous state, there is an absence of apolipoprotein C-II and despite normal levels of lipoprotein lipase, it cannot be activated. Consequently, homozygotes have triglyceride levels from 15 to above 100 mmol/L (normal range <1.7 mmol/L) and may develop acute pancreatitis. Premature atherosclerosis is unusual but has been described.

Lipoprotein(a)

There are many other familial disorders of lipid metabolism in addition to those mentioned above but most are very rare. However, a raised level of lipoprotein(a), otherwise known as Lp(a), appears to be a genetically inherited determinant of CVD. Lp(a) is a low-density lipoprotein-like particle synthesised by the liver and first described more than 40 years ago. It is found in the serum of virtually everyone in a wide concentration range (0.01–2 g/L) with up to 70% of the variation in concentration being genetically determined. The concentration of Lp(a) is not normally distributed and the contribution of inheritance to circulating Lp(a) levels is more pronounced than for any other lipoprotein or apoprotein. A parental history of early-onset CVD is associated with raised concentrations of Lp(a), and these appear to play a role in both atherogenesis and thrombosis. An important component of Lp(a) is apo(a), which is structurally and functionally similar to plasminogen and may competitively bind to fibrin and impair fibrinolysis.

Concentrations of Lp(a) above 0.3 g/L occur in about 20% of caucasians and increase the risk of coronary atherosclerosis and stroke. Under a wide range of circumstances, there are continuous, independent, and modest associations of Lp(a) concentration with the risk of CHD and stroke (Emerging Risk Factors Collaboration, 2009).

Secondary dyslipidaemia

Dyslipidaemias that occur secondary to a number of disorders (Box 24.1), dietary indiscretion or as a side effect of drug therapy (Table 24.2) account for up to 40% of all dyslipidaemias. Fortunately, the lipid abnormalities in secondary dyslipidaemia can often be corrected if the underlying disorder is treated, effective dietary advice implemented or the offending drug withdrawn.

On occasion, a disorder may be associated with dyslipidaemia but not the cause of it. For example, hyperuricaemia (gout) and hypertriglyceridaemia co-exist in approximately 50% of men. In this particular example, neither is the cause

Box 24.1 Examples of disorders known to adversely affect the lipid profile

Anorexia nervosa
Bulimia
Type 1 diabetes
Type 2 diabetes
Hypothyroidism
Pregnancy
Inappropriate diet
Alcohol abuse
Chronic renal failure
Nephrotic syndrome
Renal transplantation
Cardiac transplantation
Hepatocellular disease
Cholestasis
Myeloma

Table 24.2 Typical effects of selected drugs on lipoprotein levels

Drug	VLDL-C	LDL-C	HDL-C
Alcohol	↑	0	↑
Androgens, testosterone	↑	↑	↓
ACE-inhibitors	0	0	0
β-Blockers	↑	0	↓
Calcium channel blockers	0	0	0
Ciclosporin	↑	↑	↑
Oestrogens, oestradiol	↑	↓	↓
Glucocorticoids	↑	0	↑
Isotretinoin	↑	0	↓
Progestins	↓	↑	↓
Protease inhibitors	↑	0	0
Sertraline	↑	↑	0
Tacrolimus	↑	↑	↑
Thiazide diuretics	↑	↑	↓
Valproate	↑	0	↓

Effect seen may vary depending on dose, duration of exposure and drugs within same class.
↓, reduction; ↑, increase; 0, no change.

of the other and treatment of one does not resolve the other. There are, however, two notable exceptions to the rule with this example: nicotinic acid and fenofibrate. Both drugs reduce triglyceride levels but nicotinic acid increases urate levels while fenofibrate reduces them by an independent uricosuric effect.

Some of the more common disorders that cause secondary dyslipidaemias include the following.

Diabetes mellitus

Premature atherosclerotic disease is the main cause of reduced life expectancy in patients with diabetes. The atherosclerotic disease is often widespread and complications such as plaque rupture and thrombotic occlusion occur more often and at a younger age. The prevalence of CHD is up to four times higher among diabetic patients with more than 80% likely to die from a cardiovascular event. LDL levels are a stronger predictor of CV risk in diabetic patients than blood glucose control or blood pressure.

Type 1 diabetes. In patients with type 1 diabetes, HDL-C may appear high but for reasons which are unclear, it does not impart the same degree of protection against CVD as in those without diabetes. It is, therefore, not appropriate to use cardiovascular risk prediction charts that utilise the TC:HDL-C ratio in patients with type 1 diabetes. Patients with type 1 diabetes have a two- to three-fold increased risk of developing CVD.

Type 2 diabetes. Patients with type 2 diabetes typically have increased triglycerides and decreased HDL-C. Levels of TC may be similar to those found in non-diabetic individuals but the patient with type 2 diabetes often has increased levels of highly atherogenic small dense LDL particles.

Individuals with type 2 diabetes and aged over 40 years, but without CVD, are often considered to have the same cardiovascular risk as patients without diabetes who have survived a myocardial infarction. This assumption is generally appropriate but influenced by patient age, duration of diabetes and gender and holds better for women than men. This probably occurs because the impact of type 2 diabetes is more marked in women than men. In some guidelines, the criteria for at risk is age above 40 years but with one other risk factor present, for example, hypertension, obesity, smoker, etc.

National Institute of Health and Clinical Excellence (2008a) consider an individual with type 2 diabetes to be at high premature cardiovascular risk for their age unless he or she:

- is not overweight
- is normotensive (<140/80 mmHg in the absence of antihypertensive therapy)
- does not have microalbuminuria
- does not smoke
- does not have a high-risk lipid profile
- has no history of CVD and
- has no family history of CVD.

Where the individual is found to be at risk the patient is typically started on 40 mg simvastatin (or equivalent generic statin). Current guidance indicates the dose can be titrated up to simvastatin 80 mg a day if lipid levels are not reduced to less than 4 mmol/L for TC and less than 2 mmol/L for LDL-C on 40 mg simvastatin. In those who do not reach target with 80 mg simvastatin, 80 mg atorvastatin may be tried. However, with both drugs at the higher dose there is increasing concern about their side effect profile and consequently use is limited at these doses.

Individuals aged 18–39 with type 2 diabetes may also be at high risk and in need of treatment with a statin. Again at-risk individuals typically receive 40 mg simvastatin, or equivalent alternate statin, a day titrated up to 80 mg a day if levels for TC of less than 4 mmol/L and less than 2 mmol/L for LDL-C are not achieved. Again there are emerging concerns about use of these higher doses.

Hypothyroidism

Abnormalities of serum lipid and lipoprotein levels are common in patients with untreated hypothyroidism. Hypothyroidism may elevate LDL-C because of reduced LDL receptor activity and it frequently causes hypertriglyceridaemia and an associated reduction in HDL-C as a result of reduced lipoprotein lipase activity. Remnants of chylomicrons and VLDL-C may also accumulate. However, once adequate thyroid replacement has been instituted the dyslipidaemia should resolve.

Chronic renal failure

Dyslipidaemia is frequently seen in patients with renal failure in the predialysis phase, during haemodialysis or when undergoing chronic ambulatory peritoneal dialysis. The hypertriglyceridaemia that most commonly occurs is associated with reduced lipoprotein lipase activity and often persists despite starting chronic maintenance renal dialysis.

Nephrotic syndrome

In patients with the nephrotic syndrome, dyslipidaemia appears to be caused by an increased production of apoB-100 and associated VLDL-C along with increased hepatic synthesis of LDL-C and a reduction in HDL-C. The necessary use of glucocorticoids in patients with the nephrotic syndrome may exacerbate underlying lipoprotein abnormality.

Obesity

Chronic, excessive intake of calories leads to increased concentrations of triglycerides and reduced HDL-C. Obesity *per se* can exacerbate any underlying primary dyslipidaemia. Individuals with central obesity appear to be at particular risk of what has become known as the metabolic or DROP (***d***yslipidaemia, insulin ***r***esistance, ***o***besity and high blood ***p***ressure) syndrome which represents a cluster of risk factors. Obesity and sedentary lifestyle coupled with inappropriate diet and genetic factors interact to produce the syndrome (Kolovou et al., 2005).

Alcohol

In the heavy drinker, the high calorie content of beer and wine may be a cause of obesity with its associated adverse effect on the lipid profile. In addition, alcohol increases hepatic triglyceride synthesis, which in turn produces hypertriglyceridaemia.

Light to moderate drinkers (1–3 units/day) have a lower incidence of CVD and associated mortality than those who do not drink. This protective effect is probably due to an increase in HDL-C, and appears independent of the type of alcohol. Men should be advised to limit their alcohol intake to 3–4 units a day, and not exceed 21 units a week. For women, the equivalent recommendation is 2–3 units a day with a maximum intake of 14 units a week. Everyone should be advised not to binge drink and have one or two alcohol free days a week.

Drugs

A number of drugs can adversely affect serum lipid and lipoprotein concentrations (see Table 24.2).

Antihypertensive agents. Hypertension is a major risk factor for atherosclerosis, and the beneficial effects of lowering blood pressure are well recognised. It is, however, a concern that, although treatment of patients with some antihypertensives has reduced the incidence of cerebrovascular accidents and renal failure, there has been no major impact in reducing the incidence of CHD. It has been suggested that some of these antihypertensive agents have an adverse effect on lipids and lipoproteins that override any beneficial reduction of blood pressure.

Diuretics. Thiazide and loop diuretics increase VLDL-C and LDL-C by mechanisms that are not completely understood. Whether these adverse effects are dose dependent is also unclear. Use of a thiazide for less than 1 year has been reported to increase TC by up to 7% with no change in HDL-C. However, there is evidence that the short-term changes in lipids do not occur with the low doses in current use. Studies of 3–5 years' duration have found no effect on TC.

β-Blockers. The effects of β-blockers on lipoprotein metabolism are reflected in an increase in serum triglyceride concentrations, a decrease in HDL-C, but with no discernible effect on LDL-C. β-Blockers with intrinsic sympathomimetic activity appear to have little or no effect on VLDL-C or HDL-C. Pindolol has intrinsic sympathomimetic activity but is rarely used as an antihypertensive agent since it may exacerbate angina. Alternatively, the combined α- and β-blocking effect of labetalol may be of use since it would appear to have a negligible effect on the lipid profile.

Overall, the need to use a diuretic or a β-blocker must be balanced against patient considerations. A patient in heart failure should receive a diuretic if indicated regardless of the lipid profile. Likewise, the patient with heart failure may also benefit from a β-blocker such as bisoprolol or carvedilol. Patients who have had a myocardial infarction should be considered for the protective effect of a β-blocker and again the benefits of use will normally override any adverse effects on the lipid profile.

If an antihypertensive agent is required, that is, without adverse effects on lipoproteins, many studies would suggest that angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, calcium channel blockers or α-adrenoceptor blockers could be used.

Oral contraceptives. Oral contraceptives containing an oestrogen and a progestogen provide the most effective contraceptive preparations for general use and have been well studied with respect to their harmful effects.

Oestrogens and progestogens both possess mineralocorticoid and glucocorticoid properties that predispose to hypertension and diabetes mellitus, respectively. However, the effects of the two hormones on lipoproteins are different. Oestrogens cause a slight increase in hepatic production of VLDL-C and HDL-C, and reduce serum LDL-C levels. In contrast, progestogens increase LDL-C and reduce serum HDL-C and VLDL-C.

The specific effect of the oestrogen or progestogen varies with the actual dose and chemical entity used. Ethinyloestradiol at a dose of 30–35 µcg or less would appear to create few problems with lipid metabolism, while norethisterone is one of the more favourable progestogens even though it may cause a pronounced decrease in HDL-C.

Corticosteroids. The effect of glucocorticoid administration on lipid levels has been studied in patients treated with steroids for asthma, rheumatoid arthritis and connective tissue disorders. Administration of a glucocorticoid such as prednisolone has been shown to increase TC and triglycerides by elevating LDL-C and, less consistently, VLDL-C. The changes are generally more pronounced in women. Alternate-day therapy with glucocorticoids has been suggested to reduce the adverse effect on lipoprotein levels in some patients.

Ciclosporin. Ciclosporin is primarily used to prevent tissue rejection in recipients of renal, hepatic and cardiac transplants. Its use has been associated with increased LDL-C levels, hypertension and glucose intolerance. These adverse effects are often exacerbated by the concurrent administration of glucocorticoids. The combined use of ciclosporin and glucocorticoid contributes to the adverse lipid profile seen in transplant patients. Unfortunately, the administration of a statin to patients treated with ciclosporin increases the incidence of myositis, rhabdomyolysis (dissolution of muscle associated with excretion of myoglobin in the urine) and renal failure. Use of a statin is, therefore, contraindicated in patients receiving ciclosporin.

Case reports of similar interactions between statins and other drugs used to prevent tissue rejection, including tacrolimus and sirolimus, have also been reported.

Hepatic microsomal enzyme inducers. Drugs such as carbamazepine, phenytoin, phenobarbital, rifampicin and griseofulvin increase hepatic microsomal enzyme activity and can also increase serum HDL-C. The administration of these drugs may also give rise to a slight increase in LDL-C and VLDL-C. The overall effect is one of a favourable increase in the TC:HDL-C ratio. It is interesting to note that patients treated for epilepsy have been reported to have a decreased incidence of CVD.

Risk Assessment

Primary prevention

In patients with no evidence of CHD or other major atherosclerotic disease, there are a number of CVD risk prediction charts, including those produced by the Joint British Societies (JBS2) (British Hypertension Society, 2009) for males (Fig. 24.3) and females (Fig. 24.4). JBS2 recommends that all adults from the age of 40 years, with no history of CVD or diabetes, and not receiving treatment for raised blood pressure or dyslipidaemia, should receive opportunistic screening every 5 years in primary care. The cardiovascular risk calculated using the JBS2 charts is based on the number of cardiovascular events expected over the next 10 years in 100 women or men with the same risk factors as the individual being assessed. Those with a cardiovascular risk >20% over 10 years are deemed to require treatment according to current national and international guidelines, although individuals with a risk as low as 8% over 10 years will gain some benefit, this will be small.

Risk assessment is not required when the individual is 75 years of age or older, or they have pre-existing CVD. These individuals are already assumed to have a 10-year risk of at least 20%.

When using the JBS2 risk prediction charts a number of factors need to be taken into account at screening and include:

- *Age:* in individuals under 40 years of age the charts overestimate risk; over the age of 70 years risk is underestimated by the charts and most have a 10-year risk >20%.
- *Gender:* there are separate charts for men and women.
- *Ethnicity:* the risk prediction charts have only been validated in white caucasians and underestimate risk in individuals from the Indian subcontinent (India, Pakistan, Bangladesh and Sri Lanka) by a factor of 1.5.
- *Smoking history:* individuals who have stopped smoking within 5 years of assessment should be considered as current smokers.
- *Family history:* risk increases by a factor of 1.5 when CHD has occurred in a first-degree relative (parent, offspring, sibling) male <55 years or female <65 years, when a number of family members have developed CHD risk increases by a factor of 2 (Box 24.2).
- *Body mass index (BMI) and waist circumference:* the charts do not adjust for either BMI or waist circumference; these factors need to be taken into account in the clinical decision-making process.
- *Non-fasting blood glucose:* if non-fasting glucose >6.1 mmol/L, the individual should be assessed for impaired glucose regulation or diabetes.

Individuals with type 2 diabetes aged over 40 years and with an additional cardiovascular risk factor are considered to be at greater than 20% risk over 10 years and eligible for treatment. In those who are 40 years of age or older but without any additional risk factor, a specific risk engine is available (http://www.dtu.ox.ac.uk/riskengine/) based on data from the United Kingdom Prospective Diabetes Study.

Framingham

Up to 2008, risk charts and calculators based on Framingham data were the most widely used and researched approach for calculating cardiovascular risk, and are the data on which the risk

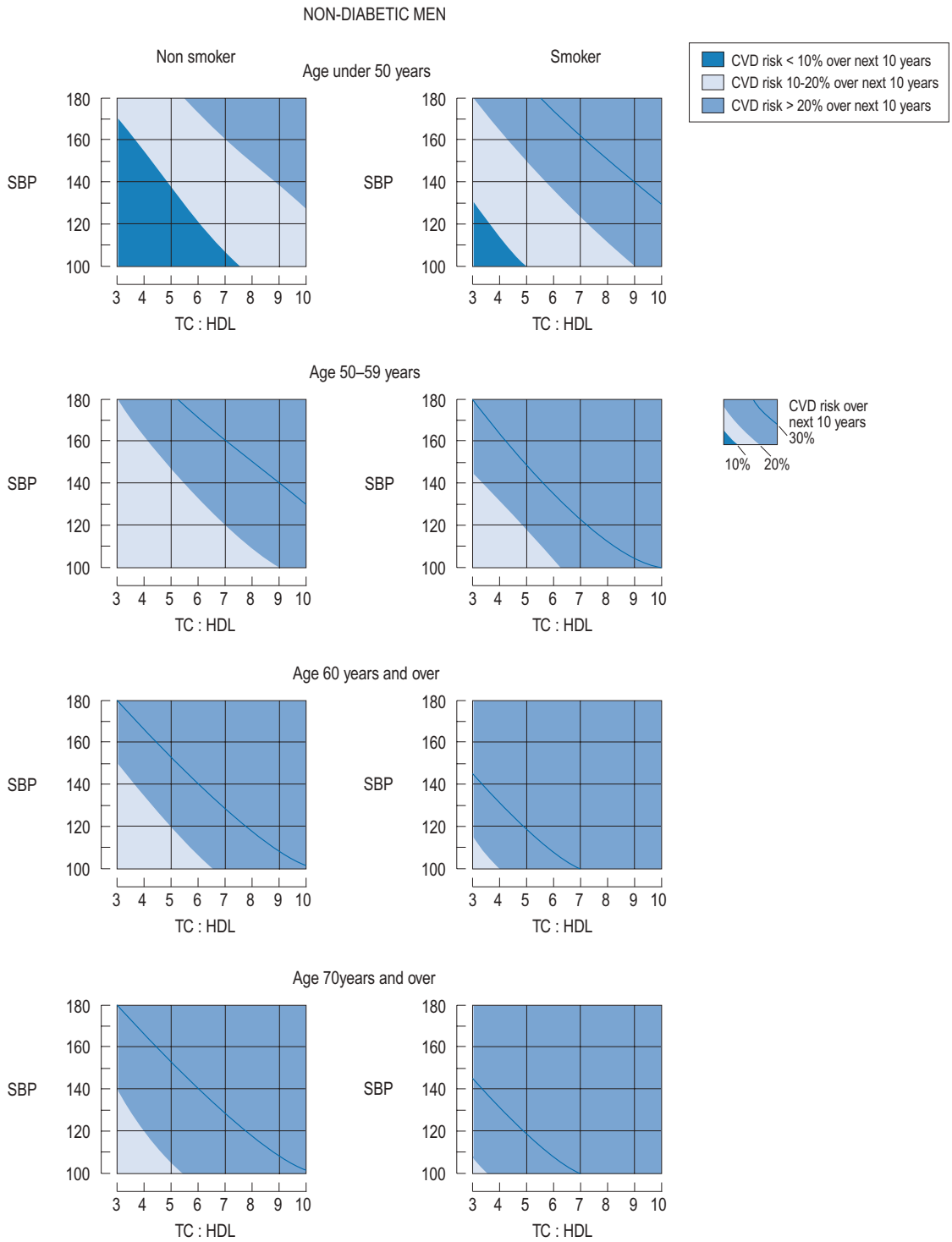


Fig. 24.3 Joint British Societies' cardiovascular disease risk prediction chart for non-diabetic men 2009 (reproduced with kind permission of University of Manchester). SBP, systolic blood pressure mmHg; TC:HDL, serum total cholesterol to HDL cholesterol ratio.

charts discussed above are based. The Framingham data derive from a North American population studied in the 1960s to 1980s. The data generally overestimate risk in the UK population but underestimate risk, as discussed, in those with a family history of premature CVD, South Asian men, people with diabetes and those from a deprived socioeconomic background.

Assign

This is a risk calculator based on data from a Scottish population and includes many of the variables utilised in the Framingham-based model. It also takes into account social status, determined by postcode of residence in Scotland, and

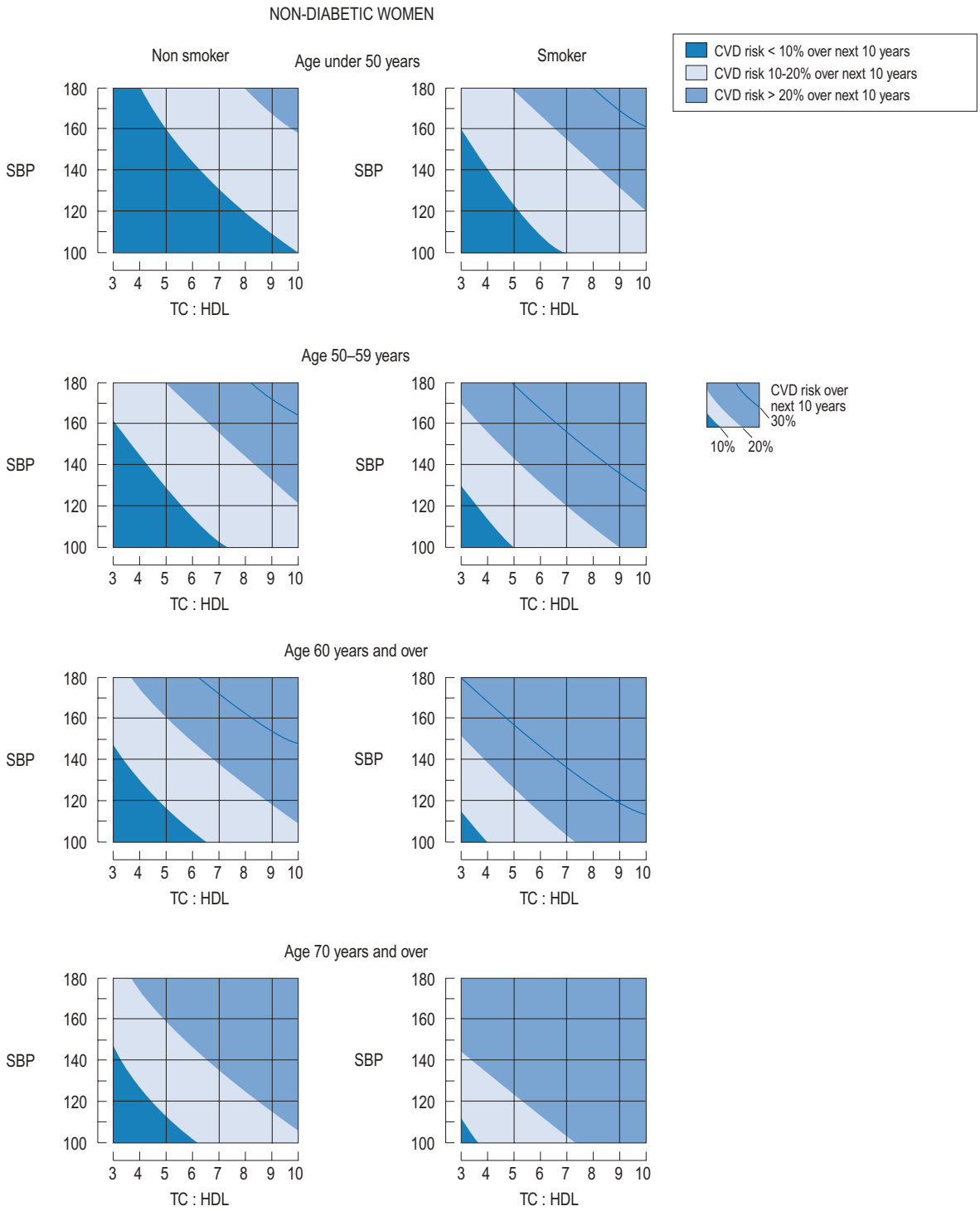


Fig. 24.4 Joint British Societies' cardiovascular disease risk prediction chart for non-diabetic women 2009 (reproduced with kind permission of University of Manchester). SBP, systolic blood pressure mmHg; TC:HDL, serum total cholesterol to HDL cholesterol ratio.

family history of CVD (Woodward et al., 2007). The calculator can be found at: http://www.assign-score.com.

QRISK2

This is a relatively new CVD risk calculator, based on a database of anonymised UK primary care patients established in 2003. It contains over 10 million sets of encrypted patient records. A cohort of 1.28 million patients without evidence of diabetes mellitus or CVD was identified, and followed up for more than 5 years looking for the first development of CVD as an endpoint.

The current version of the calculator (QRISK2) uses the following parameters with any missing values calculated by a complex averaging procedure:

Box 24.2 Criteria that indicate familial hypercholesterolaemia

Family history of dyslipidaemia or cardiovascular disease:
- in first-degree female relative less than 65 years old
- in first-degree male relative less than 55 years old

Xanthelasma or corneal arcus under the age of 45

[a]Tendon xanthomata + TC >7.5 mmol/L at any age
[a]Tendon xanthomata + LDL-C >4.9 mmol/L

[a]Tendon xanthomata may not be readily apparent in younger people

- Patient age (35–74)
- Patient gender
- Current smoker (yes/no)
- Family history of heart disease aged <60 (yes/no)
- Existing treatment with blood pressure agent (yes/no)
- Postcode (postcode is linked to Townsend score measure of deprivation)
- BMI (height and weight)
- Systolic blood pressure (use current not pre-treatment value)
- Total and HDL cholesterol
- Self-assigned ethnicity (not nationality)
- Rheumatoid arthritis
- Chronic kidney disease
- Atrial fibrillation.

The QRISK2 calculator is available at http://www.qrisk.org/

The Department of Health and NICE endorse the use of either Framingham-based risk prediction tools or QRISK2.

Secondary prevention

Patients with CVD and levels of TC >4 mmol/L and LDL-C >2 mmol/L are the ones most likely to benefit from treatment with lipid-lowering agents. Typical of individuals who fall into this category are patients with a history of angina, myocardial infarction, acute coronary syndrome, coronary artery bypass grafting, coronary angioplasty or cardiac transplantation as well as patients with evidence of atherosclerotic disease in other vascular beds such as patients post-stroke or TIA, and those with peripheral arterial disease.

As in the situation with primary prevention outlined above, if an individual is to receive a lipid-lowering agent as part of a secondary prevention strategy, the possibility of a familial dyslipidaemia and the need to assess other family members must not be overlooked (National Institute of Health and Clinical Excellence, 2008b).

Treatment

Lipid profile

When a decision has been made to determine an individual's lipid profile, a random serum TC and HDL-C will often suffice. If a subsequent decision is made to commence treatment and monitor outcome, a more detailed profile that includes triglycerides is required. Treatment should not be initiated on the basis of a single random sample.

Serum concentrations of triglycerides increase after the ingestion of a meal and, therefore, patients must fast for 12–15 h before they can be measured. Patients must also be seated for at least 5 min prior to drawing a blood sample. TC level and HDL are little affected by food intake, and this is, therefore, not a consideration if only these are to be measured. However, it is important that whatever is being measured reflects a steady-state value. For example, during periods of weight loss, lipid concentrations decline as they do following a myocardial infarction. In the case of the latter, samples drawn within 24 h of infarct onset will reflect the preinfarction state. In general, measurement should be deferred for 2 weeks after a minor illness and for 3 months after a myocardial infarction, serious illness or pregnancy.

Once the TC, HDL-C and triglyceride values are known it is usual to calculate the value for LDL-C using the Friedewald equation:

$$\text{LDL-C} = (\text{Total cholesterol} - \text{HDL-C}) - (0.45 \times \text{triglyceride})\ \text{mmol/L}.$$

The Friedewald equation should not be used in non-fasting individuals, it is less reliable in individuals with diabetes and is not valid if the serum triglyceride concentration >4 mmol/L.

Although lipid target levels are normally only defined for TC and LDL-C, increasingly non-HDL-C is measured. The value for non-HDL-C is obtained by subtracting the value for HDL-C from TC. Non-HDL-C consequently represents the total of cholesterol circulating on apoprotein B particles, that is, both LDL and triglyceride-rich lipoproteins, and represents the main atherogenic particles. A desirable value is <3 mmol/L.

Lifestyle

When a decision is made to start treatment with a lipid-lowering agent, other risk factors must also be tackled as appropriate, such as smoking, obesity, high alcohol intake and lack of exercise (Box 24.3). Underlying disorders such as diabetes mellitus and hypertension should be treated as appropriate. Issues around body weight, diet and exercise will be briefly covered in the following sections.

Body weight and waist measurement

The overweight patient is at increased risk of atherosclerotic disease and typically has elevated levels of serum triglycerides, raised LDL-C and a low HDL-C. This adverse lipid profile is often compounded by the presence of hypertension and raised blood glucose, that is, the metabolic syndrome. A reduction in body weight will generally improve the lipid profile and reduce overall cardiovascular risk.

It is useful to classify the extent to which an individual is overweight by calculating their BMI. The BMI (kg/m^2) in all but the most muscular individual gives a clinical measure of adiposity.

- BMI 18.5: underweight
- BMI 18.6 to 24.9: ideal
- BMI 25 to 29.9: overweight (low health risk)

Box 24.3 Lifestyle targets

- Do not smoke
- Maintain ideal body weight (BMI 20–25 kg/m^2)
- Avoid central obesity
- Reduce total dietary intake of fat to ≤30% of total energy intake
- Reduce intake of saturated fats to ≤10% of total fat intake
- Reduce intake of dietary cholesterol to <300 mg/day
- Replace saturated fats by an increased intake of monounsaturated fats
- Increase intake of fresh fruit and vegetables to at least five portions per day
- Regularly eat fish and other sources of omega-3 fatty acids (at least two portions of fish each week)
- Limit alcohol intake to <21 units/week for men and <14 units/week for women
- Restrict intake of salt to <100 mmol day (<6 g of sodium chloride or <2.4 g sodium/day)
- Undertake regular aerobic exercise of at least 30 min/day, most days of the week
- Avoid excess intake of coffee or other caffeine-rich containing products

- BMI 30 to 40: obese (moderate health risk)
- BMI >40: morbidly obese (high health risk)

The distribution of body fat is also recognised as a factor that influences CVD risk. Measurement of waist circumference is perhaps the easiest and most practical indicator of central obesity and correlates well with CVD risk. Target waist circumference should be <102 cm in white caucasian men, <88 cm in white caucasian females and in Asians <90 cm in men and <80 cm in females.

Diet

Diet modification should always be encouraged in a patient with dyslipidaemia but is rarely successful alone in bringing about a significant improvement in the lipid profile. Randomised controlled trials of dietary fat reduction or modification have shown variable results on cardiovascular morbidity and mortality. In pragmatic, community-based studies, reductions in TC of only 3–6% have been achieved. The overall picture is that patients with dyslipidaemia should receive dietary advice and a small number of those who adhere to the advice will experience a fall in TC.

There is a common misconception that a healthy diet is one that is low in cholesterol. However, generally it is the saturated fat content that is important, although many components of a healthy diet are not related to fat content. For example, the low incidence of cardiovascular disease in those who consume a Mediterranean-type diet suggests an increased intake of fruit and vegetables is also important. The typical Mediterranean diet has an abundance of plant food (fruit, vegetables, breads, cereals, potatoes, beans, nuts and seeds) minimally processed, seasonally fresh, and locally grown; fresh fruit as the typical daily dessert, with sweets containing concentrated sugars or honey consumed a few times per week; olive oil as the principal source of fat; dairy products (principally cheese and yoghurt) consumed daily in low to moderate amounts; 0–4 eggs consumed weekly; and red meat consumed in low to moderate amounts. This diet is low in saturated fat (<8% of energy) and varies in total fat content from <25% to >35% of energy.

Fish. Regular consumption of the long chain omega-3 fatty acids, principally ecosapentaenoic acid and docosahexaenoic acid, typically found in fatty fish and fish oils, has been linked to the low levels of CHD seen in Inuits (Eskimos). The risk of fatal myocardial infarction in those with CVD has been shown to be reduced by consuming omega-3 fatty acids. Consumption of omega-3 fatty acids decrease triglyceride levels but have little effect on LDL-C or HDL-C. The proposed mechanisms is thought to involve the omega-3 fatty acids and their antiarrhythmic properties, ability to reduce blood pressure and heart rate, lower triglyceride levels, stimulate endothelial-derived nitric oxide, increase insulin sensitivity, decrease platelet aggregation and decrease proinflammatory eicosanoids. There would appear to be benefits in consuming at least two portions (portion = 140 g) of fish per week, including a portion of oily fish, particularly in those who have had a myocardial infarction. Pregnant women are advised to limit their intake of oily fish to two portions per week because of the potential accumulation of low level pollutants in the fish.

Trans fats. Trans fats are unsaturated fatty acids with at least one double bond in the trans configuration. They are formed when vegetable oils are hydrogenated to convert them into semisolid fats that can be incorporated into margarines or used in commercial manufacturing processes. Trans fats are typically found in deep fried fast foods, bakery products, packaged snack foods, margarines and crackers. When the calorific equivalent of saturated fats, cis unsaturated fats and trans fats are consumed, trans fats raise LDL-C, reduce HDL-C and increase the ratio of TC:HDL-C. In addition to these harmful effects, trans fats also increase the blood levels of triglycerides, increase levels of Lp(a) and reduce the particle size of LDL-C, all of which further increase the risk of CHD. It is, therefore, necessary to reduce the dietary intake of trans fatty acids to less than 0.5% of total energy intake and this has led to calls for a complete ban on trans fats in foods.

Stanol esters and plant sterols. The availability of margarines and other foods enriched with plant sterols or stanol esters appears to increase the likelihood that LDL-C can be reduced by dietary change. Both stanol esters and plant sterols at a maximum effective dose of 2 g/day inhibit cholesterol absorption from the gastro-intestinal tract and reduce LDL-C by an average of 10%. They compete with cholesterol for incorporation into mixed micelles, thereby impairing its absorption from the intestine. However, as with other dietary changes, the reduction seen varies between individuals and is probably dependent on the initial cholesterol level. There is currently no evidence that ingestion lowers the risk of cardiovascular events.

Antioxidants. Antioxidants occur naturally in fruit and vegetables and are important components of a healthy diet. Their consumption is thought to be beneficial in reducing the formation of atherogenic, oxidised LDL-C. Primary and secondary prevention trials with antioxidant vitamin supplements,

however, have not been encouraging. Neither vitamin E nor beta-carotene supplements would appear to reduce the risk of CHD but likewise have not been shown to be harmful.

Salt. Dietary salt (sodium) has an adverse effect on blood pressure and, therefore, a potential impact on CHD and stroke. As part of dietary advice the average adult intake of sodium should be reduced from approximately 150 mmol (9 g)–100 mmol (6 g) of salt or even lower. This intake can be reduced by consuming fewer processed foods, avoiding many ready meals and not adding salt to food at the table.

Exercise

Moderate amounts of aerobic exercise (brisk walking, jogging, swimming, cycling) on a regular basis have a desirable effect on the lipid profile of an individual. These beneficial effects have been demonstrated within 2 months in middle-aged men exercising for 30 min, three times a week. Current advice for adults who are not routinely active is to undertake 30 min of moderate-intensity activity on at least 5 days of the week. This can be undertaken in bouts of 10 min. For active individuals, additional aerobic exercise of vigorous intensity is recommended for 20–30 min three times a week. Exercise *per se* probably has little effect on TC levels in the absence of a reduction in body weight, body fat or dietary fat. Perhaps the most important effect of regular exercise is to raise levels of HDL-C in a dose-dependent manner according to energy expenditure.

Overall, comprehensive dietary and lifestyle changes (stopping smoking, stress management training and moderate exercise) can bring about regression of coronary atherosclerosis. Unfortunately, many find it difficult to attain or sustain the necessary changes. In others, dietary and lifestyle changes alone will never be adequate or will not bring about the necessary improvement in lipid profile quickly enough. As a consequence, the use of lipid-lowering drugs is widespread.

Drugs

If an individual is found to be at risk of CVD (primary prevention) it may be appropriate to give a trial of dietary and lifestyle changes for 3–6 months. This rarely achieves the required effect on the lipid profile and drug therapy is required. This must not, however, negate a sustained effort by the individual to make appropriate dietary and lifestyle adjustments. In an individual requiring treatment for secondary prevention, a delay of several months in starting treatment is not appropriate and treatment will normally be commenced immediately with a lipid-lowering agent.

Primary prevention

In primary prevention, dyslipidaemia should not be treated in isolation and management must be embarked upon with clear goals. In addition to lifestyle advice, this will not only address management of dyslipidaemia but will also seek to optimise use of antihypertensive agents, other cardiovascular protective therapies and achieve tight blood glucose control as appropriate. In patients without evidence of arterial disease, treatment must be considered if the risk of CVD is >20% or more over 10 years. Although some dispute the benefit of statins in primary prevention (Kausik et al., 2010), treatment will normally include:

- a lipid-lowering agent such as simvastatin 40 mg/day (or alternative) but no treatment targets are set
- personalised information on modifiable risk factors including physical activity, diet, alcohol intake, weight and tight control of diabetes
- advice to stop smoking
- advice and treatment to achieve blood pressure below 140 mmHg systolic and 90 mmHg diastolic.

Some also consider an isolated raised TC:HDL ratio >6.5 warrants treatment regardless of the risk assessment outcome, but this approach has received little support in national treatment guidelines.

Secondary prevention

In individuals diagnosed with CVD or other occlusive arterial disease, treatment should include:

- a lipid-lowering agent to lower TC aiming towards a TC <4 mmol/L and LDL-C <2 mmol/L
- advice to stop smoking
- personalised information on modifiable risk factors including physical activity, diet, alcohol intake, weight and diabetes
- advice and treatment to achieve blood pressure at least below 140 mmHg systolic and 90 mmHg diastolic
- tight control of blood pressure and glucose in those with diabetes
- low-dose aspirin (75 mg daily)
- ACE inhibitors especially for those with left ventricular dysfunction, heart failure, diabetes, hypertension or nephropathy
- β-blocker for those who have had a myocardial infarction and in those with heart failure
- warfarin (or aspirin) for those with atrial fibrillation and additional stroke risk factors.

Lipid-lowering therapy

There are five main classes of lipid-lowering agents available:

- Statins
- Fibrates
- Bile acid binding agents
- Cholesterol absorption inhibitors
- Nicotinic acid and derivatives.

Agents such as soluble fibre and fish oils have also been used to reduce lipid levels. A number of new agents are also under investigation for their novel effect on different parts of the cholesterol biosynthesis pathway (Table 24.3).

Table 24.3 Mechanism of lipid-lowering agents under investigation

Drug group	Mechanism
Acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors	ACAT esterifies excess intracellular cholesterol. Inhibition of ACAT prevents transport of cholesterol into the arterial wall and thereby prevents atheroma developing. Lowers VLDL-C and triglycerides
Bile acid sequestrants	Related to first-generation resins but improved patient tolerance. Sequester bile acids and prevent re-absorption. Reduce LDL-C while HDL-C and triglycerides increase or remain unchanged
Cholesteryl ester transfer protein (CETP) inhibitors	CETP is responsible for the transfer of cholesteryl ester from HDL-C to the atherogenic LDL-C and VLDL-C
Lipoprotein lipase (LPL) activity enhancers	LPL is responsible for VLDL-C catabolism with subsequent loss of triglycerides and increase in HDL-C. Protects against atherosclerosis
Microsomal triglyceride transfer protein (MTP) inhibitors	Inhibit absorption of lipid and reduce hepatic secretion of lipoproteins, thereby reducing atherosclerotic plaque formation
Peroxisome proliferator-activated receptor (PPAR) activators	PPAR-α and -γ regulate the expression of genes involved in lipid metabolism and inhibit atherosclerotic plaque rupture. They reduce entry of cholesterol into cells, lower LDL-C and triglycerides, and increase HDL-C
Squalene synthase inhibitors	Inhibit squalene synthase, upregulate LDL receptor activity and enhance removal of LDL-C

The choice of lipid-lowering agent depends on the underlying dyslipidaemia, the response required and patient acceptability. The various groups of drugs available have different mechanisms of action and variable efficacy depending on the lipid profile of an individual. Statins are currently the drugs of choice in the majority of patients with dyslipidaemia due to the overwhelming evidence that treatment with these agents reduces cardiovascular events.

Statins

The discovery of a class of drugs, the statins, which selectively inhibit 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) was a significant advance in the treatment of dyslipidaemia. Their primary site of action is the inhibition of HMG-CoA reductase in the liver and the subsequent inhibition of the formation of mevalonic acid, the rate-limiting step in the biosynthesis of cholesterol. This results in a reduction in intracellular levels of cholesterol, an increase in expression of hepatic LDL receptor, and enhanced receptor-mediated catabolism and clearance of LDL-C from serum. Production of VLDL-C, the precursor of LDL-C, is also reduced. The overall effect is a reduction in TC, LDL-C, VLDL-C and triglycerides with an increase in HDL-C. The reduction in LDL-C occurs in a dose-dependent manner, with a lesser and dose-independent effect on VLDL-C and triglycerides.

Simvastatin was the first member of the group to be marketed in the UK and it was followed by pravastatin, fluvastatin, atorvastatin, cerivastatin and rosuvastatin. Cerivastatin was withdrawn from the market in 2001 due to an observed increased risk of fatal rhabdomyolysis whilst rosuvastatin, the newest member of the group, was launched in March 2003. Lovastatin has been available in the USA for many years whilst pitavastatin, likewise, has been available in Japan since 2003 with little attempt, until recently, to market in the UK.

The efficacy of statins has been demonstrated in a number of landmark, randomised placebo-controlled trials. A greater absolute benefit was seen in those trials that involved established CVD, that is, secondary prevention studies, compared to those that involved individuals without established CVD, that is, primary prevention studies. Statins are currently the lipid-lowering agents of choice in both primary and secondary prevention of CVD.

There is much debate around the statin of choice. Simvastatin is currently the preferred agent because of its relatively low cost, safety profile and evidence of efficacy (see Table 24.4). Perhaps more important is the need to identify patients who need treatment, ensure they receive an appropriate, effective dose of a statin and adhere to treatment. Despite overwhelming evidence of benefit, effectiveness is frequently compromised by poor adherence with up to 50% of patients discontinuing treatment within 12 months and 75% within 3 years. Patient factors that influence this include perception of risk, side effects of medication, expected treatment duration and socio-demographic factors.

Rosuvastatin is the most potent of the statins with evidence of impact on morbidity and mortality. It is normally reserved for those individuals that have had an inadequate response to their first-line statin. There remain concerns about its safety profile, and rhabdomyolysis in particular, when used at the higher dose of 40 mg/day. It is recommended that this dose should only be used in individuals with severe FH and at high cardiovascular risk under specialist supervision. In patients of Asian origin (Japanese, Chinese, Filipino, Vietnamese, Korean and Indian), the maximum dose should not exceed 20 mg/day because of their increased predisposition to myopathy and rhabdomyolysis.

Table 24.4 Typical recommendations for use of lipid-lowering agents (UKMI, 2009) (LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; TC, total cholesterol)

Drug therapy	Primary prevention (If >40 years and 10-year risk ≥ 20%)		Secondary prevention (All adults with CVD)		Acute coronary syndrome	Familial hypercholesterolaemia (adults)
	WITHOUT diabetes	WITH diabetes (any age)	WITHOUT diabetes	WITH diabetes		
FIRST LINE						
Simvastatin dose	40 mg	40 mg	40 mg	40 mg	High intensity statin*	40 mg
SECOND-LINE AFTER INITIAL TREATMENT WITH SIMVASTATIN 40 MG (OR EQUIVALENT)						
High-intensity statin (simvastatin 80 mg or equivalent alternative)	No recommendations	Consider if TC >4.0 mmol/L AND LDL-C >2 mmol/L	Consider if TC >4.0 mmol/L AND LDL-C >2 mmol/L	Consider if TC >4.0 mmol/L AND LDL-C >2 mmol/L	*Simvastatin 80 mg or atorvastatin 80 mg	Give if needed to achieve a reduction in LDL-C of >50% from baseline
OTHER TREATMENT OPTIONS						
Ezetimibe	Only if statin not tolerated	No recommendations	Only if statin not tolerated	Add to statin if there is existing or newly diagnosed CVD or increased albumin excretion rate	Only if statin not tolerated	Use as monotherapy if: statins contraindicated or not tolerated, OR combined with a statin if: TC or LDL-C not controlled
Fibrates	Only if statin not tolerated	Add to statin if: TG > 4.5 mmol/L despite optimised glycaemic control TG 2.3 – 4.5 mmol/L and high CVD risk	Only if statin not tolerated	Add to statin if TG remains >4.5 mmol/L despite optimised glycaemic control	Only if statin not tolerated	Use only on the advice of a specialist: if statins or ezetimibe are contraindicated or not tolerated, in combination with a statin on specialist advice
Bile acid sequestrants	Only if statin not tolerated	No recommendations	Only if statin not tolerated	No recommendations	Only if statin not tolerated	
Nicotinic acid	No recommendations	Do not use routinely	Only if statin not tolerated	Do not use routinely	Only if statin not tolerated	

All the statins require the presence of LDL receptors for their optimum clinical effect, and consequently they are less effective in patients with heterozygous FH because of the reduced number of LDL receptors. However, even in the homozygous patient where there are no LDL receptors they can bring about some reduction of serum cholesterol, although the mechanism is unclear.

Adverse effects

Many side effects appear mild and transient. The commonest include gastro-intestinal symptoms, altered liver function tests and muscle aches. Less common are elevation of liver transaminase levels in excess of three times the upper limit of normal, hepatitis, rash, headache, insomnia, nightmares, vivid dreams and difficulty concentrating.

Myopathy (unexplained muscle soreness or weakness) leading to myoglobulinuria secondary to rhabdomyolysis is also a rare but serious potential adverse effect of all the statins that can occur at any dose. The risk of myopathy is increased:

- when there are underlying muscle disorders, a family history of muscle disorders, renal impairment, untreated hypothyroidism, alcohol abuse, or the recipient is aged over 65 years or female
- where statins are co-prescribed with other lipid-lowering drugs, for example, fibrates, nicotinic acid
- when there is a past history of myopathy with another lipid-lowering drug or statin
- where there is co-prescription of simvastatin or atorvastatin with drugs that inhibit CYP3A4.

The statins are a heterogeneous group metabolised by different CYP450 isoenzymes. Simvastatin, atorvastatin and lovastatin are metabolised by CYP3A4, fluvastatin is metabolised by CYP 2C9, and pravastatin and rosuvastatin are eliminated by other metabolic routes and less subject to interactions with CYP450 isoenzymes than other members of the family. Nevertheless, caution is still required as a 5- to 23-fold increase in pravastatin bioavailability has been reported with ciclosporin. Simvastatin and atorvastatin do not alter the activity of CYP3A4 themselves, but their serum levels are increased by known inhibitors of CYP3A4 (Table 24.5). Advice has been published for the prescribing of simvastatin and atorvastatin with inhibitors of CYP3A4 (Table 24.6).

Pleiotropic properties

While the effect of statins on the lipid profile contributes to their beneficial outcome in reducing morbidity and mortality from CVD, other mechanisms, known as pleiotropic effects, may also play a part. These effects include plaque stabilisation, inhibition of thrombus formation, reduced serum viscosity and anti-inflammatory and antioxidant activity. These pleiotropic properties, that is, cholesterol-independent effects, are far reaching and reveal a clinical impact beyond a process of reducing TC. For example, lowering TC produces only modest reductions of a fixed, atherosclerotic, luminal stenosis but results in a qualitative change of the plaque and helps stabilise it. This protects the plaque from rupturing and triggering further coronary events.

Table 24.5 Examples of drug interactions involving statins and the cytochrome P450 enzyme pathway

CYP 450 isoenzyme	Inducers	Inhibitors
CYP3A4		
Atorvastin Lovastatin Simvastatin	Phenytoin Barbiturate Rifampicin Dexamethasone Cyclophosphamide Carbamazepine Omeprazole	Ketoconazole Itraconazole Fluconazole Erythromycin Clarithromycin Tricyclic antidepressants Nefazodone Venlafaxine Fluoxetine Sertraline Ciclosporin Tacrolimus Diltiazem Verapamil Protease inhibitors Midazolam Corticosteroids Grapefruit juice Tamoxifen Amiodarone
CYP2C9		
Fluvastatin	Rifampicin Phenobarbitone Phenytoin	Ketoconazole Fluconazole Sulfaphenazole

Table 24.6 Advice for prescribing simvastatin or atorvastatin with inhibitors of CYP3A4

Avoid simvastatin with potent inhibitors of CYP3A4:	HIV protease inhibitors, azole, antifungals, erythromycin, clarithromycin, telithromycin
Do not exceed the following doses:	Simvastatin 10 mg daily with ciclosporin, gemfibrozil or niacin (>1 g/day) Simvastatin 20 mg daily with verapamil or amiodarone Simvastatin 40 mg daily with diltiazem
Avoid grapefruit juice when taking simvastatin	
Atorvastatin to be used cautiously with CYP3A4 inhibitors:	Additional care required at high doses of atorvastatin; avoid drinking large quantities of grapefruit juice

Inflammation is thought to play a prominent part in the development of atherosclerosis and increased levels of C-reactive protein have been used to identify individuals at risk of plaque rupture and consequent myocardial infarction and stroke. Statins have been shown to reduce the levels of C-reactive protein in several trials.

An important aspect of vascular endothelium dysfunction is the impaired synthesis, release and activity of endothelial-derived nitric oxide, an important and early marker of atherosclerosis. After the administration of a statin, one of the earliest effects observed (within 3 days) is an increased endothelial nitric oxide release, thereby mediating an improvement in vasodilation of the endothelium.

For some while it has been thought that part of the beneficial effect of statins on CVD could be attributed to an effect on blood coagulation. It is now evident that statins, amongst their many actions, decrease platelet activation and activity, reduce prothrombin activation, factor Va generation, fibrinogen cleavage and factor XIII activation, and increase factor Va inactivation.

Over-the-counter sale

Low-dose (10 mg) simvastatin can be purchased from community pharmacies in the UK to treat individuals at moderate cardiovascular risk. Men aged 55–70 years with or without risk factors and men aged 45–54 years or women aged 55–70 years with at least one risk factor (smoker, obese, family history of premature CHD or of South Asian origin) are eligible for treatment. Simvastatin cannot be sold to individuals who have CVD, diabetes or familial dyslipidaemia or are taking lipid-lowering agents or medication that may interact with simvastatin. The rationale for over-the-counter sale is to reduce the risk of a first major coronary event in adults at moderate risk but sales have been low. Moreover, the evidence base to support the use of 10 mg simvastatin and achieve long-term cardiovascular benefit is limited.

Patient counselling

In patients receiving a statin, a once-daily regimen involving an evening dose is often preferred. Several of the statins (fluvastatin, pravastatin, simvastatin) are claimed to be more effective when given as a single dose in the evening compared to a similar dose administered in the morning. This has been attributed to the fact that cholesterol biosynthesis reaches peak activity at night. However, atorvastatin and rosuvastatin may be taken in the morning or evening with similar efficacy. A reduction in TC and LDL-C is usually seen with all statins within 2 weeks, with a maximum response occurring by week 4 and maintained thereafter during continued therapy.

Fibrates

Members of this group include bezafibrate, ciprofibrate, fenofibrate and gemfibrozil. They are thought to act by binding to peroxisome proliferator-activated receptor α (PPAR-α) on hepatocytes. This then leads to changes in the expression of genes involved in lipoprotein metabolism. Consequently, fibrates reduce triglyceride and, to a lesser extent, LDL-C levels while increasing HDL-C. Fibrates take 2–5 days to have a measurable effect on VLDL-C, with their optimum effect present after 4 weeks. In addition to their effects on serum lipids and lipoproteins, the fibrates may also have a beneficial effect on the fibrinolytic and clotting mechanisms. The fibrates also produce an improvement in glucose tolerance, although bezafibrate probably has the most marked effect.

In the patient with elevated triglycerides and gout, only fenofibrate has been reported to have a sustained uricosuric effect on chronic administration. Overall, there appears little to differentiate members of the group with regard to their effect on the lipid profile, with fenofibrate and ciprofibrate being the most potent members of the group.

In patients with diabetes, the typical picture of dyslipidaemia is one of raised triglycerides, reduced HDL-C and near normal LDL-C. Despite the effect of fibrates to reduce triglycerides and increase HDL-C, statins are first-line lipid-lowering agent in most guidelines because of a lack of clear evidence that fibrates prevent CVD in diabetes. It was hoped that a 5-year study of fenofibrate in individuals with type 2 diabetes (FIELD Investigators, 2005) would clarify the issue. However, in the final analysis the results provided little convincing evidence to change from recommending a statin, although they did confirm the safety of using a combination of a statin and fenofibrate. In contrast, gemfibrozil should not be used with a statin.

Overall, fibrates should not be used first line to reduce lipid levels in either primary or secondary prevention. Fibrates can be used first line in patients with isolated severe hypertriglyceridaemia. In individuals with mixed hyperlipidaemia, fibrates may be considered when a statin or other agent is contraindicated or not tolerated.

Adverse effects

Overall, the side effects of fibrates are mild and vary between members of the group. Their apparent propensity to increase the cholesterol saturation index of bile renders them unsuitable for patients with gallbladder disease. Gastro-intestinal symptoms such as nausea, diarrhoea and abdominal pain are common but transient, and often resolve after a few days of treatment. Myositis has been described, and is associated with muscle pain, unusual tiredness or weakness. The mechanism is unclear but it is thought fibrates may have a direct toxic action on muscle cells in susceptible individuals.

Fibrates have been implicated in a number of drug interactions (Table 24.7), of which two in particular are potentially serious. Fibrates are known to significantly increase the effect of anticoagulants, while concurrent use with a statin is associated with an increased risk of myositis and, rarely, rhabdomyolysis. Concurrent use of cerivastatin and gemfibrozil was noted to cause rhabdomyolysis and this contributed to the withdrawal of cerivastatin from clinical use in 2001.

Bile acid binding agents

The three members of this group in current use are colestyramine, colestipol and colesevelam. Both colestyramine and colestipol were formerly considered first-line agents in the management of patients with FH but now have limited use. Colesevalam is the most recent of the bile acid binding agents to receive marketing authorisation (in 2004) and consequently has never had a first-line indication. Each of the bile acid binding agents reduce TC and increase triglyceride levels.

Table 24.7 Typical drug interactions involving bile acid binding agents and fibrates[a]

Drug group	Interacting drug	Comment
Bile acid binding agents Colestyramine/colestipol		All medication should be taken 1 h before or at least 4 h after colestyramine/colestipol to reduce absorption caused by binding in the gut
	Acarbose	Hypoglycaemia enhanced by colestyramine
	Digoxin	Absorption reduced
	Diuretics	Absorption reduced
	Levothyroxine	Absorption reduced
	Mycophenolate mofetil	Absorption reduced
	Paracetamol	Absorption reduced
	Raloxifene	Absorption reduced
	Valproate	Absorption reduced
	Statins	Absorption reduced
	Vancomycin	Effect of oral vancomycin antagonised by colestyramine
	Warfarin	Increased anticoagulant effect due to depletion of vitamin K or reduced anticoagulant effect due to binding or warfarin in gut
Colesevelam		All medication should be taken at least 4 h before or 4 h after colesevelam to reduce absorption caused by binding in the gut
	Ciclosporin	Absorption reduced
	Digoxin	Absorption unchanged
	Glyburide	Absorption reduced
	Levothyroxine	Absorption reduced
	Oral contraceptive	Absorption reduced
	Statins	Absorption unchanged
	Valproate	Absorption unchanged
	Warfarin	Absorption unchanged. Increased anticoagulant possible due to depletion of vitamin K
Fibrates	Antidiabetic agents	Improvement in glucose tolerance
	Ciclosporin	Increased risk of renal impairment
	Colestyramine/colestipol	Reduced bioavailability of fibrate if taken concomitantly
	Statin	Increased risk of myopathy
	Warfarin	Increased anticoagulant effect

[a]Absorption studies involve concomitant administration.

Following oral administration, neither colestyramine, colestipol nor colesevelam are absorbed from the gut. They bind bile acids in the intestine, prevent re-absorption and produce an insoluble complex that is excreted in the faeces. The depletion of bile acids results in an increase in hepatic synthesis of bile acids from cholesterol. The depletion of hepatic cholesterol upregulates the hepatic enzyme 7-α-hydoxylase which increases the conversion of cholesterol to bile acids. This increases LDL receptor activity in the liver and removes LDL-C from the blood. Hepatic VLDL-C synthesis also increases and it is this which accounts for the raised serum triglycerides.

Colestyramine has a starting dose of one 4 g sachet twice a day. Over a 3- to 4-week period the dose should normally be built up to 12–24 g daily taken in water or a suitable liquid as a single dose, or up to four divided doses each day. Occasionally, 36 g a day may be required, although the benefits of increasing the dose above 16 g a day are offset by gastro-intestinal disturbances and poor patient adherence.

Colestipol is also available in a granular formulation and can be mixed with an appropriate liquid at a dose of 5 g once or twice daily. This dose can be increased every 1–2 months to a maximum of 30 g in a single- or twice-daily regimen.

Colesevalam is up to six times as potent as the other bile acid binding agents, probably because of a greater binding to glycocholic acid. Whether this translates into better clinical outcomes or more, or less, problems with drugs administered concurrently is unclear. Colesevalam is administered as a 625-mg tablet to a maximum dose of 4.375 g/day (7 tablets). There is limited evidence to suggest it may achieve a higher adherence than colestyramine or colestipol. It can be taken as a single- or twice-daily regimen.

Adverse effects

With all three agents, side effects are more likely to occur with high doses and in patients aged over 60 years. Bloating, flatulence, heartburn and constipation are common complaints. Constipation is the major subjective side effect, and although usually mild and transient, it may be severe.

Colestyramine, colestipol and colesevelam are known to interact with many drugs primarily by interfering with absorption (Table 24.7). Whether these absorption-type interactions are qualitatively and quantitatively similar between the different agents is unclear and the picture is confused when the

absorption of a given drug is known to interact with one bile acid binding agent but has not been tested with other members of the group.

Long-term use of bile acid binding agents may also interfere with the absorption of fat soluble vitamins and supplementation with vitamins A, D and K is recommended.

Patient counselling

Palatability is often a major problem with the bile acid binding agents and patients need to be well motivated and prepared for the problems they may encounter.

Both colestyramine and colestipol are available in an orange flavour and/or as a low sugar (aspartame-containing) powder. Colestipol is without taste and is odourless. Each sachet of colestyramine or colestipol should be added to at least 150 or 100 mL of liquid, respectively, and stirred vigorously to avoid the powder clumping. The powder does not dissolve but disperses in the chosen liquid, which may be water, fruit juice, skimmed milk or non-carbonated beverage. Both may also be taken in soups, with cereals, and with pulpy fruits with high moisture content, such as apple sauce.

All patients receiving a bile acid binding agent should be advised that reduced absorption with co-administered drugs should be anticipated. Medication that has to be taken should be administered 1 h before (at least 4 h for colesevelam) or at least 4 h after the bile acid binding agent. As a consequence, for individuals on multiple drug therapy, bile acid binding agents may not be appropriate for this reason alone.

Cholesterol absorption inhibitors

Ezetimibe is a 2-azetidinone derivative that interacts with a putative cholesterol transporter in the intestinal brush border membrane and thereby blocks cholesterol re-absorption from the gastro-intestinal tract. It can reduce LDL-C by 15–20% when added to diet. Ezetimibe also brings about a small increase in HDL-C and a reduction in triglycerides. When added to a statin, ezetimibe lowers LDL-C more than with a statin alone.

Ezetimibe should be prescribed either with a statin, a fibrate or a nicotinic acid derivative and rarely by itself, and then only in statin intolerant individuals. Although apparently well tolerated, no long-term trials (Kastelein et al., 2008; Rossebø et al., 2008) have demonstrated an additional reduction in cardiovascular morbidity or mortality that could be attributed to ezetimibe.

Nicotinic acid and derivatives

Nicotinic acid in pharmacological doses (1.5–6 g) lowers serum LDL-C, TC, VLDL-C, apolipoprotein B, triglycerides and Lp(a) and increases levels of HDL-C (particularly the beneficial HDL_3 subfraction). It clearly has a range of beneficial effects on the lipid profile and is licensed for use in combination with a statin, or by itself if the patient is statin-intolerant or a statin is inappropriate.

The commonest side effect of nicotinic acid is flushing which is most prominent in the head, neck and upper torso and occurs in over 90% of patients. It is cited as the major reason for discontinuation of treatment in 25–40% of patients. A number of strategies have been devised to overcome this, including co-administration of a cyclo-oxygenase inhibitor such as aspirin. Other strategies include regular consistent dosing, the use of extended-release formulations, patient education, dosing with meals or at bedtime, and the avoidance of alcohol, hot beverages, spicy foods, and hot baths or showers close to or after dosing. Less common side effects of nicotinic acid include postural hypotension, diarrhoea, exacerbation of peptic ulcers, hepatic dysfunction, gout and increased blood glucose levels.

Acipimox is structurally related to nicotinic acid, has similar beneficial effects on the lipid profile and a better side effect profile but appears to be less potent. An extended-release preparation of nicotinic acid has also been marketed to reduce the incidence of side effects, but up to 30% of users still report problems.

The most recent nicotinic acid-based product to be marketed is a fixed dose combination of nicotinic acid with laropiprant marketed as Tredaptive® in 2008. It is licensed for use in combination with a statin or as monotherapy when a statin is inappropriate or not tolerated. Tredaptive® possesses the general benefit of nicotinic acid whilst the laropiprant is a potent, selective antagonist of the prostaglandin D_2 receptor subtype 1 (DP_1). Given that prostaglandin D_2 mediates the flushing associated with nicotinic acid the rationale for the combination is sound, but there are currently no long-term trials of efficacy and tolerability.

Fish oils

Fish oil preparations rich in omega-3 fatty acids have been shown to markedly reduce serum triglyceride levels by decreasing VLDL-C synthesis, although little change has been observed in LDL-C or HDL-C levels. The effect is, however, inconsistent and significant increases in LDL-C have also been reported to accompany the use of fish oils. Data from several studies suggest that omega-3 fatty acids protect against CHD mortality, particularly sudden death, rather than non-fatal events, but this may not be due to the lipid-lowering efficacy. Commercial products available contain omega-3-acid ethyl esters (Omacor®) and omega-3-marine triglycerides (Maxepa®). Either can be used as an alternative to a fibrate or in combination with a statin.

Soluble fibre

Preparations containing soluble fibre, such as ispaghula husk, have been shown to reduce lipid levels. The fibre is thought to bind bile acids in the gut and increase the conversion of cholesterol to bile acids in the liver. However, their role in the management of dyslipidaemia is unclear and they are much less effective than statins in reducing TC and LDL-C.

Cholesterol ester transfer protein (CETP) inhibitors

Low levels of CETP are associated with increased levels of HDL-C and reduced cardiovascular risk. CETP transfers cholesterol from HDL-C to LDL-C and VLDL-C, thereby

altering the HDL-C:LDL-C ratio in a potentially unfavourable manner. As a consequence, inhibitors of CETP are expected to have a beneficial cardiovascular effect. Torcetrapib was a potent inhibitor of CETP and in trials demonstrated a dose-dependent ability to increase HDL-C, with little effect on LDL-C or triglycerides. Increases in serum HDL-C of more than 100% were reported. Unfortunately, the side effect profile of torcetrapib included an increase in cardiovascular events and all cause mortality thereby preventing it reaching the market. Newer inhibitors of CETP include dalcetrapib and anacetrapib and these look more promising.

Case studies

Case 24.1

Mr DF is a 43-year-old man who has been relatively fit and well for the past 20 years during which he has rarely visited his primary care doctor. Two weeks ago he was admitted to hospital having suffered a myocardial infarction. On questioning it was revealed that his brother had died in a road traffic accident at the age of 19 and his father had died from CHD aged 54 years.

Examination of Mr DF revealed a corneal arcus and tendon xanthomas. Blood drawn within 2 h of the onset of his myocardial infarction revealed TC 7.8 mmol/L, HDL-C 0.9 mmol/L and triglycerides 2.3 mmol/L.

Questions

1. What is the likely diagnosis of Mr DF?
2. What are the treatment options?
3. Mr DF wants to know why he was not identified as being at high risk of CHD before he suffered his myocardial infarction.

Answers

1. Mr DF has the signs and family history of classic heterozygous FH, most likely due to a genetic defect in the LDL receptor on hepatocytes. His presentation with an acute cardiac event at such an early age is indicative of the raised cardiovascular risk present for individuals with FH.
2. Mr DF has a high level of LDL-C and action is required to reduce it. Appropriate lifestyle advice is necessary but a statin will be required to achieve the desired outcome of at least a 50% reduction in LDL-C. In addition, this patient has recently suffered a myocardial infarction, which in itself is an indication for a high intensity statin first line, such as atorvastatin 80 mg daily. This patient should be managed by a specialist in the first instance and relatives, including any children, should be screened for the presence of FH to allow initiation of early lipid-lowering therapy.
3. Unfortunately, Mr DF's father probably died of heart disease at a time when the practice of detecting affected families and screening first-degree relatives was not widespread. The early, unrelated death of his brother and Mr DF's previous good health would not have given an opportunity to identify any underlying familial disorder.

   From population data it is known that the prevalence of heterozygous FH is about 1 in 500. Consequently, 120,000 cases would be expected in the UK. However, far fewer cases are known and screening programmes to track cases in affected families are now in place. A family history of elevated TC or death from CHD before the age of 55 in a first-degree male relative, as in the case of Mr DF, is an important sign that should highlight the potential risk to other family members.

Case 24.2

Mr PT is a 52-year-old active school teacher. Four years ago he was found to have a raised TC and elevated blood pressure for which he was started on 10 mg simvastatin and 2.5 mg bendroflumethiazide. Over the years his dose of simvastatin has been gradually increased to 40 mg a day, but apart from this his medication has remained unchanged. He presents at the clinic complaining of aches and pains in his legs over the past 10 days. On questioning he reveals that over recent months he has been eating fresh grapefruit and consuming the occasional glass of grapefruit juice. A tentative diagnosis of myopathy is initially made.

Questions

1. What is the likelihood that grapefruit juice has contributed to Mr PT's problem?
2. Are any additional biochemical tests warranted?
3. Would atorvastatin, rosuvastatin or pravastatin be a more appropriate statin to prescribe if Mr PT wanted to continue with the occasional glass of grapefruit juice?

Answers

1. Grapefruit juice is known to interact with statins through its inhibition of the cytochrome P450 CYP3A4 enzyme. It has been suggested that it is the furanocoumarin in the grapefruit juice which binds to CYP3A4 and inactivates it in both the liver and the gastro-intestinal tract. As little as 200 mL of grapefruit juice may inhibit CYP3A4, thereby prolonging the half-life of the statin and increasing serum levels. When taken on a regular basis this can increase the risk of dose-related side effects such as rhabdomyolysis and increase the risk of myopathy. Current advice is that grapefruit juice should be avoided altogether when taking simvastatin, regardless of whether it is fresh grapefruit or grapefruit juice, grapefruit juice diluted from concentrate or frozen grapefruit juice.
2. A creatine kinase (CK) level should be checked in patients complaining of significant muscle pain to exclude overt myopathy.
   - If CK is raised significantly (>5 times upper normal level), temporary withdrawal of the statin is warranted. Once the CK falls to normal levels, and in view of the suspicion that grapefruit intake was a precipitating factor, the statin could be reinitiated and the patient warned to avoid grapefruit and seek advice promptly should the muscle aches recur.
   - If the CK is normal, then this is a simple myalgia. Grapefruit should be avoided and hopefully the symptoms resolve. If the pain does not resolve this may have an impact on adherence and an alternate statin should be considered. Of all the agents currently on the UK market, simvastatin is more likely to cause myalgia and myopathy.
3. Atorvastatin is also metabolised by CYP3A4. Although the effect is less dramatic than with simvastatin, the concurrent intake of large quantities of grapefruit juice with atorvastatin is not recommended. Neither pravastatin nor rosuvastatin is substantially metabolised by P450 and may be better alternatives. However, when there is a past history of myopathy the need for caution remains as the risk of recurrence is enhanced whatever lipid-lowering agent is prescribed. It should also be noted that rosuvastatin, unlike pravastatin, has no clinical outcome data and would not be appropriate for use in this

patient. There are also separate concerns regarding the muscle toxicity of rosuvastatin, especially when used at the higher dose of 40 mg. This again would indicate that rosuvastatin is not the best option for Mr PT.

As this patient is being treated with a statin for primary prevention, National Institute of Health and Clinical Excellence (2008a) guidelines suggest that only generic statin agents are cost-effective and, therefore, pravastatin should be considered as a first-line alternative for this patient.

Case 24.3

Mrs MC is a very active, 51-year-old caucasian lady who for the past 6 months has been suffering from the classic symptoms of the menopause. Six months ago on a routine visit to her doctor she had her lipid profile measured and this revealed an HDL-C of 0.8 mmol/L and TC of 5 mmol/L. Her blood pressure was 140/80 mmHg. She is currently prescribed no medication but is receiving intensive lifestyle support to lower her cholesterol. She has no other medical history of note other than a record that her mother died at the age of 66 years from a heart attack.

Mrs MC would like to be prescribed hormone replacement therapy to control her menopausal symptoms and reduce her risk of CVD.

Questions

1. Is it appropriate to prescribe hormone replacement therapy to reduce Mrs MC's cardiovascular risk?
2. What is the value of measuring HDL-C?
3. Does Mrs MC have a risk of CVD that requires treatment with a lipid-lowering agent?

Answers

1. Most epidemiological studies have demonstrated a beneficial effect of hormone replacement therapy on the development of CHD in postmenopausal women. However, randomised controlled trials with defined clinical endpoints have failed to support a reduction in cardiovascular events. Whether this has arisen because of how the body responds to hormone replacement therapy, the age of the women studied or the influence of the type of hormone replacement therapy, the dose, route of administration and duration of treatment is unclear. At present there are no compelling data to justify the use of hormone replacement therapy for the prevention or treatment of CVD in postmenopausal women. In fact, current evidence indicates that HRT may increase the risk of breast cancer, ovarian cancer, CVD and thromboembolic disease. If Mrs MC is to be prescribed HRT, then this should be based on the need to control her menopausal symptoms and improve her quality of life.
2. HDL-C is a major fraction of cholesterol in serum and an important determinant of cardiovascular risk in men and women, even when the level of TC appears to be within the normal range. The incidence of myocardial infarction is positively correlated with the cholesterol concentration and inversely related to the concentration of HDL-C. The TC:HDL-C ratio is another way to represent this risk and has been shown to have good predictive capabilities in women. Until the menopause, women generally have high levels of HDL-C as a result of the circulating oestrogen. However, following the menopause, HDL-C levels fall rapidly. Lifestyle advice may improve the TC/HDL ratio, especially via increased physical activity.
3. With reference to the Joint British Societies risk prediction charts, it can be determined that with a TC:HDL-C ratio of 6.25 (5/0.8) and a systolic blood pressure of 140 mmHg, Mrs MC has a 10–20% risk of developing CVD over the next 10 years. This would not automatically make her a candidate for treatment with a lipid-lowering agent as her 10-year cardiovascular risk is not >20%. Knowledge of Mrs MC's BMI and blood glucose level would be useful additional information, as would a more detailed insight into her family history of CVD. It is only when all the relevant information has been gathered that a final decision on the use of a lipid-lowering agent can be made. It would also be of interest to determine whether the lifestyle support has brought about any improvement in Mrs MC's lipid profile or blood pressure.

Case 24.4

Mr EC is a 48-year-old executive for a large multinational company who works long hours and frequently has to travel abroad. He has a family history of CHD and 9 months ago he attended a coronary screening clinic for a health check. At the clinic he was found to have a normal blood pressure but a blood screen revealed a TC of 5.7 mmol/L and triglycerides of 11.8 mmol/L. When he revisited the clinic 4 weeks later after trying to follow dietary advice, a fasting blood sample revealed a TC of 5 mmol/L and triglycerides of 2.7 mmol/L. Liver function tests were normal. He is a non-smoker and claims never to drink more than 10 units of alcohol per week.

After repeated requests to revisit the clinic he eventually turned up stating he had been away from home for 6 months on a series of business trips. He was trying to keep to a low-fat diet and his blood profile revealed TC 5.7 mmol/L, triglycerides 4.3 mmol/L, HDL-C 0.8 mmol/L and LDL-C 3 mmol/L.

Questions

1. Is Mr EC at high risk of CHD?
2. Is Mr EC a candidate for lipid-lowering therapy?
3. Should Mr EC's children be screened for dyslipidaemia?

Answers

1. Mr EC has a TC:HDL-C ratio of 7.1 (5.7/0.8). If the Joint British Societies risk charts were used they would indicate he has a 10-year risk of CHD of 10–20% and does not require lipid-lowering treatment. However, the tables underestimate the risk of CHD in those with familial hyperlipidaemia or a history of premature CHD.

   Mr EC would appear to have a mixed lipaemia, although it is difficult to interpret non-fasting triglycerides because of the influence of food intake. The low HDL-C suggests he is overweight and/or has a non-ideal lifestyle. Exclusion of diabetes, high alcohol intake, liver and renal impairment is necessary. The possibility of impaired glucose tolerance should not be overlooked and a glucose tolerance test should be performed.
2. Given the elevated triglycerides and TC, Mr EC is certainly a candidate for lifestyle advice. The use of a statin may be considered if the lifestyle changes do not bring about the necessary improvements in the lipid profile. However, the dyslipidaemia may be secondary to obesity, alcoholism, diabetes or hypothyroidism. If any of these disorders are present the appropriate treatment may correct the underlying dyslipidaemia.

3. The family history of CHD is important but is only significant if the age of onset in a parent or sibling was under 55 years of age for an affected male or under 65 years for an affected female. A rare familial disorder, for example, familial dysbetalipoproteinaemia, may be the causative factor. If this was confirmed his children should be screened after puberty as the offending gene may not express itself in the younger child.

   Mr EC was subsequently found to have diabetes for which he initially received metformin together with a statin. In this scenario where a patient is diagnosed with type 2 diabetes, it is also important to consider advising children about lifestyle issues and the need to control weight throughout life.

Case 24.5

Mr JT is a 68-year-old man with stable angina. He is currently receiving simvastatin 40 mg daily with well controlled lipid levels (TC 3.8 mmol/L; LDL-C 1.8 mmol/L; HDL-C 0.9 mmol/L, triglycerides 1.3 mmol/L). He has been on simvastatin for the past 7 years, and has complained previously about muscle aches, but on this visit he states that his muscle pain has become more troublesome, to the extent that he wishes to come off the statin. He asks if there is nothing else he can take to control his cholesterol.

Questions

1. What action would you take immediately?
2. What options are available for Mr JT?
3. What would you recommend to Mr JT?

Answers

1. A CK level should be checked to exclude myopathy in this patient, as this can occur at any time during statin treatment. Assuming the CK is normal and this is myalgia, then it is still essential to address this patient's concerns, as this muscle pain is likely to impact on patient adherence over time.

   An important issue is to ensure that the patient understands why they are taking a statin. The emphasis should be on the expected reduction in the risk of death, heart attack or stroke; rather than on simply achieving cholesterol treatment targets.

   It may be worth temporarily stopping the statin to demonstrate the causal relationship. If the aches and pains remain despite cessation of simvastatin, then this is unlikely to be a statin-related issue. Many people complain of aches and pains, particularly as they get older and it is easy to blame the statin for all these complaints.
2. Options for Mr JT include:
   a. Reducing the dose of simvastatin

      Mr JT has been on simvastatin for many years and a simple reduction in dose to 20 mg may improve tolerability without compromising the lipid control substantially. While an increase in TC and LDL-C is expected with dose reduction, this is usually small (in the order of 6%) and should have little overall impact on risk.
   b. Substituting an alternative statin

      Simvastatin causes more myalgia and myopathy than other statins; therefore, an alternative agent may be better-tolerated. Pravastatin is particularly well tolerated and may be a suitable alternative in this patient where potency is less of an issue. Where greater potency is required, atorvastatin (starting at a dose of 10–20 mg daily and increasing as required to control lipids) or rosuvastatin are a possibility.
   c. Switching to an alternative agent, such as ezetimibe

      Non-statin agents could be used to lower cholesterol but should be reserved for patients unable to tolerate statins. Ezetimibe monotherapy may be a suitable alternative, although use is not supported by cardiovascular outcome data.
   d. Using a low dose of statin plus an alternative agent, such as ezetimibe

      This may be a suitable option if this patient can only tolerate small doses of statins, and the ezetimibe is introduced to increase the degree of cholesterol lowering achieved. This is a useful combination in some patients, but every effort should be made to maximise the statin dose prior to adding ezetimibe to ensure maximal outcome benefits.
3. In this patient, a good starting point would be a reduction in the dose of simvastatin to 20 mg daily, providing the patient is willing to continue to take this drug. Myalgia appears to be dose related and the symptoms may resolve with the lower dose. An alternative is to try pravastatin, perhaps at a starting dose of 20 mg to see if this is better tolerated. The dose will probably need increasing to give adequate control of lipid levels. The use of ezetimibe should be reserved as an add-in if only low doses of statins can be tolerated or for monotherapy if that patient cannot be persuaded to take any statin at all. This patient should be reviewed regularly over the next few months until his concerns regarding his lipid-lowering therapy have been addressed, to encourage on-going adherence.

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25 Asthma

K. P. Gibbs and D. Cripps

Key points

- Asthma is a common and chronic inflammatory condition of the airways whose cause is not completely understood.
- Common symptoms are caused by hyperresponsive airways and include coughing, wheezing, chest tightness and shortness of breath.
- The only reliable, simple and objective way to diagnose asthma is to demonstrate reversible airflow limitation.
- In the UK, there are approximately 1400 deaths from asthma each year.
- Asthma is still a poorly controlled disease despite effective treatments.
- Asthma triggers should be avoided or controlled.
- Pharmacological therapy should involve early anti-inflammatory treatment in all but the mildest asthmatics and follow national, evidence-based guidance.
- Optimum treatment involves the lowest doses of therapy that provide good symptom control with minimal or no side effects, and the best drug delivery device is one that the patient can use correctly.
- Patients should be encouraged and educated to take an active role in their disease management, be given individualised self-management plans and be regularly supervised by the health care team.

Asthma means 'laboured breathing' in Greek and was first described 3000 years ago. It is a broad term used to refer to a disorder of the respiratory system that leads to episodic difficulty in breathing. The national UK guidelines (BTS/SIGN, 2009) define asthma as 'a chronic inflammatory disorder of the airways which occurs in susceptible individuals; inflammatory symptoms are usually associated with widespread but variable airflow obstruction and an increase in airway response to a variety of stimuli. Obstruction is often reversible either spontaneously or with treatment'.

Epidemiology

The exact prevalence of asthma remains uncertain because of the differing ways in which airway restriction is reported, diagnostic uncertainty (especially for children under 2 years) and the overlap with other conditions such as chronic obstructive pulmonary disease (COPD). Over 5 million people in the UK have asthma (Asthma UK, 2001) and around 300 million worldwide. Mortality from asthma is estimated at approximately 0.4 per 100,000 with around 1400 deaths per annum in the UK. Most deaths occur outside hospital; the most common reasons for death are thought to be inadequate assessment of the severity of airway obstruction by the patient and/or clinician and inadequate therapy with inhaled or oral steroids.

The probability of children having asthma-like symptoms is estimated to be between 5% and 12%, with a higher occurrence in boys than girls and in children whose parents have an allergic disorder. Between 30% and 70% of children will become symptom free by adulthood. Individuals who develop asthma at an early age, however, do have a poorer prognosis.

The prevalence of asthma actually appears to be rising despite advances in therapy. There is some doubt about this, however, due to the differing criteria for the diagnosis of asthma used in different studies. Asthma is considered to be one of the consequences of Western civilisation and appears to be related to a number of environmental factors. Air pollution resulting from industrial sources and transport may be interacting with smoking, dietary and other factors to increase the incidence of this debilitating problem.

Aetiology

The two main causes of asthma symptoms are airway hyperresponsiveness and bronchoconstriction. Hyperresponsiveness is an increased tendency of the airway to react to stimuli or triggers to cause an asthma attack. Bronchoconstriction is a narrowing of the airways that causes airflow obstruction. Possible triggers are listed in Table 25.1. One of the most common trigger factors is the allergen found in the faeces of the house dust mite, which is almost universally present in bedding, carpets and soft furnishing. Pollen from grass (prevalent in June and July) can lead to seasonal asthma. The role of occupation in the development of asthma has become apparent with increased industrialisation. There are many causes of occupational asthma, and bronchial reactivity may persist for years after exposure to the trigger factor. Drug-induced asthma can be severe and the most common causes are β-blocker drugs and prostaglandin synthetase inhibitors. The administration of β-adrenoceptor blockers to a patient, even in the form of eye drops, can cause β_2-receptor

Table 25.1 Examples of asthma triggers

Trigger	Examples
Allergens	Pollens, moulds, house dust mite, animals (dander, saliva and urine)
Industrial chemicals	Manufacture of, for example, isocyanate-containing paints, epoxy resins, aluminium, hair sprays, penicillins and cimetidine
Drugs	Aspirin, ibuprofen and other prostaglandin synthetase inhibitors, β-adrenoceptor blockers
Foods	A rare cause but examples include nuts, fish, seafood, dairy products, food colouring, especially tartrazine, benzoic acid and sodium metabisulfite
Environmental pollutants	Traffic fumes. cigarette smoke, sulphur dioxide
Other industrial triggers	Wood or grain dust, colophony in solder, cotton, dust, grain weevils and mites
Miscellaneous	Cold air, exercise, hyperventilation, viral respiratory tract infections, emotion or stress, swimming pool chlorine

blockade and consequent bronchoconstriction. Selective β-adrenoceptor blockers are thought to pose slightly less risk, but as these lose their selectivity at higher doses, it is generally recommended that this group of drugs is avoided altogether in asthma patients. Aspirin and related non-steroidal anti-inflammatory drugs can cause severe bronchoconstriction in susceptible individuals. Aspirin inhibits the enzyme cyclo-oxygenase, which normally converts arachidonic acid to (bronchodilatory) prostaglandins. When this pathway is blocked, an alternative reaction predominates, leading to an increase in production of bronchoconstrictor (cys-) leukotrienes. Figures from differing studies vary, but between 2% and 20% of the adult asthma population are thought to be sensitive to aspirin.

Pathophysiology

Asthma can be classified according to the underlying pattern of airway inflammation with the presence or absence of eosinophils in the airways (eosinophilic vs. non-eosinophilic). Traditionally patients are described as having 'extrinsic asthma' when an allergen is thought to be the cause of their asthma. This is more common in children with a history of atopy, where triggers, such as dust mite, cause IgE production. Other environmental factors are also important, such as exposure to rhinovirus during the first 3 years of life (Holgate et al., 2010). 'Intrinsic asthma' develops in adulthood, with symptoms triggered by non-allergenic factors such as a viral infection, irritants which cause epithelial damage and mucosal inflammation, emotional upset which mediates excess parasympathetic input or exercise which causes water and heat loss from the airways, triggering mediator release from mast cells. In practice, patients often have features of both types of asthma and the classification is unhelpful and oversimplifies the pathogenesis of asthma.

Mast cell components are released as a result of an IgE antibody-mediated reaction on the surface of the cell. Histamine and other mediators of inflammation are released from mast cells, for example, leukotrienes, prostaglandins, bradykinin, adenosine and prostaglandin-generating factor of anaphylaxis, as well as various chemotactic agents that attract eosinophils and neutrophils. Macrophages release prostaglandins, thromboxane and platelet-activating factor (PAF). PAF appears to sustain bronchial hyperreactivity and cause respiratory capillaries to leak plasma, which increases mucosal oedema. PAF also facilitates the accumulation of eosinophils within the airways, a characteristic pathological feature of asthma. Eosinophils release various inflammatory mediators such as leukotriene C_4 (LTC_4) and PAF. Epithelial damage results and thick viscous mucus is produced that causes further deterioration in lung function. These cell-derived mediators also play a role in causing marked hypertrophy and hyperplasia of bronchial smooth muscle (these structural changes are described as 'airway remodelling'), mucus gland hypertrophy leading to excessive mucus production and airway plugging, airway oedema, acute bronchoconstriction and impaired mucociliary clearance.

Mucus production is normally a defence mechanism, but in asthma patients, there is an increase in the size of bronchial glands and goblet cells that produce mucus. Mucus transport is dependent on its viscosity. If it is very thick, it plugs the airways, which also become blocked with epithelial and inflammatory cell debris. Mucociliary clearance is also decreased due to inflammation of epithelial cells. The environmental insults causing asthma are also thought to affect the structure and function of the airway epithelium. The exact role of these cytokines, cellular mediators and the interrelationships with each other and with the causative allergenic or non-allergenic mechanisms has, however, yet to be fully determined and may vary over time (Douwes et al., 2002; Holgate et al., 2010). Fig. 25.1 outlines the main cellular mechanisms involved.

Clinical manifestations

Asthma can present in a number of ways. It may manifest as a persistent cough, but most commonly, it is described as recurrent episodes of difficulty in breathing (dyspnoea) associated with wheezing (a high-pitched noise due to turbulent airflow through a narrowed airway). Diagnosis is usually made from the clinical history confirmed by demonstration of reversible airflow obstruction and measures of lung function. The history of an asthma patient often includes the presence of atopy and allergic rhinitis in the close family. Symptoms of asthma are often intermittent, and the frequency and severity of an episode can vary from individual to individual. Between periods

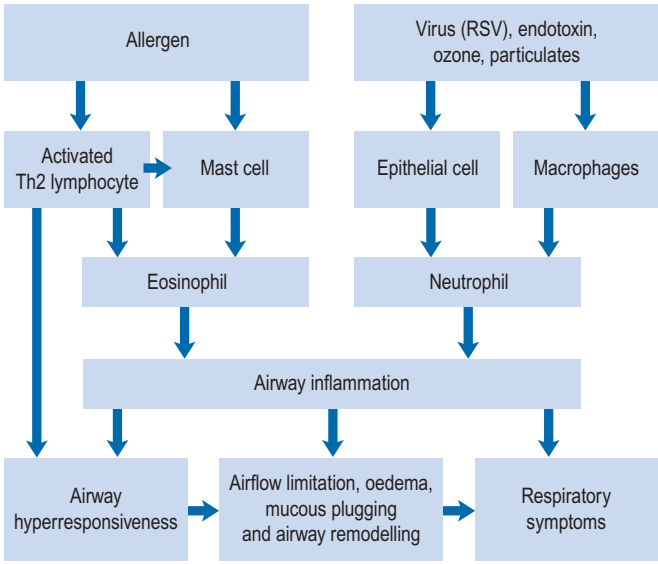

Fig. 25.1 Postulated cellular mechanisms involved in airway inflammation (adapted from Douwes et al., 2002).

of wheezing and breathlessness, patients may feel quite well. The absence of an improvement in ventilation, however, cannot rule out asthma, and in younger children, it is sometimes very difficult to perform lung function tests; in this case, diagnosis relies on subjective symptomatic improvement in response to bronchodilator therapy.

Acute severe asthma is a dangerous condition that requires hospitalisation and immediate emergency treatment. It occurs when bronchospasm has progressed to a state where the patient is breathless at rest and has a degree of cardiac stress. This is usually progressive and can build up over a number of hours or even days. The breathlessness, with a peak flow rate <100 L/min, is so severe that the patient often cannot talk or lie down. Expiration is particularly difficult and prolonged as air is trapped beneath mucosal inflammation. The pulse rate can give an indication of severity; severe acute asthma can increase the pulse rate to more than 110 beats/min in adults. It is common to see hyperexpansion of the thoracic cavity and lowering of the diaphragm, which means that accessory respiratory muscles are required to try to inflate the chest. Breathing can become rapid (>30 breaths/min) and shallow, leading to low oxygen saturation (SpO_2 < 92%) with the patient becoming fatigued, cyanosed, confused and lethargic. The arterial carbon dioxide tension ($PaCO_2$) is usually low in acute asthma. If it is high, it should respond quickly to emergency therapy. Hypercapnia (high $PaCO_2$ level) that does not diminish is a more severe problem and indicates progression towards respiratory failure.

Some patients remain difficult to control with persistent symptoms and/or despite treatment at BTS/SIGN step 4 or 5. This is known as 'refractory' or 'difficult to treat' asthma. These patients must be carefully evaluated by a respiratory specialist; this will include confirming an accurate diagnosis of asthma, adherence to therapy and individual psychological factors.

Investigations

The function of the lungs can be measured to help diagnose and monitor various respiratory diseases. A series of routine tests has been developed to assess asthma as well as other respiratory diseases such as COPD.

The most useful test for abnormalities in airway function is the forced expiratory volume (FEV). This is measured by means of lung function assessment apparatus such as a spirometer. The patient inhales as deeply as possible and then exhales forcefully and completely into a mouthpiece connected to a spirometer. The FEV_1 is a measure of the FEV in the first second of exhalation. The forced vital capacity (FVC) can also be measured, which is an assessment of the maximum volume of air exhaled with maximum effort after maximum inspiration. The FEV_1 is usually expressed as a percentage of the total volume of air exhaled, reported as the FEV_1/FVC ratio. This ratio is a useful and highly reproducible measure of the capabilities of the lungs. Normal individuals can exhale at least 70% of their total capacity in 1 s. In obstructive lung disorders, such as asthma, the FEV_1 is usually decreased, the FVC normal or slightly reduced and the FEV_1/FVC ratio decreased, usually <0.7 (Fig. 25.2).

A peak flow meter is a useful means of self-assessment for the patient. It gives slightly less reproducible results than the spirometer but has the advantage that the patient can do regular tests at home with a hand-held meter. The peak flow meter measures peak expiratory flow (PEF) rate, the maximum flow rate that can be forced during expiration. The PEF can be used to assess the improvement or deterioration in the disease as well as the effectiveness of treatment. For all three measurements (FEV_1, FVC and PEF), there are normal values with which the patient's results can be compared. However, these normal values vary with age, race, gender, height and weight. The measurement of FEV_1, FVC or PEF does not detect early deterioration of lung function such as bronchospasm and mucus plugging in the smaller airways.

The diagnosis of asthma can be confirmed by measuring the response to a bronchodilator or by examining a patient's day-to-day variation in PEF readings. A diurnal variability of 60 L/min (or more than 20%) is highly suggestive of asthma

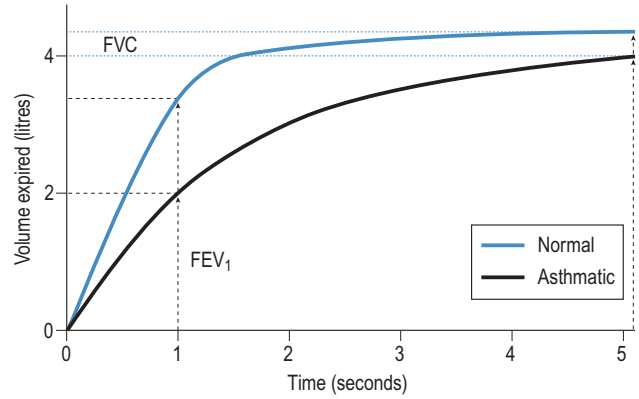

Fig. 25.2 Typical lung spirometry in normal subjects and asthma patients.

(GINA, 2009). However, individuals may not have airflow obstruction at the time of the test, so the absence of an improvement does not rule out asthma. In this situation, peak flow readings can be done at home with repeated pre- and post-bronchodilator readings taken at various times of the day.

Treatment

As asthma involves inflammation and bronchoconstriction, treatment should be directed towards reducing inflammation and increasing bronchodilation. Treatment aims should include a lack of day and nighttime symptoms, no asthma exacerbations, no need for rescue medication, normal PEFs and no unwanted side effects from medication (BTS/SIGN, 2009; GINA, 2009). Anti-inflammatory drugs should be given to all but those with the mildest of symptoms. Other measures, such as avoidance of recognised trigger factors, may also contribute to the control of this disease. The lowest effective dose of drugs should be given to minimise short-term and long-term side effects. It should, however, always be remembered that asthma is a potentially life-threatening illness, is often undertreated and not all patients will achieve optimal control. Common therapeutic and practice problems encountered in the management of asthma are outlined in Box 25.1.

Chronic asthma

The pharmacological management of asthma depends upon the frequency and severity of a patient's symptoms. Infrequent attacks can be managed by treating each attack when it occurs, but with more frequent attacks, preventive therapy needs to be used.

Box 25.1 Management of common practice problems

- Reducing exposure to trigger risk factors may help to improve asthma control.
- Successful management of asthma requires a partnership between the patient and the health care provider.
- Aim to give patients the ability to control their asthma by supporting guided self-management.
- Individualised action plans improve health outcomes, particularly in moderate to severe disease.
- Increased use of reliever medication is a warning of deterioration of asthma control.
- Assessment of asthma control is essential when deciding to step up or step down treatment.
- At each treatment review, inhaler technique and adherence to treatment should be checked.
- The main treatments for exacerbations of asthma include repeated β_2-agonists, early use of corticosteroids and oxygen to raise S_aO_2 above 92%.
- Mild exacerbations (PEF reduction of <20%) can often be managed in community settings.
- After exacerbations, patients should be reviewed early to identify possible triggers and review the action plan.

S_aO_2, arterial oxygen concentration.

The preferred route of administration of the agents used in the management of asthma is by inhalation. This allows the drugs to be delivered directly to the airways in smaller doses and with fewer side effects than if systemic routes were used. Inhaled bronchodilators also have a faster onset of action than when administered systemically and give better protection from bronchoconstriction.

Treatment of chronic asthma should be managed in a stepwise progression. This section concentrates on management in adults, as outlined in Fig. 25.3, but corresponding management steps for children are available (BTS/SIGN, 2009). Therapy is moved up the steps according to the severity of the patient's asthma symptoms and response to current treatment. When a patient has been stable for at least 3 months (GINA, 2009), therapy should be stepped back down; for example, by halving the inhaled corticosteroid (ICS) dose. International guidelines aim for management to achieve and maintain clinical control, which is defined in Table 25.2. A model for patient review and adjustment of therapy, based on assessment of asthma control, has been suggested (Crompton et al., 2006) and is shown in Fig. 25.4. To help in patient education, the terms used to describe the effects of asthma medication are similar across all manufacturers and sources of education. 'Reliever' is used for agents that give immediate relief of symptoms. Agents that act to reduce inflammation or give long-term bronchodilation are referred to as 'controllers' or 'preventers'.

Reliever medication

Short-acting β-adrenoceptor agonist bronchodilators. β-Adrenoceptor agonists are the mainstay of asthma management. Salbutamol and terbutaline are selective β_2-agonists and have few β_1-mediated side effects such as cardiotoxicity. β_2-Receptors are, however, also present in myocardial tissue; cardiovascular stimulation resulting in tachycardia and palpitations is still the main dose-limiting toxicity with these agents when used in high dosage.

An inhaled β_2-agonist is the first-line agent in the management of asthma. This is used as required by the patient for the symptomatic relief of breathlessness and wheezing, for example, salbutamol 200 µcg when required. This may be the only treatment necessary for those with infrequent symptoms. There is no advantage to regular administration.

Additional bronchodilators. Additional bronchodilators may be required if the above therapy does not adequately control symptoms (Tables 25.3 and 25.4).

Inhaled anticholinergic agents. These block muscarinic (M1, M2, M3) receptors in bronchial smooth muscle but are generally of little additional value in asthma management. Ipratropium has a slower onset of action than β_2-agonists but a longer duration of action. Anticholinergics may be helpful in patients who also have a degree of obstructive airways disease.

Long acting β-adrenoreceptor agonist bronchodilators. When low-dose inhaled steroids fail to control asthma symptoms adequately at step 3, long-acting β_2-agonists should be added instead of increasing the steroid dose. Symptom relief after a trial period, for example, 4–6 weeks, must then be assessed to

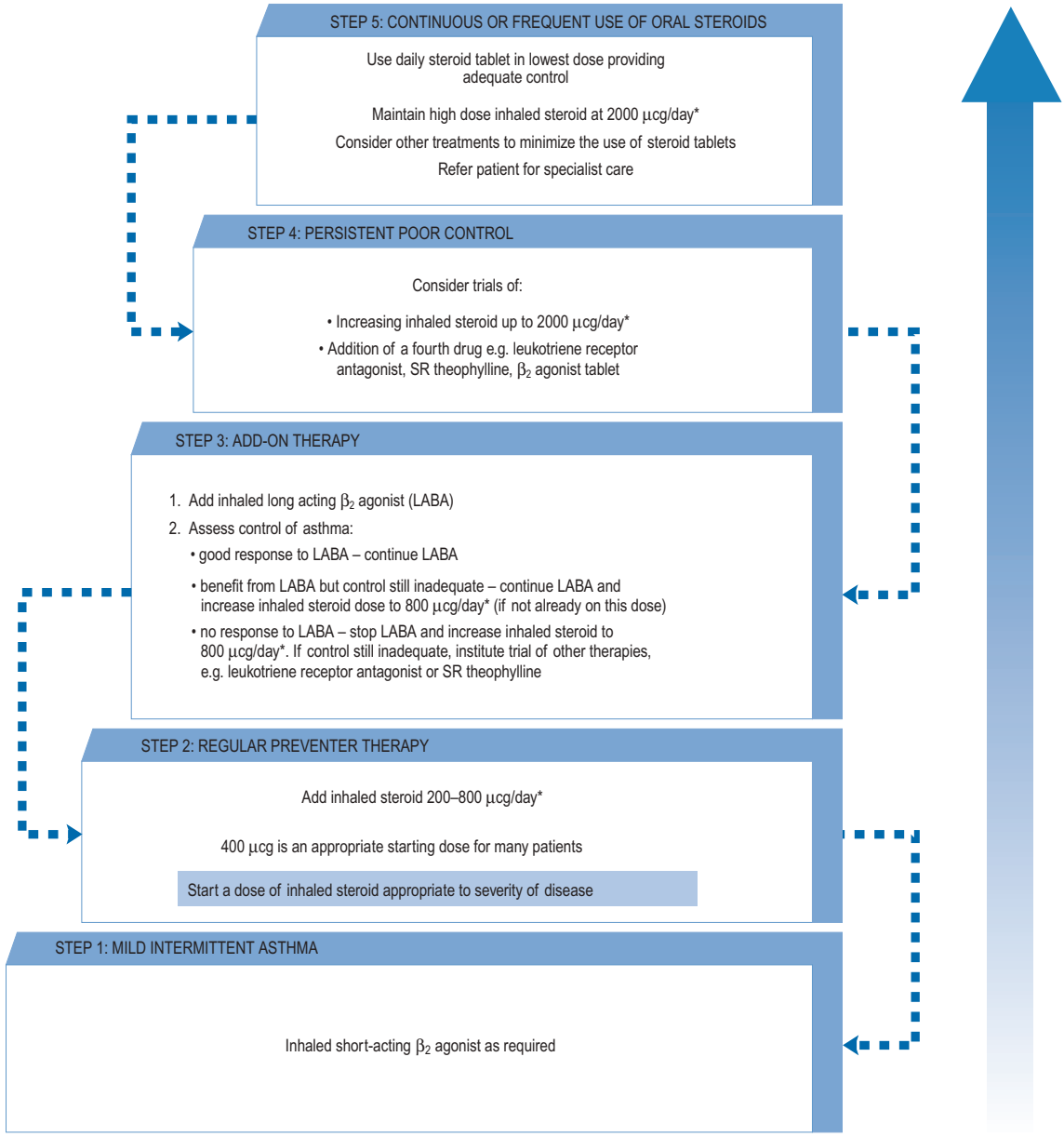

Fig. 25.3 Summary of stepwise management in adults (reproduced by permission of the BMJ Publishing Group, from BTS/SIGN, 2009).

Table 25.2 Levels of asthma control (GINA, 2009)

Characteristic	Controlled all of the following	Partly controlled any measure present in any week	Uncontrolled
Daytime symptoms	Twice or less/week	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitation of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	Twice or less/week	More than twice/week	
Lung function (PEF or FEV_1)	Normal	<80% predicted or personal best (if known)	
Any exacerbation should prompt a review of maintenance treatment to ensure that it is adequate.			

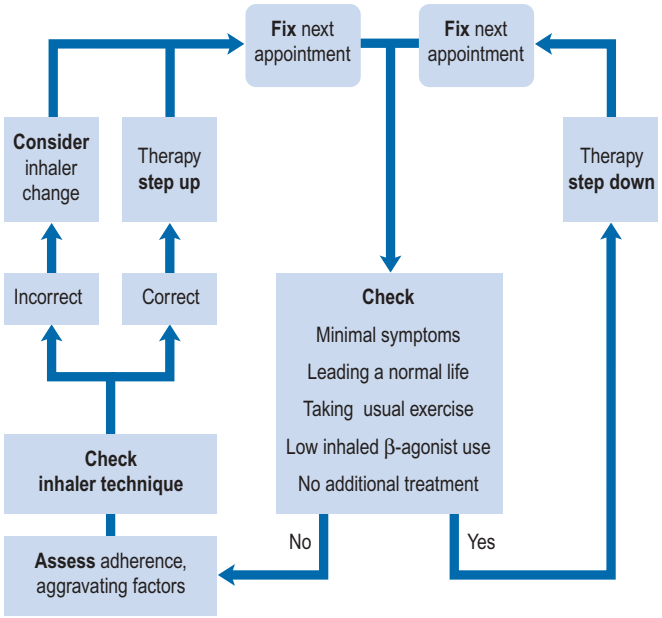

Fig. 25.4 Adjusting therapy to achieve asthma control (from Crompton et al., 2006 reproduced by permission. Copyright Elsevier publishing).

see if the LABA has been effective and whether further treatment needs to be added to or existing treatment changed.

Meta-analysis of LABA trials has shown a potential increase in asthma deaths of 1 death in 1000 patient-years of use, but this increased risk is lessened when used alongside ICSs (Saltpeter et al., 2006). Taking this evidence into account, it is advised that LABAs should

- only be added if regular use of standard-dose ICS has failed to control asthma adequately
- not be initiated in patients with rapidly deteriorating asthma
- be introduced at a low dose and the effect properly monitored before considering dose increase
- be discontinued in the absence of benefit
- be reviewed as appropriate; stepping down therapy should be considered when good long-term asthma control has been achieved (MHRA, 2008).

Combination ICS/LABA inhalers are available which may improve adherence compared to separate inhalers; as adherence to ICS is generally poor, using combination inhalers may ensure that the LABA is not used alone for variable periods of time.

A formoterol and budesonide combination inhaler can be given both as maintenance therapy and for symptomatic relief. Current trial evidence shows that this dosing method is an alternative at step 3 for adults who are poorly controlled on SABA and ICS, have experienced one or more severe exacerbations in the previous 12 months, or as an alternative to increasing the ICS dose to above 2 mg/day at step 4 (NPC, 2008).

Oral bronchodilators. Oral bronchodilators can also be added, for example, theophylline at steps 3–4 or β_2-agonists at step 4 for additional symptom control. Slow-release forms should be used, usually twice daily, although these can be used in a single night-time dose if nocturnal symptoms are troublesome.

Theophylline should be started at a dose of 400–500 mg/day in adults and, if required, increased after 7 days to 800–1000 mg/day. In children, higher doses may be required but this will be determined by the age of the child (see Chapter 10).

Theophylline has a narrow therapeutic index and its hepatic metabolism varies greatly between individuals. Theophylline clearance is affected by a variety of factors, including disease states and concurrent drug therapy. The dose used should, therefore, take into account these factors, which are listed in Table 25.5. Plasma levels may be taken after 3–4 days at the higher dose, and it has been normal practice to adjust the dose to keep the plasma level within a therapeutic window of 10–20 mg/L, although improvements in respiratory function are seen at levels as low as 5 mg/L in some patients. As the bronchodilating effects of theophylline are proportional to the log of the plasma concentrations, there is proportionally less bronchodilation as the plasma level increases. The mild side effects such as nausea and vomiting are seen at concentrations as low as 13 mg/L but are more common over 20 mg/L. Significant cardiac symptoms, tachycardia and persistent vomiting are usually seen at concentrations of 40 mg/L while severe CNS effects, such as seizures, have been seen at 30 mg/L but are more common above 50 mg/L.

Table 25.3 Comparison of inhaled bronchodilators

Drug	Onset of action (min)	Peak action (min)	Duration of action (h)
Ipratropium	3–10	60–120	4–6
Formoterol	2–3		12
Salbutamol	5–15	60[a]	4–6
Salmeterol	10-14	150[a]	12[a]
Terbutaline	5–30	60–120	3–6

[a]Approximate or median value.

Table 25.4 Daily dose range for selected bronchodilators

Drug and route	Age and total daily dosage range			
Aminophylline				
Intravenous injection	Adult; 5 mg/kg (single dose)	1 month–18 years; 5 mg/kg (single dose) up to 500 mg maximum		
Intravenous infusion	16 years–adult; 500 mg/kg/h	9–16 years; 800 mg/kg/h	1 month–9 years; 1 mg/kg/h	
Oral	Child over 40 kg–adult; 225–450 mg m/r twice a day			
Formoterol				
Inhaled	6 years–adult; 12–24 µcg twice a day			
Ipratropium bromide				
Inhaled	12 years–adult; 20–40 µcg 3–4 times daily	6–12 years; 20–40 µcg 3 times daily	1 month–6 years; 20 µcg 3 times daily	
Nebulised for acute bronchospasm	Adult; 500 µcg repeated as necessary	6–12 years; 250–500 µcg repeated as necessary (max. 1 mg daily)	Under 5 years; 125–250 µcg repeated as necessary (max. 1 mg daily)	
Salbutamol				
Inhaled	5 years–adult; 200 µcg when required, up to 4 times a day	Child, 100 µcg when required, up to 4 times a day		
Nebulised for acute bronchospasm	Adult; 2.5–5 mg repeated as necessary	6–18 years; 2.5–5 mg repeated every 20–30 min if necessary	2–5 years; 2.5 mg repeated every 20–30 min if necessary	Under 2 years; 2.5 mg repeated every 20–30 min if necessary
Salmeterol				
Inhaled	12 years–adult; 50–100 µcg twice a day	4–12 years; 50 µcg twice a day	2–4 years; 25 µcg twice a day	
Terbutaline				
Inhaled	5 years–adult; 500 µcg when required, up to four times a day			
Nebulised for acute bronchospasm	Adult; 5–10 mg repeated as necessary	6–18 years; 5–10 mg repeated every 20–30 min if necessary	2–5 years; 5 mg repeated every 20–30 min if necessary	Under 2 years; 5 mg repeated every 20–30 min if necessary
Theophylline				
Oral	12 years–adult; 175–500 mg (m/r) twice a day	6–12 years; 175–250 mg (m/r) twice a day		

Differing brands of theophylline have differing bioavailabilities, so brands should not be interchanged.

High-dose β_2-agonists. High-dose β_2-agonists are only considered if conventional doses do not achieve adequate symptom control. Nebulised drugs such as salbutamol 2.5–5 mg per dose are given.

Terbutaline has been given by continuous subcutaneous infusion in the maintenance treatment of difficult to treat asthma.

Preventer medication

Anti-inflammatory agents. Regular anti-inflammatory treatment should be used for patients who are not controlled on a SABA alone (BTS/SIGN, 2009). Corticosteroids are the most commonly used anti-inflammatory agents (Table 25.6), but others such as the cromones are available.

Inhaled corticosteroids. Corticosteroids suppress the chronic airway inflammation associated with asthma. At present, ICSs are the initial drugs of choice, with a starting dose for an adult of beclometasone or budesonide 400 µcg/day (or an equivalent) given in divided doses.

The threshold frequency of β_2-agonist use which prompts the start of ICSs has not been fully established but national guidance (BTS/SIGN, 2009) recommends considering ICS for patients with any of the following:

- Exacerbations of asthma in the past 2 years
- Using inhaled β_2-agonists three times a week or more
- Symptoms three times a week or more
- Waking one night a week with symptoms

Table 25.5 Factors affecting theophylline clearance

Decreased clearance	Increased clearance
Congestive cardiac failure	Cigarette smoking
Cor pulmonale	Children 1–12 years
Chronic obstructive pulmonary disease	High-protein, low-carbohydrate diet
Viral pneumonia	Barbecued meat
Acute pulmonary oedema	Carbamazepine
Cirrhosis	Phenobarbital
Premature and term babies	Phenytoin
Elderly	Sulfinpyrazone
Obesity	
High-carbohydrate, low-protein diet	
Cimetidine	
Erythromycin	
Oral contraceptives	
Ciprofloxacin	
Propranolol	

If symptoms persist, the ICS dose is increased stepwise accordingly. The ICS dose should be reduced, if possible, once symptoms and PEF rates have improved and stabilised. If a patient's asthma cannot be controlled by the above ICS dose and the inhaler technique and adherence are adequate, the dose can be increased to a maximum of 1.5–2 mg a day.

All ICSs have dose-related side effects. Adrenal suppression occurs at around doses of >1500 µcg/day of beclometasone in adults. In children, doses of 400 µcg/day of beclometasone or more are associated with growth failure and adrenal suppression; children treated at these doses should be under the care of a specialist paediatrician. Oropharyngeal side effects such as candidiasis are also more common at higher doses (Box 25.2). Measures to minimise this can be tried, such as using a large-volume spacer device and rinsing the mouth with water or brushing teeth after inhalation, but there is little evidence to confirm how effective these are.

Cromones. Inhaled sodium cromoglicate and nedocromil sodium are less effective than corticosteroids in asthma. Although rarely used, they may be possible alternatives if corticosteroids cannot be tolerated.

Leukotriene receptor antagonists. Two leukotriene receptor antagonists, montelukast and zafirlukast, are currently licensed in the UK. Leukotriene receptor antagonists are included in step 4 as add-on therapy for adult patients but are less effective than LABAs in controlling asthma when added to ICSs. If these agents are initiated, then a 4–6 week trial should be undertaken; if there is no improvement in control, the drug should be stopped. They seem to be of particular value in aspirin-induced asthma, possibly due to the role of leukotrienes in this form of asthma.

Anti-IgE monoclonal antibodies. The first of these, omalizumab, is used for the treatment of severe persistent IgE (30–1500 iu/mL)-mediated asthma as add-on therapy to existing optimised therapy in adults and individuals over 12 years of age who have severe unstable disease (NICE, 2007). Patient response should be measured and omalizumab discontinued after 16 weeks if no adequate response is seen.

Oral corticosteroids. Oral corticosteroids should only be used, at step 5, if symptom control cannot be achieved with maximum doses of inhaled bronchodilators and steroids. They should be given as a single morning dose to minimise adrenal suppression. Alternate-day dosing produces fewer side effects but is less effective in controlling asthma.

Short courses (of up to 3 weeks) of high-dose oral steroids, 40–50 mg daily, can be safely used during exacerbations of asthma.

Steroid-sparing agents. Immunosuppressive agents can be tried in an attempt to reduce a regular steroid dose. Methotrexate, ciclosporin and gold have been tried with varying

Table 25.6 Inhaled corticosteroids used for the prophylaxis of asthma

	Total daily dosage range (MDI)	
Drug and age range	Standard dose	High dose
Beclometasone diproprionate or budesonide[a]		
Adult	100–400 µcg twice a day	400–1000 µcg twice a day
12–18 years	100–400 µcg twice a day	400–1000 µcg twice a day
Under 12 years	100–200 µcg twice a day	200–400 µcg twice a day
Ciclesonide		
Adult	80 µcg once daily	160 µcg once daily
Fluticasone		
Adult	50–200 µcg twice a day	400–1000 µcg twice a day
12–18 years	50–200 µcg twice a day	200–500 µcg twice a day
4–12 years	50–100 µcg twice a day	100–200 µcg twice a day
Mometasone		
Adult	200–400 µcg once daily	400 µcg twice a day
12-18 years	200 µcg twice a day	Up to 400 µcg twice a day

[a]There are bioavailability differences between CFC-free steroid inhalers. Always check dosing for specific brands.

Box 25.2 Adverse reactions associated with drugs used in the management of asthma

β_2-Agonists
- *By inhalation*: adverse drug reactions are uncommon
- *Nebulisation, orally or parenterally*: fine tremor (usually the hands), nervous tension, headache, peripheral vasodilation, tachycardia. The adverse reactions often diminish as tolerance develops with continued administration
- *High doses*: hypokalaemia, aggravation of angina

Inhaled corticosteroids
- Hoarseness, oral or pharyngeal candidiasis
- Adrenal suppression may occur with high doses, for example, beclometasone diproprionate above 1500 µcg daily

Oral corticosteroids
- Prolonged use of these results in exaggeration of some of the normal physiological effects of steroids
- Mineralocorticoid effects include: hypertension, potassium loss, muscle weakness, and sodium and water retention. These effects are most notable with fludrocortisone, are significant with hydrocortisone, occur only slightly with prednisolone and methylprednisolone and are negligible with dexametasone and betametasone
- Glucocorticoid effects include: precipitation of diabetes, osteoporosis, development of a paranoic state, depression, euphoria, peptic ulceration, immunosuppression, Cushing's syndrome (moon face, striae and acne), growth suppression in children, worsening of infection, skin thinning, striae atrophicae, increased hair growth, perioral dermatitis and acne
- Adrenal suppression occurs with high doses and/or prolonged treatment. Steroid therapy must be gradually withdrawn in these patients to avoid precipitating an adrenal crisis of hypotension, weight loss, arthralgia and, sometimes, death

Ipratropium bromide
- Occasionally: dry mouth
- Precipitation of acute glaucoma with nebulised therapy, possibly worsened by co-administration of salbutamol. A mouthpiece should be used to minimise the exposure of the eyes to the nebulised drug
- Rarely: systemic anticholinergic effects such as urinary retention and constipation

Methotrexate
- Myelosuppression, mucositis and, rarely, pneumonitis

Nedocromil sodium
- Mild and transient nausea, coughing, transient bronchospasm, throat irritation, headache and a bitter taste

Sodium cromoglicate
- Coughing, transient bronchospasm and throat irritation due to inhalation of the powder

Theophylline
- Although about 5% of the population experience minor adverse effects (nausea, diarrhoea, nervousness and headache), increasing the plasma concentration results in more serious effects. The following is a guide to the plasma levels at which the adverse reactions usually occur:
  - Above 20 mg/L: persistent vomiting, insomnia, gastro-intestinal bleeding, cardiac arrhythmias
  - Above 35 mg/L: hyperglycaemia, hypotension, more serious cardiac arrhythmias, convulsions, permanent brain damage and death
- Individual patients may suffer these effects at plasma levels other than those quoted, for example, convulsions have occurred in patients at 25 mg/L

Leukotriene receptor antagonists
- Abdominal pain, headache, diarrhoea, dizziness, upper respiratory tract infections. Rarely: acute hepatitis (associated with zafirlukast), Churg–Strauss syndrome

success. All have potentially toxic side effects and need to be closely monitored.

Acute severe asthma

The management of acute asthma depends on the severity of the attack and its response to treatment, as well as an appreciation of the patient's past history and present treatment. If an acute attack becomes persistent and difficult to treat, it is known as acute severe asthma. The aims of treatment are to prevent any deterioration in the patient's condition and hasten recovery.

Prevention. The ideal way of treating an acute attack is to empower patients to recognise when their condition is deteriorating so they can initiate treatment to prevent the attack becoming severe. This can be achieved with an individualised self-management plan.

The dose of inhaled β_2-agonist should be increased, and a short course of oral steroids commenced, for example, prednisolone at a dose of 40–50 mg every morning for 1 week. The dose of ICS is often also increased, but there is limited evidence to support this.

If the condition deteriorates further, hospital admission may become necessary. This could be a self-referral from the patient, responding to criteria drawn up by the doctor, such as their PEF falling below 50% of their usual best. The education of patients and their relatives in the management of

acute attacks should always stress the prompt initiation of further treatment and early referral.

Immediate management. The immediate treatment of acute severe asthma should take place in the patient's home if a moderate attack. Admission to hospital is considered if PEF drops below 50% predicted or normal, or the patient cannot complete sentences in one breath or is too breathless to talk, or if life-threatening features are present. A suggested treatment protocol for management in hospital is outlined in Fig. 25.5.

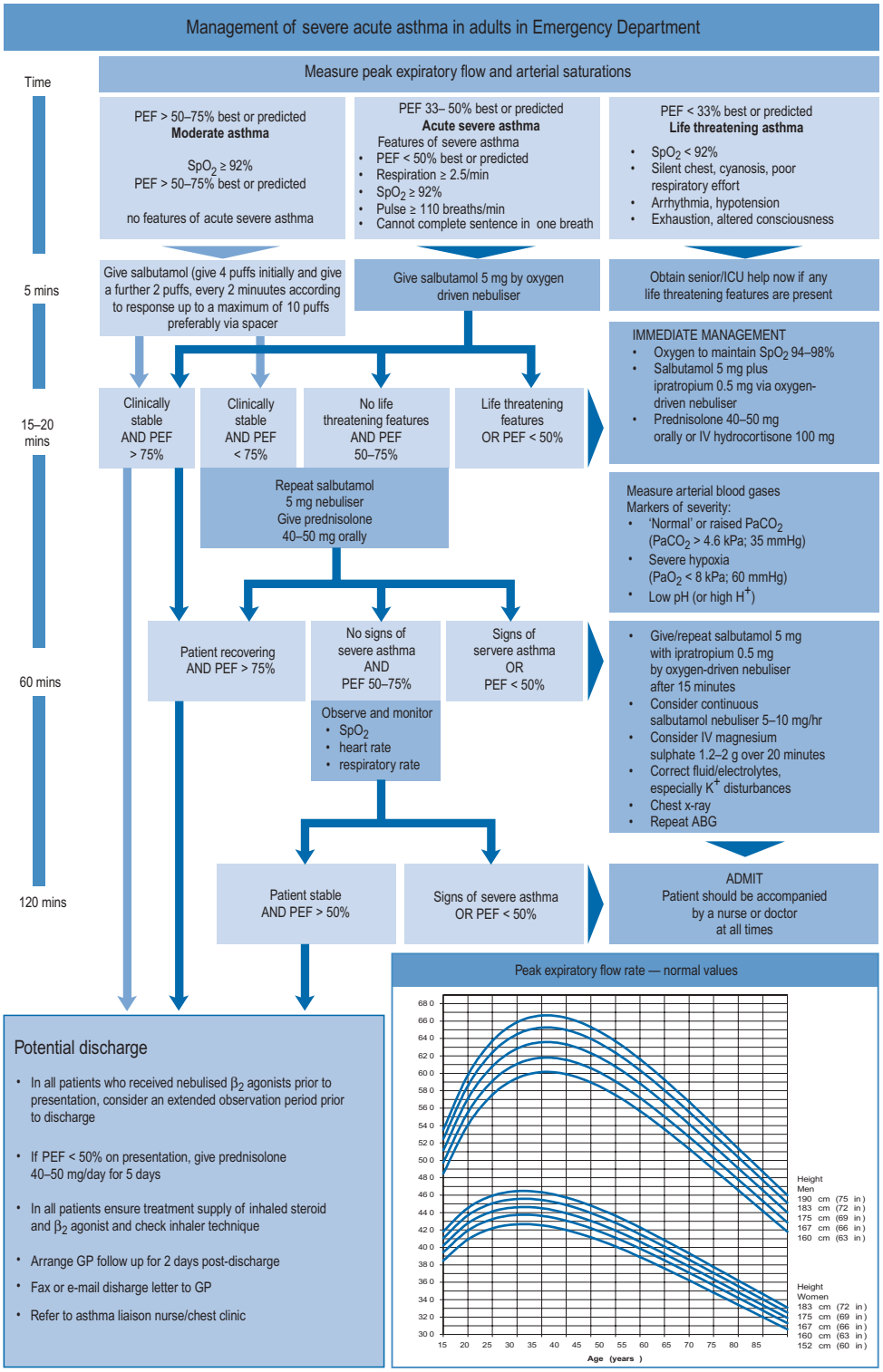

Fig. 25.5 Management of acute severe asthma in adults in hospital reproduced by permission of the Scottish Intercollegiate Guidelines Network from BTS/SIGN, 2009.

Oxygen is administered to achieve an oxygen saturation of 92% or more. A β_2-agonist is administered by metered dose inhaler (MDI) with a spacer attachment (4 puffs, then 2 puffs every 2 min until 10 mg or symptom relief) as there is no demonstrable difference between this and using a nebuliser. With more severe symptoms, or during an admission to hospital, nebulisers are used because they permit a high dose (10–20 times the dose of a MDI) and they require no coordination on the part of the patient between inspiration and actuation, which is helpful in those distressed. Patients undergoing an acute attack often have an inspiratory rate that is too low to use an MDI effectively.

Corticosteroids are also given in the acute attack; oral prednisolone (40–50 mg daily, for 5 days). Intravenous hydrocortisone (100 mg) should only be required if the patient cannot take oral medication. This reduces and prevents the inflammation that causes oedema and hypersecretion of mucus and hence helps to relieve the resultant smooth muscle spasm. The clinical response to both oral and parenteral steroids has an onset at 1–2 h with a peak effect at 6–8 h. If life-threatening features are present, such as cyanosis, bradycardia, confusion, exhaustion or unconsciousness, higher dose bronchodilators are used: nebulised salbutamol 5 mg with ipratropium bromide 500 µcg, repeated after 15 min; with subsequent consideration to continuous nebulisation of salbutamol at 5–10 mg/h. The addition of an anticholinergic such as ipratropium often gives a response that is greater than that of the two agents used alone.

Intravenous aminophylline can be given with a bolus dose of 250 mg over 30 min, followed by a continuous infusion of 500 µcg/kg/h. The bolus should be omitted if the patient is known to take oral theophylline or aminophylline. The choice between intravenous aminophylline and β_2-agonist depends on concurrent therapy and side effect profiles. The dose of intravenous aminophylline used must also take into account recent theophylline therapy in addition to other factors (Table 25.7). Serious toxicity can occur with parenteral aminophylline and patients must be carefully monitored for nausea and vomiting, the most common early signs of toxicity.

Table 25.7 Intravenous aminophylline dosing in acute severe asthma

	Aminophylline dose	Patient characteristics
Loading dose	5 mg/kg over 20–30 min	Adults and children
	3 mg/kg over 10–15 min	Previous theophylline therapy (although some authorities do not use a loading dose in these patients)
Maintenance dose	500 µcg/kg/h	Non-smoking adults
	700 µcg/kg/h	Children under 12 or smokers
	200 µcg/kg/h	Cardiac failure, liver impairment, pneumonia

If the aminophylline infusion is continued for more than 24 h, the plasma theophylline concentration may be measured to guide any necessary alteration in infusion rate in order to maintain the level in the optimum range of 10–20 mg/L.

Intravenous magnesium sulphate, 1.2–2 g as a 20-min infusion, has been shown to help in some patients who have not had a good response to initial treatment. There is, however, no evidence to support repeated dosing regardless of therapeutic outcome.

Further deterioration in condition may require assisted mechanical ventilation on an intensive care unit. Regular monitoring of arterial blood gases and oxygen saturation is performed to help detect any deterioration in condition.

Antibiotics are only indicated where there is evidence of a bacterial infection.

Ongoing management. The subsequent management of acute severe asthma depends on the patient's clinical response. All patients should be monitored throughout their treatment with objective measures of their PEFs before and after bronchodilator treatment and with continual monitoring of their arterial blood gas concentrations to ensure adequate oxygen is being given.

As the patient responds to treatment, infusions can be stopped and other treatment changed or tailed off as described above. As improvement continues, an inhaled β_2-agonist is substituted for the nebulised form and the oral corticosteroids stopped or reduced to a maintenance dose if clinically necessary. Throughout the treatment programme, potential drug interactions should be anticipated and managed appropriately (Table 25.8).

All patients should have a follow-up after an acute attack with symptoms monitored, reasons for admission addressed and inhaler technique checked. A self-management plan should be drawn up and discussed with each patient.

Patient care

The correct use of drugs and the education of patients are the cornerstones of asthma management. There are three main steps in the education of the asthmatic patient.

1. The patient should have an understanding of the action of each of the medicines they use.
2. The appropriate choice of inhalation device(s) should be made and the patient educated to use them correctly.
3. An individualised action (self-management) plan should be developed for each patient.

All members of the health care team should provide education and support for the asthmatic patient at regular intervals. The need for each patient to understand their asthma and its management must be balanced against the dangers of overwhelming the patient with information, particularly when the asthma has been newly diagnosed. To try to overcome this, a 'ladder of asthma knowledge' has been proposed. Patients are counseled in a gradual manner, each session adding to the previous one in content and reinforcing existing knowledge (Box 25.3).

Table 25.8 Common clinically significant interactions with drugs used in the management of asthma

Drug	Interacting drug	Probable mechanism and clinical result
β_2-Agonists	Methyldopa	Acute hypotension possible with β_2-agonist infusions
Corticosteroids	Anticoagulants	High-dose steroids enhance anticoagulant effect of coumarins
	Antifungals	Metabolism of steroids possibly affected by antifungal agents
	Barbiturates	Accelerates steroid metabolism
	β_2-Agonists	Increased risk of hypokalaemia with high doses
	Carbamazepine	Reduced steroid effect due to increased metabolism
	Ciclosporin	Increases plasma concentration of prednisolone
	Methotrexate	Increased risk of haematological toxicity
	Phenytoin	Reduced steroid effect due to increased metabolism
	Rifampicin	Reduced steroid effect due to increased metabolism
Theophylline	Azithromycin	May increase theophylline plasma levels
	β_2-Agonists (high dose)	Increased risk of hypokalaemia
	Carbamazepine	Induction of theophylline metabolism resulting in decreased plasma levels
	Clarithromycin	Inhibition of theophylline metabolism resulting in increased plasma levels
	Cimetidine	Inhibition of theophylline metabolism resulting in increased plasma levels
	Ciprofloxacin	Increased plasma concentration. Possible risk of convulsions
	Diltiazem	Increased theophylline plasma levels
	Erythromycin (oral)	Inhibition of theophylline metabolism resulting in increased plasma levels
	Fluconazole	Possible increase in theophylline plasma level
	Dihydropyridine calcium antagonists	May increase theophylline plasma levels
	Fluvoxamine	Increased theophylline plasma levels, halve theophylline dose
	Isoniazid	May increase theophylline plasma levels
	Ketoconazole	Possible increase in theophylline plasma level
	Lithium carbonate	Reducing plasma lithium concentrations as theophylline enhances lithium renal clearance
	Norfloxacin	Increased plasma concentration. Possible risk of convulsions
	Phenytoin	Plasma concentrations of theophylline and phenytoin both reduced
	Primidone	Induction of theophylline metabolism resulting in decreased plasma levels
	Rifampicin	Induction of theophylline metabolism resulting in decreased plasma levels
	Ritonavir	Metabolism of theophylline increased
	Smoking (tobacco)	Induction of theophylline metabolism resulting in decreased plasma levels
	St John's wort	Reduced theophylline plasma levels
	Verapamil	Increased theophylline plasma levels

Box 25.3 Ladder of asthma knowledge for patients

Step 1: Patient/carer understands what relief medication does, side effects which may occur, aims of treatment, what is happening to them and their chest. Education material is made available
Step 2: Patient/carer accepts and agrees about use of medication, importance of preventers and recognition of symptoms
Step 3: Patient/carer knows how to monitor PEF and symptoms, when to increase dose of inhaled steroids and contact their medical practice
Step 4: Patient/carer confident to manage own medication, increasing and decreasing dose using PEF or symptom monitoring, start oral steroids and attend their medical practice

Knowledge

Increasing the patients' knowledge about their asthma therapy is a necessary component of asthma management. However, education alone has not been shown to have a beneficial effect on morbidity. Education programmes must, therefore, also look at modifying their behaviour and attitude to asthma. Counselling should lead to increased patient confidence in the ability to self-manage asthma, thereby decrease hospital admission rates and emergency visits by primary care doctors, increase adherence and improve quality of life.

Specific counselling on drug therapy should concentrate on three areas: drugs used to relieve symptoms, drugs used to prevent asthma attacks, and drugs which are given only as reserve treatment for severe attacks.

Inhalation device

The choice of a suitable inhalation device is vital in asthma management. The incorrect use of inhalers will lead to sub-optimal treatment. A review of inhaler technique studies has concluded that up to 50% of patients in Europe are unable to use their inhaler correctly (Crompton et al., 2006). There is no demonstrable difference in efficacy between the various devices available. Other factors, therefore, need to be considered when choosing the appropriate device, including the patient's age, severity of disease, manual dexterity, co-ordination and personal preference. The range of different devices available for the drugs commonly used in asthma is shown in Table 25.9.

Table 25.9 Inhalation devices and spacer devices available

Drug	Type of inhaler device						
	Metered dose	Breath-actuated spacer for MDI	Single-dose spacer for MDI	Multiple-dose dry powder inhaler	Nebuliser dry powder inhaler	Large-volume	Small-volume
Salbutamol	✓	✓	✓	✓	✓	✓	✓
Ipratropium	✓		✓		✓		✓
Terbutaline				✓	✓		
Salmeterol	✓			✓			✓
Formoterol			✓				
Tiotropium[a]	✓[b]		✓				
Beclometasone	✓	✓	✓	✓			✓
Budesonide	✓			✓	✓	✓	✓
Ciclesonide	✓						✓
Fluticasone	✓			✓	✓	✓	✓
Mometasone				✓			
Cromoglicate	✓	✓	✓		✓		✓
Nedocromil	✓						✓

[a]Only licensed for use in COPD.
[b]Delivers a soft aerosol 'mist'.

Metered dose aerosol inhalers

The pressurised MDI is the most widely prescribed inhalation device in the UK (Fig. 25.6). It usually contains a solution or suspension of active drug, with a typical particle size of 2–5 µm, in a liquefied propellant. Operation of the device releases a metered dose of the drug with a droplet size of 35–45 µm. The increased droplet size is due to the propellant, which evaporates when expelled from the inhaler. Inhalers have now been switched from chlorofluorocarbon (CFC) propellants to newer, non-CFC, hydrofluoroalkanes.

MDIs have the advantage of being multidose, small and widely available for most drugs used in asthma management. Their main disadvantage is that correct use requires a good technique. A particular problem for many patients is co-ordinating the beginning of inspiration with the actuation of the inhaler. Even when this is done correctly, MDIs only deliver about 10% of drug to the airways, with 80% deposited in the oropharynx. Corticosteroids administered by MDIs can cause dysphonia and oral candidiasis. The candidiasis can be minimised either by advising patients to gargle with water after using the inhaler and to expel the water from the mouth afterwards, or by using a spacer device. Newer devices are utilising other mechanisms to produce an aerosol such as a soft mist inhaler (SMI) which may give benefits in lung deposition and ease of use.

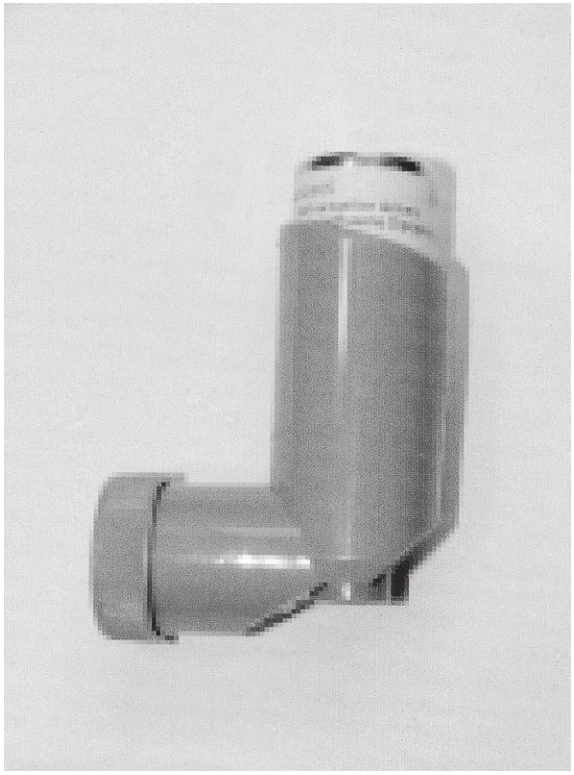

Fig. 25.6 Pressurised metered dose inhaler.

Table 25.10 Inhaler device choice for children

Age group	Drug group	First choice device	Second choice device
0–2 years	All	MDI + spacer + facemask	Nebuliser
3–4 years	All	MDI + spacer	Nebuliser or dry powder
5–15 years	Bronchodilators	MDI or dry	Powder or breath-actuated MDI
5–15 years	Corticosteroids	MDI + spacer	Dry powder or breath-actuated MDI

Younger children, in particular, find MDIs difficult to use and the addition of a spacer device can make this easier, allowing inhalation over several ambient breaths.

The correct technique for using MDIs is as follows:

1. MDIs have a mouthpiece dust cap which has to be removed before use (patients may fail to remove this). The cap must be replaced after use to prevent subsequent inhalation of foreign bodies.
2. The MDI must be vigorously shaken. This distributes the drug particles uniformly throughout the propellant (newer CFC-free inhalers may be solutions and not require shaking – see manufacturer's literature). The MDI must be held upright.
3. The patient should breathe out gently, but not fully.
4. The tongue should be placed on the floor of the mouth and the inhaler placed between the lips, which are then closed round the mouthpiece.
5. The patient should now start to breathe in slowly and deeply through the mouth.
6. The canister is pressed to release the dose while the patient continues to breathe in. This synchronisation of inspiration and actuation, so that there is a supporting stream of air to carry the drug to the lungs, is probably the most common point of failure in those with bad inhalation technique. Patients who are very short of breath, for example, during a severe asthma attack, find this particularly difficult.
7. The breath is held for at least 10 s. This allows the drug particles reaching the periphery of the lung to settle under gravity. Using this technique, about 15% of a dose may reach the lungs. Exhalation should be through the nose.
8. If a second dose is required, 30–60 s should elapse before repeating the inhalation procedure to allow the dosing chamber to re-fill.

Studies indicate that personal tuition improves inhaler technique, particularly if regularly repeated. Other methods of instruction include videos (see http://medguides.medicines.org.uk/demonstrations.aspx), package inserts and information leaflets or booklets provided by organisations such as Asthma UK and the pharmaceutical industry. Regular patient review, at least annually, is recommended. This can be used as an opportunity to check technique, along with assessment of the ability to generate the appropriate inspiratory flow for the device (Broeders et al., 2009).

Metered dose inhaler with a spacer extension

Extension devices allow greater evaporation of the propellant, so reducing particle size and velocity. This also reduces oropharyngeal deposition and potentially increases lung deposition. Oral candidiasis and dysphonia (impaired voice) from ICSs may also be reduced by using these devices. Spacers are useful for people who have poor co-ordination between inspiration and actuation and several types of spacer are available. In younger children, these offer advantages over MDIs alone with respect to adherence. Recommendations (see Table 25.10) have been published regarding device choice (NICE, 2000, 2002).

Large-volume (750 mL) spacers are available such as the Volumatic® (Fig. 25.7); these are manufacturer specific and have not been assessed or licensed for use with devices of other companies. These spacers have one-way valves that allow several inhalations of one dose from the spacer's chamber. No co-ordination is required between actuation of the MDI and inhalation. A large-volume spacer can be used instead of a nebuliser to deliver high doses of a β_2-agonist in acute severe asthma attacks. Disadvantages of these spacers include their large size, which renders them less portable, and their proven efficacy only with inhalers from the same manufacturer. Spacers should be washed regularly in warm, soapy water and left to drip dry without rinsing. Cloths should not be used for drying a spacer as this affects the antistatic coating of plastic spacers. All spacers should be replaced every 6–12 months. Facemasks are available for young children.

Small- and medium-volume spacer devices are available, either as an integral part of the design of some MDIs or as

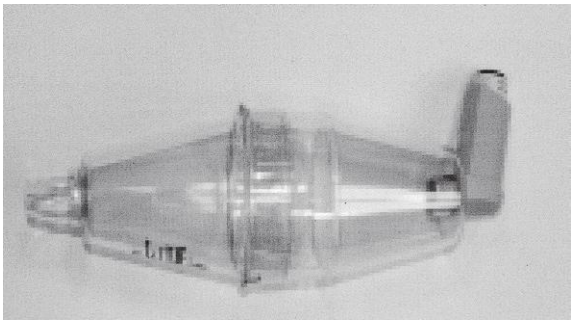

Fig. 25.7 Large-volume spacer (Volumatic®).

a separate device (Fig. 25.8). These spacers have also been used to compensate for poor inhaler technique in adults and reduce the oropharyngeal deposition of steroids. These are more convenient to carry around than the larger spacers. The published evidence of additional benefit from these devices in either increasing efficacy or decreasing adverse effects is more limited than with large volume spacers.

Breath-actuated metered dose inhalers

These MDIs are actuated automatically by inspiratory flow rates of about 22–36 L/min. A breath-actuated MDI is illustrated in Fig. 25.9. These eliminate the need for the correct co-ordination of inspiration and actuation but require priming before each actuation.

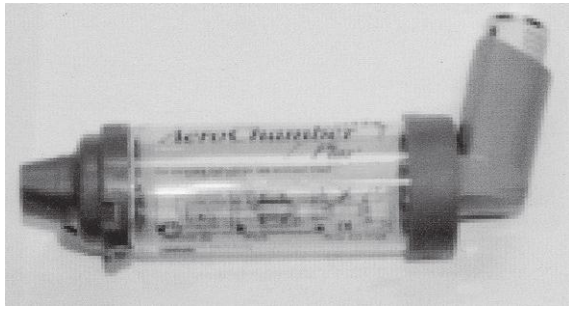

Fig. 25.8 Medium-volume spacer (Aerochamber Plus®).

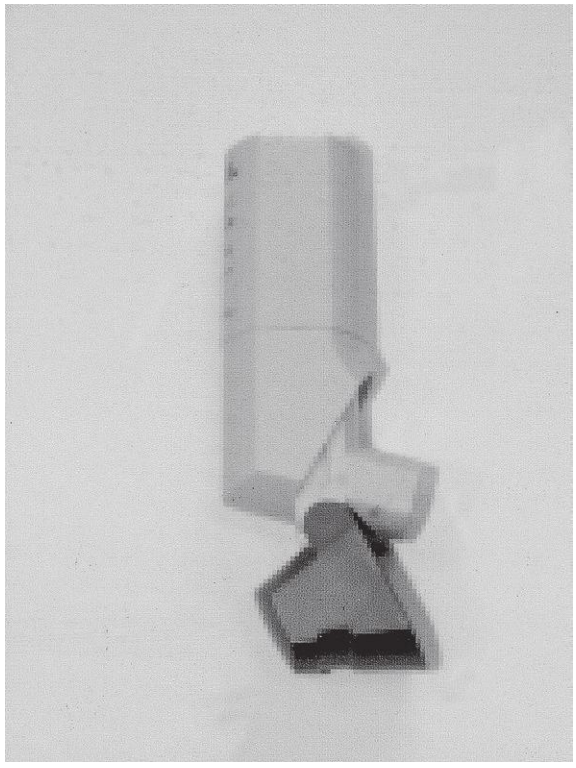

Fig. 25.9 Breath-actuated metered dose inhaler (Easi-breathe®).

Dry powder inhalers

Several types of dry powder inhalers (DPIs) are available. These are propellant free and are designed to be easier to use than conventional MDIs. They are useful for those who have difficulty co-ordinating an MDI and can be used by children as young as 4 years old. Table 25.10 sets out the recommendations for device choice in children.

DPIs are available as either single-dose or multiple-dose devices (Fig. 25.10). Single-dose devices pierce or break a gelatin capsule to release the contents and must be regularly cleaned to avoid powder clogging the device. Multiple-dose devices are preferred by many patients since they avoid having to reload for each dose. Care must be taken to hold these devices in the correct orientation to avoid the powder falling out of the device before inhalation. Patients commenced on DPIs are sometimes concerned at the absence of any taste or spray plume which they have become accustomed to when using an MDI; reassurance that this is perfectly normal and that correct use of the DPI (including a check that the device is not empty) will ensure that the required dose is delivered should overcome this problem.

Nebulisers

A nebuliser produces an aerosol by blowing air or oxygen through a solution to produce droplets of 5 µm or less in size. Nebulisers require little co-ordination from the patient as any drug is inhaled through a facemask or mouthpiece using normal tidal breathing. Only about 13%

Fig. 25.10 Multiple-dose dry powder inhaler (Turbohaler®).

of the dose used is deposited in the lungs, but because the doses used are higher than those used in other aerosol devices, patients will generally receive a higher dose than from an MDI. However, in mild and moderate exacerbations of asthma, no benefit has been shown over using 4–6 puffs of a MDI.

Nebulisers are useful in patients who are unable to use conventional inhalers, for example, children under 2 years old, patients with severe attacks of asthma unable to produce sufficient inspiratory effort and those lacking the co-ordination to use other inhalers. Nebulised bronchodilators can be used in acute severe asthma attacks, often avoiding the need for intravenous drugs.

Most of the short-acting β_2-agonists, as well as ipratropium bromide, fluticasone, budesonide and sodium cromoglicate, are available for nebulisation.

The safe and correct use of nebulisers requires careful counselling, especially if they are to be used in the home. The following points are critical for the correct use of a nebuliser.

1. Nebulisers should only be driven by compressed air or by oxygen at flow rates of at least 5–6 L/min to ensure that droplets of the correct size are produced.
2. To maximise nebulised drug, a minimum volume of 3–4 mL should be nebulised. This volume is required to reduce the amount of drug that is unavoidably left in the 'dead-space' (typically about 1 mL) at the end of nebulisation. This 'dead space' is less with newer nebulisers and no further dilution of commercial nebuliser solutions is used. Sodium chloride 0.9% must be used if solutions are diluted.
3. Most nebuliser chambers are disposable but will last 3–4 months when used by a patient at home. The chamber must be emptied after use, and each day, the chamber should be rinsed in hot water and dried by blowing air through the device. Several centres advocate that once a week the chamber should be sterilised using 0.02% hypochlorite to prevent bacterial contamination; the chamber is then thoroughly rinsed to remove all traces of hypochlorite and then dried.
4. The nebuliser should be serviced at least once a year.

There are disadvantages with the use of nebulisers. Of particular concern is the overreliance on the nebuliser by some patients which results in a delay in seeking medical advice. The high doses of bronchodilators used can also increase the incidence of side effects, and these vary depending on the drug nebulised.

Self-management programmes

Every individual with asthma should be considered for a self-management education programme. These programmes will contain structured education along with an individualised action plan. They aim to give the individual more confidence by involving them in the management of their own asthma. The individual should then be able to deal with any fluctuation in their condition and know when to seek medical advice. Personalised action plans have been shown to improve health outcomes in individuals with asthma (Gibson et al., 2002).

Key elements of an action plan include being able to monitor symptoms, measure peak flow, understand their medicine and how it should be used, and knowing how to deal with fluctuations in severity of asthma according to written guidance. Symptom diaries, management guidance cards and peak flow reading diary cards are available from organisations such as Asthma UK and pharmaceutical companies who manufacture asthma products.

An action plan can also include details of when to increase the dose of an inhaled steroid, when to take a short course of oral corticosteroids and when to self-refer to a general medical practitioner or local hospital (Table 25.11).

Table 25.11 Example of a personalised action plan setting out the action required in response to a given peak flow reading and/or symptoms

Peak flow	Example of symptoms	Action
>80% of personal best value	Intermittent or few symptoms	When required, β_2-agonist for symptom relief, continue regular inhaler corticosteroid, consider reducing the dosage every 3 months if stable
61–80% of best	Waking at night Symptoms of a cold	Double dose of inhaled corticosteroid if taking <400 µcg day BDP Start oral corticosteroid if taking >400 µcg/day BDP
40–60% of best	Increasing breathlessness or using a β_2-agonist every 2–3 h	Start oral corticosteroid course. Contact a doctor
<40% of best	Severe attack Poor response to β_2-agonist	Call emergency doctor or ambulance urgently

BDP, equivalent dose of beclometasone dipropionate.

Case studies

Case 25.1

Mr GT is 54 years old and has been diagnosed with asthma for 4 years. He is 180 cm tall and weighs 95 kg. He has recently been admitted to hospital with an acute exacerbation of his asthma, precipitated by a lower respiratory tract infection. During his admission, his steroid medication was altered from Qvar Easi-breathe® 100 µcg twice daily to Symbicort 400/12 Turbohaler® 1 puff twice daily. He also takes Salbutamol Easi-breathe® inhaler 200 µcg when required.

Questions

1. By how much has his ICSs dose been increased?
2. Should Mr GT be reviewed after discharge?
3. Would Mr GT benefit from self-management information and a personalised action plan?
4. Four months after his discharge, Mr GT has had no further exacerbations and his daily best PEF reading is around 520 L/min; he has no limitations of activity because of his asthma and uses his salbutamol inhaler between two and three times a week. How can Mr GT's level of asthma control be determined?
5. You determine that Mr GT's asthma is now controlled. Could his therapy now be stepped down? If so, how should this be done?

Answers

1. Qvar® is a hydrofluoroalkane CFC-free inhaler with microfine particles of a mass median diameter of 1.1 µm. Clinical studies show that adult patients require approximately half the dose of Qvar® to achieve the same degree of asthma control as with CFC-containing beclometasone inhalers. Care must always be taken when switching between ICS brands (see http://www.mhra.gov.uk/). Tables exist to help with determining equivalent doses (BTS/SIGN, 2009). Qvar® 200 µcg daily is equivalent to 400 µcg of other beclometasone/budesonide preparations, so Mr GT's ICS dose has been doubled.
2. He should be reviewed within 1 month of hospital discharge. This has been associated with a reduced risk of further acute episodes.
3. He would benefit from self-management information and a personalised action plan. The evidence of improved health outcomes for asthmatic patients is particularly good for those with moderate to severe disease and those who have had recent exacerbations.

   A personalised action plan should contain:

   - Advice about recognising loss of asthma control, as assessed by symptoms and PEF readings
   - The action to take if asthma deteriorates, including when and how to seek emergency help and when to commence a course of emergency oral steroids, which should be prescribed in advance.
4. Asthma control is usually assessed on the basis of clinical history, symptoms, inhaler usage and technique. An acute exacerbation is often indicative of poor control over a period of time.

   The level of asthma control for Mr GT can be determined by utilising tools such as the levels of asthma control in the GINA guidelines (GINA, 2009; Table 25.2) and the commonly used Royal College of Physicians, '3 questions':

   - Have you had difficulty sleeping because of your asthma symptoms (including cough)?
   - Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)?
   - Has your asthma interfered with your usual activities (e.g. housework, work/school, etc.)?

Management issues should also be discussed:

- Any issues of importance to the patient
- Inhaler technique must be checked, any deficiencies corrected, and if necessary a different device tried
- Adherence to prescribed medication should be assessed
- Mr GT has to be willing to try a step-down in his therapy. His ICS dose can be reduced slowly; a reduction of between 25% and 50% is usually tried every 3 months. A reduction to Symbicort® 200/6 1 puff twice daily could be attempted at this stage. The potential for worsening symptoms and the increased risk of exacerbation should be explained when step-down is attempted, particularly as the LABA dose is also being reduced. Opportunity should be taken to also promote general lifestyle advice:
  - Mr GT's body mass index is 29.3 and he is classed as overweight. He should be advised that a healthy diet and regular exercise will help with weight reduction and improve asthma control
  - Offer stop smoking advice if relevant
  - Advise him to avoid exposure to tobacco smoke
  - Provide allergen avoidance advice

  Mr GT should be asked to keep twice daily PEF readings and a symptom diary. He will need to be reviewed again in 3 months unless symptoms deteriorate before then. Mr GT should be advised to consider increasing his medication again if his asthma deteriorates; his action plan can be adjusted accordingly.

Case 25.2

Mrs LJ is 32 years old and was recently diagnosed on hospital admission with breathlessness following exposure to cold air. You are conducting a follow-up review after her hospital admission.

Questions

1. What advice should you cover in your consultation with Mrs LJ? Mrs LJ tells you that she has a cat and wonders if this could be affecting her asthma.
2. What information can you give Mrs LJ on allergen avoidance?

Answers

1. Effective management of asthma requires a partnership between the patient and the health care professionals involved in providing the care. The aim is to enable and empower the patient to gain the confidence, skills and knowledge to take a major role in the management of their asthma (GINA, 2009). Open-ended questions such as 'If we could make one thing better about your asthma what would it be?' may help to elicit a patient-centred agenda (BTS/SIGN, 2009). Topics that should be covered in this and subsequent consultations include:

   - Nature of the disease
   - Nature of the treatment
   - Identification of areas where the patient most wants treatment to have effect
   - How to use the treatment, particularly inhaler technique. Websites with video instruction, such as http://www.medicines.org.uk/Guides/Pages/how-to-use-your-inhaler-videos can be used to reinforce verbal instruction and demonstration.

- Develop self-monitoring/self-assessment skills
- Negotiate a personalised action plan in light of identified patient goals
- Recognise and manage acute exacerbations
- Appropriate allergen or trigger avoidance, for example, smoking, pollen, exercise, air pollution and stress
- Ensure Mrs LJ has received a current influenza vaccination

Practical information and treatment plans should be reinforced with written instruction; this can also be from patient support groups such as Asthma UK http://www.asthma.org.uk/. Every subsequent consultation with any health care professional should be an opportunity to review reinforce and extend both knowledge and skills.

2. There is no doubt that increased allergen exposure in sensitised individuals is associated with an increase in asthma symptoms, bronchial hyperresponsiveness and deterioration in lung function (BTS/SIGN, 2009); this includes animal allergens. However, the removal of cats from the home has not been shown to always benefit individuals with asthma. The reduction of exposure to other allergens, such as house dust mite, may also be considered for their potential effect on asthma symptoms. There is no evidence for the effectiveness of dust mite reduction strategies (Getzsche and Johansen, 2008).

   If Mrs LJ wishes to try and reduce the burden of allergens in her home, then the following can be considered:

   - Complete barrier bed-covering systems
   - Remove carpets
   - Remove soft toys from beds for children
   - High temperature washing of bed linen
   - Use acaricides on soft furnishings
   - Ensure good ventilation with or without dehumidification
   - Use a high-efficiency vacuum cleaner with an inbuilt air filter to reduce cat allergens.

If these measures provide no benefit to asthma symptoms or quality of life after a trial of a few months, they should be stopped.

Case 25.3

Mr KM is a 49-year-old man who has been diagnosed with asthma since childhood. He also suffers from allergic rhinitis with symptoms following exposure to grass pollen in the early summer. He is also allergic to cats. Over the past 2 years his asthma has been steadily deteriorating with a marked reduction in his ability to walk without becoming breathless. He now experiences daily symptoms and is woken up at night several times a week with shortness of breath which is temporarily relieved using a salbutamol inhaler. His current medication is:

Salbutamol DPI 200 µcg when required (currently using three or four times every day)
Seretide-250® evohaler® 2 puffs twice daily
Montelukast 10 mg at night
Aminophylline m/r (Phyllocontin®) 450 mg twice daily

He has had five exacerbations in the past 18 months, requiring hospitalisation. His last admission was 1 month ago with a severe exacerbation requiring a short period of ventilation support. He was discharged with a course of prednisolone 40 mg daily for 14 days but has had to continue taking prednisolone and currently takes 10 mg daily.

Questions

1. At which step of the BTS/SIGN guidelines is Mr KM, and what is his likely diagnosis?
2. What should be the next step in his management?
3. Is there a link between asthma and allergic rhinitis?
4. Mr KM has a positive skin prick test for animal dander and his IgE titre measures 425 IU/L. Is Mr KM suitable for treatment for omalizumab and, if so, for how long should this be given?

Answers

1. He is at step 5, with uncontrolled asthma despite taking 1000 µcg of inhaled fluticasone daily (equivalent to 2000 µcg of beclometasone), a LABA, and three other medications, including oral steroids. It is likely that Mr KM has 'difficult to treat' asthma.
2. Mr KM should be referred to a respiratory specialist. He requires careful assessment which will include:

   - Confirmation or verification of the diagnosis of asthma, including asthma subsets such as steroid-resistant asthma (PEF increase less than 15% after 2 weeks of steroids), psychosocial asthma, premenstrual asthma, aspirin-induced asthma, rhinitis, occupational asthma, allergic bronchopulmonary aspergillosis
   - Identification of preventable causes of persistent symptoms
   - A review of inhaler technique
   - An assessment of adherence to treatment. A significant proportion of patients who may be considered difficult to treat are non-adherent with their corticosteroid therapy. The number of ICS and SABA inhalers dispensed per year can be an indicative measure of non-adherence
   - IgE titre.

3. Allergic rhinitis co-exists with asthma in the majority of patients. The rhinitis should be treated with intranasal steroids as this has been demonstrated to improve asthma morbidity.
4. Mr KM meets the criteria for omalizumab to be given. Omalizumab takes between 12 and 16 weeks to demonstrate effectiveness. Mr KM should be reviewed at 16 weeks and omalizumab only continued if there is a marked improvement in symptoms.

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Chronic obstructive pulmonary disease 26

D. Cripps and K. P. Gibbs

Key points

- Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide.
- COPD is the most prevalent manifestation of obstructive lung disease and mainly comprises chronic bronchitis and emphysema.
- The reduction of exposure to tobacco smoke, occupational dusts, chemicals and pollutants is an important goal to prevent the onset and progression of COPD.
- Risk factors for COPD include host factors (α_1-antitrypsin deficiency and airway hyper-responsiveness) and exposures (tobacco smoke, occupational dusts and chemicals, indoor and outdoor pollutants, infections) and socio-economic status.
- Smoking cessation is the single most effective intervention to reduce the risk of developing COPD and slow disease progression. This should be the primary focus of management.
- The management of COPD should follow both national and international guidance.
- COPD care should be delivered by a multidisciplinary team; assessing and managing patients, advising patients on self-management strategies and exercise, identifying and monitoring patients at high risk of exacerbations and educating patients and other health professionals.
- Patients should undergo non-pharmacological pulmonary rehabilitation, such as breathing exercises.

Chronic obstructive pulmonary disease (COPD) is a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases (GOLD, 2009).

COPD is a general term that covers a variety of other disease labels including chronic obstructive airways disease (COAD), chronic obstructive lung disease (COLD), chronic bronchitis and emphysema.

COPD has been defined (National Institute for Health and Clinical Excellence, 2010) as:

- Airflow obstruction with a reduced FEV_1/FVC ratio of less than 0.7.
- If FEV_1 is ≥80% of predicted normal, a diagnosis of COPD should only be made in the presence of respiratory symptoms, for example breathlessness or cough.

Epidemiology

COPD is the fifth leading cause of death in the UK and the fourth in the world. It is expected to rise to third position by 2020. It is estimated that over 3 million people have the disease in the UK, with 2 million having undiagnosed COPD (National Clinical Guideline Centre, 2010). COPD is the largest single cause of lost working days in the UK. It is accountable for more than 10% of all hospital admissions and directly costs the NHS around £491 m/year. The burden of COPD on the UK healthcare system exceeds that of asthma and is outlined in Table 26.1.

Respiratory diseases including chronic bronchitis are more common in areas of high atmospheric pollution and in people with dusty occupations such as foundry workers and coal miners. Areas that are highly industrialised generally have the highest incidence of COPD. The UK has around twice the rate of mortality from respiratory disease compared to the European average.

Pathology

The major pathological changes in COPD affect four different compartments of the lung and all are affected in most individuals to varying degrees (American Thoracic Society/European Respiratory Society Task Force, 2004).

Central airways (<2 mm diameter, cartilaginous)

The bronchial glands hypertrophy and goblet cell proliferation occurs. This results in excessive mucus production (chronic bronchitis). Epidemiologically chronic bronchitis is defined as a chronic or recurrent cough with sputum production on most days for at least 3 months of the year during at least 2 consecutive years, in the absence of other diseases recognised to cause sputum production. There is a loss of ciliary function with increase in inflammatory cells, notably lymphocytes, macrophages and, later in the disease, neutrophils.

Table 26.1 Annual morbidity and mortality from COPD (National Clinical Guideline Centre, 2010)

	Hospital admissions	GP consultations	Deaths
England and Wales	130,000	1.4 million	30,000

Peripheral airways (<2 mm diameter, non-cartilaginous)

Bronchiolitis is present from early disease with a pathological increase in goblet cells and in inflammatory cells in the airway walls. With disease progression, fibrosis develops along with increased deposition of collagen in the airway walls.

Lung parenchyma (respiratory bronchioles, alveoli and capillaries)

In emphysema, elastases destroy elastin, thus resulting in dilation and destruction of the respiratory bronchioles and alveolar sacs and ducts. Because of this there is a loss of the alveolar wall attachments and peripheral airway collapse.

Emphysema is defined as an abnormal enlargement of the air spaces distal to the terminal bronchioles. There are two main forms: (1) centrilobular emphysema which involves dilation and destruction of respiratory bronchioles, alveolar ducts and alveoli and (2) panacinar emphysema which involves destruction of the whole acinus. The former predominates in COPD, the latter in patients with α_1-antitrypsin deficiency.

Pulmonary vasculature

Vessel walls thicken early in the course of the disease along with endothelial dysfunction. The vessel walls become infiltrated by inflammatory cells, including macrophages and lymphocytes, and there is increased vascular smooth muscle which can lead to pulmonary hypertension. In advanced disease, there is emphysematous destruction of the vascular bed and collagen deposition.

Aetiology

Tobacco smoking is the most important and dominant risk factor in the development of COPD but other noxious particles also contribute, such as occupational exposure to chemical fumes, irritants, dust and gases. A person's exposure can be thought of in terms of the total burden of inhaled particles. These cause a (normal) inflammatory response in the lungs. Smokers, however, seem to have an exaggerated response which eventually causes tissue destruction and impaired repair mechanisms. In addition to inflammation, the other main processes involved in the pathogenesis of COPD are an imbalance of proteinases and antiproteinases in the lungs, and oxidative stress.

Not all smokers go on to develop clinically significant COPD; genetic factors seem to modify each individual's risk. The age at which an individual begins smoking, total pack-years smoked and current smoking status are predictive of COPD mortality. Passive exposure to cigarette smoke may also contribute to respiratory symptoms and COPD by increasing the lungs' total burden of inhaled particles and gases (GOLD, 2009). Tobacco exposure is quantified in 'pack-years':

$$\text{Total pack years} = \frac{\text{Number of cigarettes smoked per day}}{20} \times \text{number of years of smoking}$$

Additional risk factors include the natural ageing process of the lungs. Males are currently more at risk of developing chronic bronchitis, but as the number of women who smoke increases, the incidence of chronic bronchitis in females will also rise. The major risk factors are summarised in Table 26.2.

Table 26.2 Risk factors for the development of COPD

Risk factor	Comment
Smoking	Risk increases with increasing consumption but there is also large interindividual variation in susceptibility
Age	Increasing age results in ventilatory impairment; most frequently related to cumulative smoking
Gender	Male gender was previously thought to be a risk factor but this may be due to a higher incidence of tobacco smoking in men. Women have greater airway reactivity and experience faster declines in FEV_1, so may be at more risk than men
Occupation	The development of COPD has been implicated with occupations such as coal and gold mining, farming, grain handling and the cement and cotton industries
Genetic factors	α_1-Antitrypsin deficiency is the strongest single genetic risk factor, accounting for 1–2% of COPD. Other genetic disorders involving tissue necrosis factor and epoxide hydrolase may also be risk factors
Air pollution	Death rates are higher in urban areas than in rural areas. Indoor air pollution from burning biomass fuel is also implicated as a risk factor, particularly in underdeveloped areas of the world
Socio-economic status	More common in individuals of low socio-economic status
Airway hyper-responsiveness and allergy	Smokers show increased levels of IgE, eosinophils and airway hyper-responsiveness but how these influence the development of COPD is unknown

Inflammation

COPD is characterised by chronic inflammation throughout the airways, parenchyma and pulmonary vasculature. This is a different pattern of inflammation from that of asthma, with an increase in neutrophils, macrophages and T-lymphocytes (particularly $CD8^+$); increased eosinophils occur in some patients during exacerbations. These inflammatory cells cause the release of inflammatory mediators and cytokines such as leukotriene B4, interleukin-8 and tumour necrosis factor-α (TNF-α). Over time the actions of these mediators damages the lungs and leads to the characteristic pathological changes observed.

Proteinase and antiproteinase imbalance

The observation that α_1-antitrypsin-deficient individuals are at increased risk of developing emphysema has led to the theory that an imbalance between proteinases and antiproteinases leads to lung destruction. In COPD, there is either an increased production/activity of proteinases or a decreased production/activity of antiproteinases. The main proteinases, proteolytic enzymes such as neutrophil elastin are released by macrophages or neutrophils. The antiproteinases inhibit the damage caused by the proteolytic enzymes. The main antiproteinase is α_1-antitrypsin, also known as α_1-proteinase inhibitor. Cigarette smoke has been shown to inactivate this protein. Oxidative stress also decreases the activity of antiproteinases.

Oxidative stress

An imbalance of oxidants and antioxidants exists in COPD with the balance in favour of the oxidants. This state of oxidative stress contributes to the development of the disease by damaging the intracellular matrix, oxidising biological molecules which cause cell destruction and promoting histone acetylation. There also seems to be a link between oxidative stress and the poor response to corticosteroids seen in COPD. To work, corticosteroids must recruit histone deacetylase to switch off the transcription of inflammatory genes. In COPD, the activity of histone deacetylase is impaired by the oxidative stress, thereby reducing the responsiveness to corticosteroids. Cigarette smoke also impairs the function of histone deacetylase.

Pathophysiology

The pathogenic mechanisms and pathological changes described above lead to the physiological abnormalities of COPD: mucus hypersecretion, ciliary dysfunction, airflow limitation and hyperinflation, gas exchange abnormalities, pulmonary hypertension and systemic effects (American Thoracic Society/European Respiratory Society Task Force, 2004).

Mucus hypersecretion, ciliary dysfunction and complications

Enlarged mucus glands cause hypersecretion of mucus and the squamous metaplasia of epithelial cells results in ciliary dysfunction. These are typically the first physiological abnormalities in COPD.

Normally, cilia and mucus in the bronchi protect against inhaled irritants, which are trapped and expectorated. The persistent irritation caused by cigarette and other smoke causes an exaggeration in the response of these protective mechanisms and leads to inflammation of the small bronchioles (bronchiolitis) and alveoli (alveolitis). Cigarette smoke also inhibits mucociliary clearance, which causes a further build-up of mucus in the lungs. As a result, macrophages and neutrophils infiltrate the epithelium and trigger a degree of epithelial destruction. This, together with a proliferation of mucus-producing cells, leads to plugging of smaller bronchioles and alveoli with mucus and particulate matter.

This excessive mucus production causes distension of the alveoli and loss of their gas exchange function. Pus and infected mucus accumulate, leading to recurrent or chronic viral and bacterial infections. The primary pathogen is usually viral but bacterial infection often follows. Common bacterial pathogens include *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Haemophilus influenzae*.

Bronchiectasis is a pathological change in the lungs where the bronchi become permanently dilated. It is common after early attacks of acute bronchitis during which mucus both plugs and stretches the bronchial walls. In severe infections, the bronchioles and alveoli can become permanently damaged and do not return to their normal size and shape. The loss of muscle tone and loss of cilia can contribute to COPD because mucus has a tendency to accumulate in the dilated bronchi.

Airflow limitation and hyperinflation

Fibrosis and narrowing (airway remodelling) of the smaller conducting airways (<2 mm diameter) is the main site of expiratory airflow limitation in COPD. This is compounded by the loss of elastic recoil (destruction of alveolar walls), destruction of alveolar support/attachments and the accumulation of inflammatory cells mucus and plasma exudates during exercise. The degree of airflow limitation is measured by spirometry.

This progressive destructive enlargement of the respiratory bronchioles, alveolar ducts and alveolar sacs is referred to as emphysema. Adjacent alveoli can become indistinguishable from each other, with two main consequences. The first is loss of available gas exchange surfaces, which leads to an increase in dead space and impaired gas exchange. The second consequence is the loss of elastic recoil in the small airways, vital for maintaining the force of expiration, which leads to a tendency for them to collapse, particularly during expiration. Increased thoracic gas volume and hyperinflation of the lungs result. The causes of airflow limitation in COPD are summarised in Box 26.1.

Box 26.1 Causes of airflow limitation in COPD (GOLD, 2009)

Irreversible	• Fibrosis and narrowing of the airways • Loss of elastic recoil due to alveolar destruction • Destruction of alveolar support that maintains patency of small airways
Reversible	• Accumulation of inflammatory cells, mucus and plasma exudates in the bronchi • Smooth muscle contraction in peripheral and central airways • Dynamic hyperinflation during exercise

Gas exchange abnormalities

This occurs in advanced disease and is characterised by arterial hypoxaemia with or without hypercarbia. The anatomical changes during COPD result in an abnormal distribution of ventilation and perfusion within the lungs and create the abnormal gaseous exchange.

Pulmonary hypertension and cor pulmonale

Pulmonary hypertension develops late in COPD after gas exchange abnormalities have developed. The thickening of the bronchiole and alveolar walls resulting from chronic inflammation and oedema leads to blockage and obstruction of the airways. Alveolar distension and destruction result in distortion of the blood vessels that are closely associated with the alveoli. This causes a rise in the blood pressure in the pulmonary circulation. Reduction in gas diffusion across the alveolar epithelium leads to a low partial pressure of oxygen in the blood vessels (hypoxaemia) due to an imbalance between ventilation and perfusion. By a mechanism that is not clearly established, chronic vasoconstriction results and causes a further increase in blood pressure and further compromises gas diffusion from air spaces into the bloodstream. The chronic low oxygen levels lead to polycythaemia, thereby increasing blood viscosity. In advanced disease, persistent hypoxaemia develops along with pathological changes in the pulmonary circulation. Sustained pulmonary hypertension results in a thickening of the walls of the pulmonary arterioles, with associated pulmonary remodelling and an increase in right ventricular pressure within the heart.

The consequence of continued high right ventricular pressure is eventual right ventricular hypertrophy, dilation and progressive right ventricular failure (cor pulmonale). Pulmonary oedema develops as a result of physiological changes subsequent to the hypoxaemia and hypercapnia, such as activation of the renin–angiotensin system, salt and water retention and a reduction in renal blood flow.

Systemic effects

Systemic inflammation and skeletal muscle wasting can occur in COPD which limit exercise capacity and worsen prognosis. Osteoporosis, depression, normocytic normochromic anaemia are potential sequelae, as well as increased risk of cardiovascular disease associated with elevated levels of C-reactive protein.

Clinical manifestations

Diagnosis

A diagnosis of COPD should be considered in any patient who has symptoms of cough, wheeze, regular sputum production or exertional dyspnoea and/or a history of exposure to COPD risk factors (see Table 26.2). Spirometry is then used to confirm the diagnosis. There is no single diagnostic test for COPD.

Clinical features

COPD is a progressive disorder, which passes through a potentially asymptomatic mild phase, before the moderate phase and then severe disease. The traditional description of COPD symptoms, particularly in severe disease, depends on whether bronchitis or emphysema predominate. Chronic bronchitic patients exhibit excess mucus production and a degree of bronchospasm, resulting in wheeze and dyspnoea. Hypoxia and hypercapnia (high levels of carbon dioxide in the tissues) are common. This type of patient has a productive cough, is often overweight and finds physical exertion difficult due to dyspnoea. The bronchitic patient is sometimes referred to as a 'blue bloater'. This term is used because of the tendency of the patient to retain carbon dioxide caused by a decreased responsiveness of the respiratory centre to prolonged hypoxaemia that leads to cyanosis, and also the tendency for peripheral oedema to occur. Bronchitic patients lose the ability to increase the rate and depth of ventilation in response to persistent hypoxaemia. The reason for this is not clear, but decreased ventilatory drive may result from abnormal peripheral or central respiratory receptors. As the disease progresses, patients will experience an increasing frequency of exacerbations of acute dyspnoea triggered by excess mucus production and obstruction. In severe disease, the chest diameter is often increased, giving the classic barrel chest. As obstruction worsens, hypoxaemia increases, leading to pulmonary hypertension. Right ventricular strain leads to right ventricular failure, which is characterised by jugular venous distension, hepatomegaly and peripheral oedema, all of which are consequences of an increase in systemic venous blood pressure. Recurrent lower respiratory tract infections can be severe and debilitating. Signs of infection include an increase in the volume of thick and viscous sputum, which is yellow or green in colour and may contain bacterial pathogens, squamous epithelial cells, alveolar macrophages and saliva, but pyrexia may not be present. Eventually, cardiorespiratory failure with hypercapnia will occur, which may be severe, unresponsive to treatment and result in death.

The clinical features of emphysema are different from those of bronchitis. A patient with emphysema will experience increasing dyspnoea even at rest, but often there is minimal cough and the sputum produced is scanty and mucoid. Generally,

bronchial infections tend to be less common in emphysema. The patient with emphysema is sometimes referred to as a 'pink puffer' because he or she hyperventilates to compensate for hypoxia by breathing in short puffs. As a result, the patient appears pink with little carbon dioxide retention and little evidence of oedema. The patient will breathe rapidly (tachypnoea), because the respiratory centres are responsive to mild hypoxaemia, and will have a flushed appearance. Typically, a patient with emphysema will be thin and have pursed lips in an effort to compensate for a lack of elastic recoil and exhale a larger volume of air. Such a patient will tend to use the accessory muscles of the chest and neck to assist in the work of breathing. Hypoxaemia is not a problem until the disease has progressed. Emphysema patients will become progressively dyspnoeic, without exacerbations triggered by increased sputum production. Eventually, cor pulmonale will develop very rapidly, usually in the late stages of the disease, leading to intractable hypercapnia and respiratory arrest. The bronchitic 'blue bloater' and emphysemic 'pink puffer' represent two ends of the COPD spectrum. In reality, the underlying pathophysiology may well be a mixture, and the resulting signs and symptoms somewhere between the two extremes described.

The clinical progress of COPD depends on whether bronchitis or emphysema predominates.

Additional specific problems are also common in patients with COPD:

- Obstructive sleep apnoea hypopnoea syndrome (OSAHS)
- Acute respiratory failure

The sleep apnoea syndrome is a respiratory disorder characterised by frequent or prolonged pauses in breathing during sleep. It leads to a deterioration in arterial blood gases and a decrease in the saturation of haemoglobin with oxygen. Hypoxaemia is often accompanied by pulmonary hypertension and cardiac arrhythmias, which may lead to premature cardiac failure.

Acute respiratory failure is said to have occurred if the PaO_2 suddenly drops and there is an increase in $PaCO_2$ that decreases the pH to 7.3 or less. The most common cause is an acute exacerbation of chronic bronchitis with an increase in volume and viscosity of sputum. This further impairs ventilation and causes more severe hypoxaemia and hypercapnia. The clinical signs and symptoms of acute respiratory failure include restlessness, confusion, tachycardia, cyanosis, sweating, hypotension and eventual unconsciousness.

Investigations

Lung function tests are used to assist in diagnosis. A spirometer is used to measure lung volumes and flow rates. The main measurement made is the forced expiratory volume in the first second of exhalation (FEV_1). Other tests can be performed, such as:

- *Vital capacity (VC)*: the volume of air inhaled and exhaled during maximal ventilation;
- *Forced vital capacity (FVC)*: the volume of air inhaled and exhaled during a forced maximal expiration after full inspiration;
- *Residual volume (RV)*: the volume of air left in the lungs after maximal exhalation.

Airflow obstruction is defined as:

- FEV_1 less than 80% of that predicted for the patient and
- FEV_1/FVC less than 0.7.

VC decreases in bronchitis and emphysema. RV increases in both cases but tends to be higher in patients with emphysema due to air being trapped distal to the terminal bronchioles. Total lung capacity is often normal in patients with bronchitis but is usually increased in emphysema, again due to air being trapped. Smoking increases the normal deterioration in FEV_1 over time, from about 30 mL/year to about 45 mL/year. The major criticism of measuring FEV_1 and FVC is that they detect changes only in airways greater than 2 mm in diameter. As airways less than 2 mm in diameter contribute only 10–20% of normal resistance to airflow, there is usually severe obstruction and extensive damage to the lungs by the time the lung function tests (FEV_1 and FVC) detect abnormalities. Additionally, lung function tends to deteriorate with age even in the absence of COPD, and so use of FEV_1/FVC can lead to overdiagnosis in the elderly. Underdiagnosis may also be a problem in patients under 45 years of age.

Both UK and international COPD guidelines use spirometry to categorise the severity of COPD. These are summarised in Table 26.3. Testing should be carried out after a dose of inhaled bronchodilator to prevent overdiagnosis or overestimation of severity.

At diagnosis and evaluation, patients may receive other investigations as outlined in Table 26.4.

Chest radiographs reveal differences between the two disease states. A patient with emphysema will have a flattened diaphragm with loss of peripheral vascular markings and the appearance of bullae. These are indicative of extensive trapping of air. A patient with bronchitis will have increased bronchovascular markings and may also have cardiomegaly (increased cardiac size due to right ventricular failure) with prominent pulmonary arteries.

Table 26.3 Assessment of severity of airflow obstruction (adapted from National Institute for Health and Clinical Excellence, 2010; GOLD, 2009)

FEV_1	Severity (NICE)	Severity (GOLD)
Greater than 80% predicted		Stage I: Mild
50–80% predicted	Mild	Stage II: Moderate
30–49% predicted	Moderate	Stage III: Severe
Less than 30% predicted	Severe	Stage IV: Very severe

Table 26.4 Additional investigations at the diagnosis of COPD

Investigation	Note
Chest X-ray	To exclude other pathologies
Full blood count	To identify anaemia or polycythaemia
Serial domiciliary peak flow measurements	To exclude asthma if there is a doubt about diagnosis
α_1-Antitrypsin	Particularly with early-onset disease or a minimal smoking/family history
Transfer factor for carbon monoxide	To investigate symptoms that seem disproportionate to the spirometric impairment
CT scan of the thorax	To investigate symptoms that seem disproportionate to the spirometric impairment To investigate abnormalities seen on the chest X-ray To assess suitability for surgery
ECG	To assess cardiac status if features of cor pulmonale
Echocardiogram	To assess cardiac status if features of cor pulmonale
Pulse oximetry	To assess need for oxygen therapy If cyanosis or cor pulmonale is present or if FEV_1 <50% of predicted value
Sputum culture	To identify organisms if sputum is persistently present and purulent

Treatment

Stable COPD

Drug treatments, together with other measures such as physiotherapy and artificial ventilation, have not been shown to improve the natural progression of COPD. Quality of life and symptoms will, however, improve with suitable treatment and it is likely that the correct management of the patient will lead to a reduction in hospital admissions and prevent premature death. In patients with severe COPD and hypoxaemia, long-term oxygen therapy (LTOT) is the only treatment known to improve the prognosis.

The aims of treatment for patients with COPD are shown in Box 26.2 and the common therapeutic problems associated with COPD in Box 26.3. Drug treatment itself can only relieve symptoms; it does not modify the underlying pathology. Most patients with COPD are considered to have irreversible obstruction, in contrast to patients with asthma, but a significant number do seem to respond to bronchodilators.

Box 26.2 Treatment aims for patients with COPD

- Prevent disease progression
- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat complications such as hypoxaemia and infections
- Prevent and treat exacerbations
- Reduce mortality

Smoking cessation

Smoking is the most important factor in the development of obstructive airways disease. All COPD patients who are still smoking, regardless of age, should be encouraged to stop and be offered help to do so, at every opportunity. Unless contraindicated, all patients who are planning to stop smoking should be offered nicotine replacement therapy (NRT), varenicline or bupropion, as appropriate along with a support programme (NRT) (National Institute for Health and Clinical Excellence, 2010). Individually targeted advice may prove to be more successful in persuading individuals to give up, especially in those who are well.

Bronchodilators

Bronchodilators in COPD are used to reverse airflow limitation. As the degree of limitation varies widely, their effectiveness should be assessed in each patient using respiratory function tests and by assessing any subjective improvement reported by the patient. Patients may experience

Box 26.3 Common therapeutic problems associated with COPD

- Failure of patient to stop smoking
- Inadequate inhaler technique leading to subtherapeutic dosing
- Poor adherence with treatment regimen
- Inappropriate prescribing of antibiotics in an acute exacerbation of COPD
- Failure to properly assess a patient for home nebuliser therapy
- Failure to ensure adherence to 15 h a day of home oxygen therapy

improvements in exercise tolerance or relief of symptoms such as wheeze and cough. Treatment options for the use of bronchodilators and inhaled corticosteroids (ICSs) are outlined in Fig. 26.1.

Initial empiric therapy with short-acting bronchodilators, prescribed 'when required', for the relief of breathlessness and exercise limitation are recommended for initial use (National Institute for Health and Clinical Excellence, 2010). If patients remain breathless or have exacerbations despite short-acting bronchodilators then maintenance therapy is recommended, with:

- FEV_1 ≥50% predicted: long-acting β_2-adrenoceptor agonist (LABA) or long-acting antimuscarinic (LAMA)
- FEV_1 <50% predicted: a combination of either LABA and ICSs or LABA and LAMA

If the patient remains breathless, or has exacerbations, then triple therapy should be considered (i.e. ICS and LABA in a combination inhaler together with a LAMA).

Short-acting bronchodilators (short-acting β_2-adrenoceptor agonist or short-acting antimuscarinic). Selective β_2-agonists provide rapid relief and have a low incidence of side effects. Inhaled treatment is as efficacious as oral agents and is, therefore, preferred because of fewer side effects. The dose–response curve for β_2-agonists in COPD is almost flat and there is little benefit in giving more than 1 mg. The effects of short-acting β_2-agonists last for 4 h and they should be used 'as required' for symptom relief. Used before exercise, they can improve exercise tolerance. Poor patient response to bronchodilators may be due to poor inhalation technique, so this should be checked as often as possible and the inhaler device changed if necessary.

In patients with COPD, parasympathetic (vagal) airway muscle tone is the major reversible component. Inhaled anticholinergic drugs reverse this vagal tone and have a significant bronchodilator effect, especially in the elderly.

Long-acting bronchodilators. Long-acting bronchodilators include LAMAs and LABAs. The only LAMA in the UK, tiotropium, has a 24-h duration of action and can reduce exacerbation rates, increase exercise tolerance and reduce rates of hospital admissions, though not the rate of decline in lung function. There is no strong evidence to favour either a LABA or LAMA for monotherapy (National Clinical Guideline Centre, 2010).

High-dose bronchodilators. Some patients with distressing or debilitating breathlessness despite maximal inhaled therapy may benefit from higher doses, either by inhaler or via a nebuliser. These patients should have their inhaled therapy optimised, possibly using a protocol as outlined in Box 26.4.

Theophylline. Theophylline is a weak bronchodilator but seems to have useful additional physiological effects in COPD

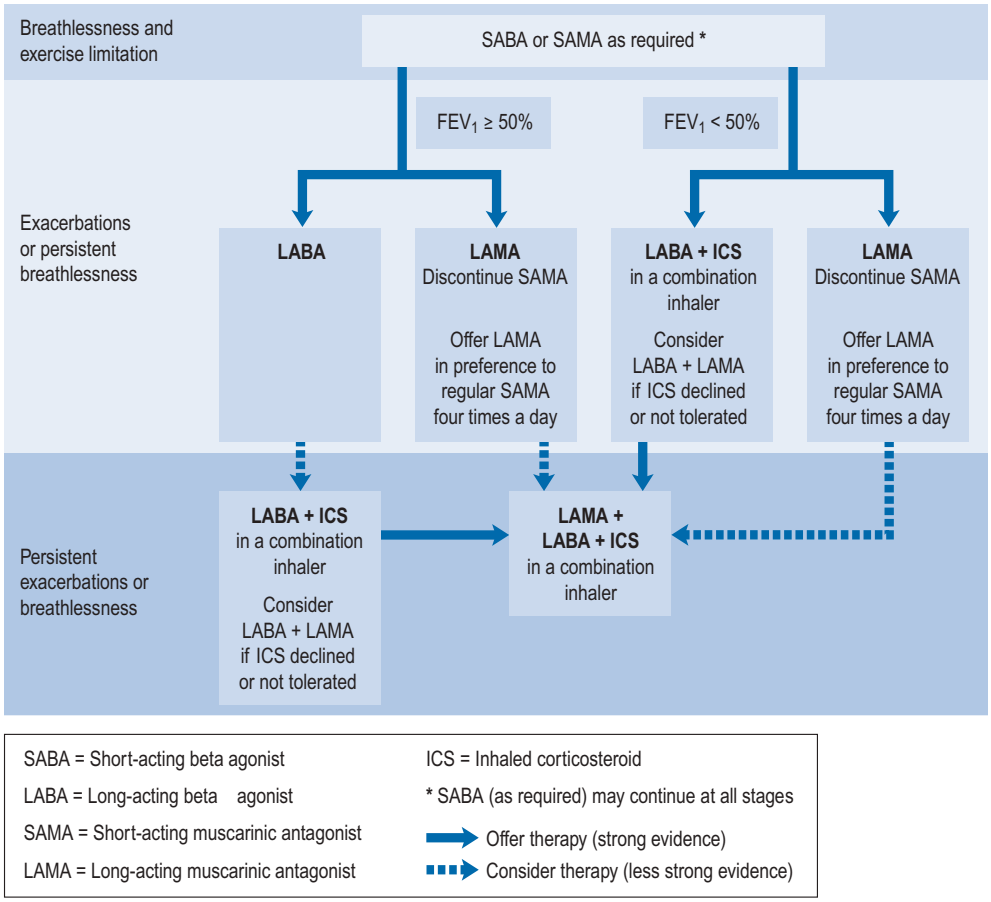

Fig. 26.1 Stepwise approach to the pharmacological management of chronic COPD (National Institute for Health and Clinical Excellence, 2010; with kind permission from National Institute for Health and Clinical Excellence).

Box 26.4 Optimisation of high dose inhaled and nebulised therapy for patients with severe COPD (adapted from Boe et al., 2001; National Institute for Health and Clinical Excellence, 2010; O'Driscoll, 1997)

1. Assessment by a respiratory specialist. Check diagnosis and confirm severity. Ensure optimal inhaler technique
2. Ensure all other therapies have been tried
3. Optimise hand-held inhaler dosing, for example:
   - Salbutamol 200–400 µcg four times a day
   - Ipratropium bromide 40 µcg four times a day or tiotropium 18 µcg once daily

   or a combination of these agents
4. Try further increasing the dose of the hand-held inhaler to:
   - Salbutamol up to 1 mg four times a day, and/or
   - Ipratropium bromide up to 160 µcg four times a day (although the effect of alternative use of tiotropium at this stage is unknown)

   These doses are unlicensed in the UK
5. If a poor response at step 4, consider a period of home nebulizer therapy with careful examination of patient response, over at least 2 weeks
   - Reduction in symptoms
   - An increase in the patient's ability to undertake activities of daily living
   - An increase in exercise capacity
   - An improvement in lung function
   - The occurrence of side effects such as tachycardia and tremor
6. Initial therapy: try nebulised salbutamol 2.5 mg or terbutaline 5 mg four times a day and assess response at 2 weeks
7. If the response to monotherapy is poor, consider one or more of the following:
   - Salbutamol 5 mg or terbutaline 10 mg four times a day, or
   - Iptratropium bromide 250–500 µcg four times a day, or the combination
   - Salbutamol 2.5–5 mg and ipratropium 500 µcg four times a day
8. Decide which treatment in step 7 was the most beneficial

such as increased respiratory drive, improved diaphragmatic function and improved cardiac output, although the exact clinical benefits have not been quantified. The use of theophylline should only be considered after a trial of short acting with long-acting bronchodilators. Whenever theophylline is tried in the management of COPD, an initial therapeutic trial of several weeks should be carried out. If subjective and objective measures of lung function show an improvement, then theophylline can be continued as maintenance therapy. Persistent nocturnal symptoms such as cough or wheeze may be helped by the night-time use of long-acting theophylline.

Care must be taken when prescribing theophylline. Its clearance is affected by many factors, including cigarette smoking, viral pneumonia, heart failure and concurrent drug treatment, such as macrolide antibiotics used during exacerbations (see Chapter 25).

Theophylline is being investigated in low concentrations for its ability to reverse the decrease in histone deacetylase activity associated with oxidative stress. This may prove to be of benefit in reversing corticosteroid resistance.

Corticosteroids

Patients with COPD show a poor response to corticosteroids and have a largely steroid-resistant pattern of inflammation (Barnes, 2004). It is postulated that the oxidative stress of COPD inhibits the mechanism by which corticosteroids, acting through histone deacetylase, switch off activated inflammatory genes.

The long-term benefits of ICSs in COPD have only been shown in patients with moderate-to-severe disease, with an FEV_1 less than 50% of predicted value and who are having exacerbations requiring treatment with antibiotics and oral corticosteroids (National Institute for Health and Clinical Excellence, 2010). A reduction in the number of exacerbations and a slowing of the decline in health status have been shown, but these have no effect on improving lung function and result in an increased risk of pneumonia.

ICSs should be used, although there is no consensus over the minimum effective dose. In the UK, no inhaled steroid is licensed for use in COPD except when used with LABA in combination devices.

There is little place for oral steroids in stable COPD. Some patients with advanced disease may require maintenance oral therapy if this cannot be withdrawn after a short course prescribed to treat an exacerbation. In this instance, the lowest dose possible should be used. The patient should be regularly assessed for osteoporosis and the need for osteoporosis prevention. Patients over 65 years receiving maintenance therapy should automatically receive prophylactic treatment for osteoporosis.

Mucolytics

Mucolytics may be of benefit in stable COPD if there is a chronic cough productive of sputum. Benefit must be assessed, for example, with a reduction in the frequency of cough and/or sputum production. If there is no benefit, then mucolytics should be stopped.

Antibiotics and immunisation

Prophylactic antibiotics have no place in the management of COPD. Antibiotic therapy is, however, vital if a patient develops purulent sputum. If a patient frequently develops acute infective exacerbations of bronchitis then they should be given a supply of antibiotics to keep at home to start at the first sign of an exacerbation.

Initial routine sputum cultures are unhelpful in these patients as they are unreliable in identifying the pathogenic organisms.

The normal pathogens involved are *S. pneumoniae*, *H. influenzae* or *M. catarrhalis*. The usual antibiotics of choice are co-amoxiclav, amoxicillin, erythromycin or doxycycline. If the infection follows influenza, *Staphylococcus aureus* may be present and an anti-staphylococcal agent such as flucloxacillin should be added to the regimen. If the infection is considered atypical in presentation or if the purulent sputum is still present after 1 week of treatment, then sputum cultures

should be taken to try to identify the pathogenic organisms. A single dose of pneumococcal vaccine and annual influenza vaccinations have been shown to reduce hospitalisations and the risk of death in the elderly with chronic lung disease, and should be offered to those with chronic airflow obstruction. The prevalent strains of influenza change, so the vaccine composition is, correspondingly, altered annually.

Acute exacerbations of COPD

Patients with COPD suffer acute worsenings of the disease, referred to as acute exacerbations. These exacerbations can be spontaneous but are often precipitated by infection and lead to respiratory failure with hypoxaemia and retention of carbon dioxide. Many patients can be managed at home (see National Institute for Health and Clinical Excellence, 2010) but some will require admission to hospital.

Bronchodilators

Bronchodilators are used to treat the increased breathlessness that is associated with exacerbations. These can be given by metered-dose inhaler (MDI) or nebuliser, although practically breathless patients are often unable to use MDIs effectively. A β_2-agonist can be given with or without an anticholinergic agent, depending on the benefits obtained.

Antibiotics

Bacteria can be isolated from the sputum of patients with stable COPD but antibiotics can be used to treat exacerbations of COPD associated with a history of more purulent sputum. The choice of antibiotic should be dependent on local policy, sensitivity patterns and any previous treatments. An aminopenicillin or a macrolide with increased activity against *H. influenzae* or oxytetracycline is generally suitable as a first-line agent. Sputum should be sent for culture in order to check the appropriateness of initial therapy, and the antibiotic changed if necessary.

Corticosteroids

A short course of oral steroids has been shown to benefit FEV_1 and reduce the duration of hospitalisation. Patients managed at home who have increased breathlessness which interferes with daily activities and all those admitted to hospital should be treated. A suitable course is prednisolone 30 mg every morning, given for 7–14 days.

Other treatment

Intravenous aminophylline can be considered, if there is an inadequate response to bronchodilators. The loading dose and maintenance dose required should be carefully chosen as these depend on various factors (see Chapter 25).

Oxygen therapy is necessary to improve hypoxia. In about a quarter of patients with COPD, a predisposition to carbon dioxide retention will be present. Administration of high concentrations of oxygen to these individuals can lead to an increase in retention of carbon dioxide and, thus, to respiratory acidosis. The widely held view that this effect is due to loss of hypoxic ventilatory drive has been questioned; a more complex process involving a mismatch between ventilation and perfusion is now thought to play a significant role. The goal is an initial oxygen saturation of between 88% and 92% to avoid respiratory acidosis but to allow enough oxygen to be administered to overcome potentially life-threatening hypoxia (O'Driscoll et al., 2008). The initial concentration used should be 24–28% and then titrated to oxygen saturation. Arterial blood gases should be monitored regularly.

During an acute attack, pyrexia, hyperventilation and the excessive work of breathing can result in an inability to eat or drink. This can lead to dehydration which requires treatment with intravenous hydration.

Chest physiotherapy is employed to mobilise secretions, promote expectoration and expand collapsed lung segments. Nebulised 0.9% sodium chloride has also been used to help.

Although largely superseded by non-invasive ventilatory support, doxapram (as a continuous infusion at a rate of 1–4 mg/min) can be tried in patients with acute respiratory failure, carbon dioxide retention and depressed ventilation. Doxapram stimulates the respiratory and vasomotor centres in the medulla, increases the depth of breathing and may slightly increase the rate of breathing. Arterial oxygenation is usually not improved because of the increased work of breathing induced by doxapram. This agent has a narrow therapeutic index with side effects such as arrhythmias, vasoconstriction, dizziness and convulsions and may be harmful if used when the $PaCO_2$ is normal or low.

Treatment of hypoxaemia and cor pulmonale

COPD is responsible for over 90% of cases of cor pulmonale. Although patients often tolerate mild hypoxaemia, once the resting PaO_2 drops below 8 kPa signs of cor pulmonale develop. Treatment is symptomatic and involves managing the underlying airways obstruction, hypoxaemia and any pulmonary oedema that develops. Peripheral oedema is managed using thiazide or loop diuretics, although there are concerns over their metabolic effects reducing respiratory drive. Oxygen is used to treat hypoxaemia, and this should also promote a diuresis. All patients should be assessed for the need for LTOT.

Domiciliary oxygen therapy

The aim of therapy is to improve oxygen delivery to the cells, increase alveolar oxygen tension and decrease the work of breathing to maintain a given PaO_2. Domiciliary oxygen therapy can be given in two ways.

Intermittent (short burst) administration. Intermittent administration is used to increase mobility and capacity for exercise and to ease discomfort. Intermittent administration is of most benefit in patients with emphysema.

Continuous LTOT. LTOT for at least 15 h/day has been shown to improve survival in patients with severe, irreversible

Box 26.5 Guidelines for prescribing long-term oxygen therapy in COPD (National Institute for Health and Clinical Excellence, 2010)

A. PaO_2 is consistently below 7.3 kPa whilst the patient is clinically stable
B. PaO_2 between 7.3 and 8 kPa if secondary polycythaemia, pulmonary hypertension, nocturnal hypoxaemia or peripheral oedema is present

airflow obstruction, hypoxaemia and peripheral oedema (MRC Working Party, 1981). LTOT can only be prescribed if specific conditions are met, as described in Box 26.5. The main aim of treatment is to achieve a PaO_2 of at least 8 kPa without causing a rise in $PaCO_2$ of more than 1 kPa, achieved by adjusting the oxygen flow rate. Before LTOT can be prescribed each individual must be assessed accordingly (see Box 26.5).

Oxygen can be prescribed as oxygen cylinders but 15 h/day at 2 L/min requires ten 1340-L cylinders a week. A more convenient system is to use a concentrator, which converts ambient air to 90% oxygen using a molecular sieve. The concentrator is sited in a well-ventilated area in the home with plastic tubing to terminals in rooms such as the living room and bedroom. Tubing from the terminals delivers oxygen to the patient, who wears a mask or uses the more convenient nasal prongs. This tubing should be long enough to allow some mobility.

Patient care

Pulmonary rehabilitation

Early pulmonary rehabilitation should be considered for patients at all stages of disease progression when symptoms and disability are present. Patients should participate in a co-coordinated programme of non-pharmacological treatment including:

- advice and support to stop smoking
- nutritional assessment
- aerobic exercise training to increase capacity and endurance for exercise
- strength training for upper and lower limbs
- relaxation techniques
- breathing retraining, for example, diaphragmatic and pursed lips breathing to improve the ventilatory pattern and improve gas exchange
- education about their medicines, nutrition, self-management of their disease and lifestyle issues
- psychological support because COPD patients often have decreased capacity to participate in social and recreational activities and can become anxious, depressed or fatigued.

A multidisciplinary team should deliver these programmes and should include a minimum of 6 and a maximum of 12 weeks of physical exercise, disease education, psychological and social interventions (National Institute for Health and Clinical Excellence, 2010).

Pulmonary rehabilitation programmes that include at least 4 weeks exercise training have been shown to improve dyspnoea and exercise capacity. The long-term effects, however, of these programmes has yet to be established, although personalised education to COPD patients about their condition has been shown to reduce their need for health services.

Stopping smoking

The health hazards associated with smoking are well known and publicised. To give up smoking, which has been described as a form of drug addiction, requires self-motivation. Stopping smoking does not, however, have an immediate effect. A reduction in COPD mortality is not seen until about 10 years or more after cessation of smoking.

Members of the healthcare team can educate smokers about the dangers and actively encourage and motivate those who want to give up. Brief conversations between individuals and health professionals about stopping smoking are both effective and cost-effective in encouraging individuals to quit (National Institute for Health and Clinical Excellence, 2006).

Once a decision to quit has been made, it is the degree of dependence rather than the level of motivation that will influence the success rate. Smokers need both initial advice from all healthcare professionals and follow-up support. For example, especially in the early stages, symptoms such as coughing increase after the cigarettes are stopped. The patient must be closely supported to avoid a return to the habit. Strategies such as individual behavioural counselling, group behaviour therapy and use of self-help materials and telephone counselling and 'quit lines' have been advocated as effective interventions.

There are a number of therapeutic options to help an individual to stop smoking and these include NRT, bupropion and varenicline.

Nicotine replacement

The major mode of action of NRT is thought to involve stimulation of nicotine receptors in the brain and the subsequent release of dopamine. This, together with the peripheral effects of nicotine, leads to a reduction in nicotine withdrawal symptoms. NRT may also act as a coping mechanism, making cigarette smoking less rewarding. NRT does not, however, completely eliminate the effects of withdrawal as none of the available products reproduces the rapid and high levels of nicotine obtained from cigarettes.

There is little research comparing the relative effectiveness of NRT products, but all seem to have similar success rates. Choice of product should be made on the number of cigarettes smoked (irrespective of the nicotine content), the smoker's personal preference and tolerance to side effects. An individual is more likely to adhere to the cessation programme if using a product which suits him or her. The types of NRT available are summarised in Table 26.5.

NRT approximately doubles smoking cessation rates compared with controls (either placebo or no NRT), irrespective of the intensity of adjunctive therapy. The strongest evidence is

Table 26.5 Comparison of selected nicotine replacement products

Formulation	Use and comments	Specific side effects
Patch: 24 h: 7, 14 and 21 mg; 16 h: 5, 10, 15 and 25 mg	One daily on clean, non-hairy, unbroken skin. Remove before morning (16 h) or next morning (24 h). Apply to fresh site or non-hairy skin, usually at the hip, trunk or upper arm. Should not be applied to broken skin	Local skin irritation and rashes, insomnia. Do not use with generalised skin disease
Gum: 2 and 4 mg	Chew until taste is strong then rest gum between gum and cheek; chew again when taste has faded. Repeat this for 30 min or until taste dissipates. Avoid acidic drinks for 15 min before and during chewing the gum	Jaw ache, headache and dyspnoea. Mild burning sensation in the mouth and throat
Sublingual tablet: 2 or 4 mg each	Rest under tongue until dissolved	
Lozenge: 1, 2 or 4 mg each	Place between gum and cheek and allow to dissolve. Delivers slightly more nicotine than the equivalent gum	Nasal irritation, rhinorrhoea, sneezing, throat irritation and cough. This usually dissipates with continued use
Inhalator: 10 mg per cartridge	Inhale as required. Helps to satisfy the hand-to-mouth ritual of using a cigarette which may help some people. The nicotine is absorbed through the mouth rather than the lungs. Use with caution in people with asthma	Nasal irritation, rhinorrhoea, sneezing, throat irritation and cough. This usually dissipates with continued use
Nasal spray: 500 µcg per spray	One spray into each nostril as needed. More rapidly absorbed than other forms of NRT so often used for acute relief of cravings. Not recommended for people with nasal or sinus conditions, allergies or asthma	

for use of patches and gum. The choice of product and initial dose is also influenced by the degree of tobacco dependence; heavy smokers (15 to 20+ cigarettes a day and/or smoking within 30 min of waking) will require higher NRT doses. The available types of NRT product are set out below:

Long acting. Long-acting transdermal patches are considered to be most suitable for people who smoke regularly through the day. The 24-h patch, worn overnight, is better for people who crave nicotine first thing in the morning. Use of the patch can cause insomnia or vivid dreams and so can either be removed before bedtime or a 16-h patch used instead. Heavy smokers should be started on the high-dose patches.

Short acting. There are several short-acting products available:

Gum. It is important to chew nicotine gum correctly. The gum should be chewed slowly until the taste becomes strong and then allowed to rest between the cheek and teeth to allow absorption. When the taste has faded the gum should be chewed again. Nicotine gum is not a good choice for people with dentures or other vulnerable dental work. Most gum users do not consume enough in a day to match the nicotine levels from smoking. Patients should be encouraged to use 10–15 pieces of gum a day, for example, as one piece an hour.

Lozenge. These are allowed to dissolve in the mouth and periodically moved around, until completely gone. One lozenge per hour is recommended during the initial period of use to provide adequate nicotine absorption.

Inhalator. Inhalators may be particularly useful for people who miss the physical act of smoking. Nicotine is absorbed via the buccal mucosa, peaking in 20–30 min. To achieve sufficient blood levels, the user should puff on the inhalator for 2 min each hour, changing the cartridge after three 20-min sessions.

Nasal spray. A nasal spray is most useful for people who smoke 20 or more cigarettes per day. The side effects of sneezing and a burning sensation in the nose usually wear off after a day or two, so patients should be encouraged to persevere.

Sublingual tablets. These tablets dissolve under the tongue and may be useful for people with dentures who have difficulty using nicotine gum. Hourly use should be recommended.

Bupropion (amfebutamone)

Originally used as an antidepressant, bupropion has been licensed for use in smoking cessation. It inhibits neuronal noradrenaline and dopamine uptake, reducing tobacco withdrawal symptoms by increasing CNS dopamine levels. Treatment should be started while the patient is still smoking with a target date to stop smoking set during the second week of use. The total treatment period should be for 7–9 weeks. The initial dose should be 150 mg daily for 6 days, increasing to 150 mg twice a day thereafter (with at least 8 h between doses). Bupropion is as effective as NRT and intensive behavioural support. There is no clear evidence of benefit over NRT but there is some evidence of better results if used in combination with NRT.

Bupropion should not be used in patients with a current or previous seizure disorder or in patients with bulimia, anorexia

nervosa, bipolar disorder, severe hepatic cirrhosis or those taking monoamine oxidase inhibitors; nor is it appropriate for use in smokers under the age of 18. Bupropion inhibits cytochrome P450 enzymes and so may inhibit the metabolism of other drugs. The main side effects experienced include dry mouth, insomnia (avoid bedtime dosing), headache, dizziness, allergic reactions, taste disorder and seizures.

Varenicline

Varenicline is an oral selective partial $\alpha_4\beta_2$ agonist at the neuronal nicotinic acetylcholine receptor. Varenicline alleviates the symptoms of craving and withdrawal, whilst reducing the rewarding and reinforcing effects of smoking by preventing nicotine binding to $\alpha_4\beta_2$ receptors. Trial evidence suggests use may result in a higher abstinence rate than either bupropion or NRT, although this may not be sustained after 12 months. Use is recommended as an option for smokers aged 18 or over wishing to quit, ideally in the context of a behavioural support programme (National Institute for Health and Clinical Excellence, 2007). Varenicline should be started 1–2 weeks before stopping smoking. The main side effects are nausea, vomiting, abnormal dreams and insomnia. Fears over a possible increased risk of depression and suicide have been allayed (Gunnell et al., 2009), although individuals who develop agitation, depressed mood or suicidal thoughts are required to seek prompt medical advice.

Combination therapy involving varenicline and bupropion (either with each other or in conjunction with NRT) is not recommended.

Use of inhaled therapy

For individuals suffering from obstructive airways disease with a degree of reversibility, the correct use of inhaled therapy is a vital part of overall management.

Medication counselling needs to highlight the modes of action of the bronchodilators, particularly the more rapid onset of the β_2-agonists to relieve breathlessness rather than the slower-acting anticholinergics. If inhaled steroids are prescribed, the importance of regular administration must be stressed. The incorrect use of any inhaler will lead to subtherapeutic dosing. The correct use of inhalers is, therefore, as vital in the management of COPD patients as it is for patients with asthma (see Chapter 25). The advantages and disadvantages of each type of inhaler device are summarised in Table 26.6.

Domiciliary oxygen therapy

Studies have shown that only about 50% of patients on LTOT comply with the requirement for 15 h of treatment a day. Counselling will be required to persuade the patient to comply with this minimum figure. Emphasis must be given to the improvement in quality of life gained from treatment rather than the idea of being continually 'tied' to the oxygen supply. If an oxygen concentrator is used, limited mobility can be gained by installing at least two terminals for the unit (usually in the living room and bedroom) with long tubing between the terminal and nasal prongs.

Patients should be actively encouraged to stop smoking if they still do; because of the fire risk if they use LTOT. Moreover, the carbon monoxide present in tobacco smoke binds to haemoglobin and forms carboxy-haemoglobin, which decreases the amount of oxygen that can be transported by the blood and will partially or completely negate the beneficial effects of LTOT.

The long-term, chronic nature of COPD may leave a patient with a fear of exercise as this will cause dyspnoea (breathlessness). Thus, the patient with COPD may decide not to undertake any exercise. Ambulatory oxygen cylinders can be used to encourage mobility and increase exercise tolerance during travel outside the home.

Patients using domiciliary oxygen are followed up to provide education and support, to assess the oxygen saturation of the patient and to assess the suitability of the delivery device for ambulatory oxygen if provided. Suitable devices have been suggested (National Institute for Health and Clinical Excellence, 2010) depending on the amount of time required for use (Table 26.7).

Table 26.6 Comparison of inhaler devices

Inhaler type	Compact	Hand–lung co-ordination required	Easy to use	Reduces oropharynx deposition
MDI	+	+	−	−
MDI + small spacer	+	±	±	+
MDI + large spacer	−	−	±	+
Breath-actuated MDI	+	−	+	−
Dry powder	+	−	±	−
Breath-actuated dry powder	+	−	+	−
Nebuliser	−	−	±	−

MDI, metered-dose inhaler; +, feature present; ±, feature present for some patients; −, feature absent.

Table 26.7 Oxygen delivery for ambulatory oxygen therapy (National Institute for Health and Clinical Excellence, 2010)

How long is the oxygen used by the patient?	Best type of delivery device
Less than 90 min	Small cylinder
90 min to 4 h	Small cylinder with oxygen-conserving device
More than 4 h	Liquid oxygen
More than 30 min, with flow rates greater than 2 L/min	Liquid oxygen

Case studies

Case 26.1

Mr JF, a 74-year-old man, has a long-standing history of COPD. He has a 70-pack-year history of smoking, but finally managed to give up 4 years ago, after numerous admissions to hospital for infective exacerbations. He is recovering on the respiratory ward from his first admission for 6 months. His consultant believes he may be a candidate for long-term oxygen therapy.

Questions

1. What criteria should Mr JF fill in order to be eligible for long-term oxygen therapy?
2. How is long-term oxygen therapy delivered?
3. Why might Mr JF be anxious about starting long-term oxygen therapy?
4. How would you allay these concerns?
5. What is the intended outcome of using long-term oxygen therapy?

Answers

1. In order to be eligible for long-term oxygen therapy, patients should have, when stable and on two separate occasions at least 3 weeks apart:
   pO_2 <7.3 kPa
   or
   pO_2 >7.3 kPa and <8.0 kPa as well as at least one of the following:
   - secondary polycythaemia
   - nocturnal hypoxaemia (O_2 saturations <90% for >30% of the time)
   - peripheral oedema
   - pulmonary hypertension
2. It is impractical to deliver long-term oxygen therapy using cylinders. Instead, an oxygen concentrator, a device which increases the relative concentration of oxygen in environmental air via a molecular 'sieving' process, is used. In most cases, a flow rate of 2 L/min is delivered via nasal cannulae. Patients must use the concentrator for at least 15 h, and preferably over 20 h a day to achieve intended therapeutic outcomes (see below).
3. Mr JF may be concerned for several reasons listed:
   - the length of time he will be tied to the machine each day
   - restrictions on leaving the house once he starts his 15 h a day
   - the cost of the electricity required to drive the concentrator
   - loss of supply if there is a power cut
4. Mr JF's concerns are logical but he can be reassured. The concentrator can be used while he is asleep (generally two outlets are installed, one in the living room and the other in the bedroom) and so this leaves him up to 9 h a day where he does not need to be using oxygen. The 15-h minimum does not have to be continuous, and so he can leave the house or interrupt the oxygen delivery as necessary to carry out activities of daily living. The cost of the electricity is covered by the oxygen contractor, who will monitor usage using a meter. Contractors are required to install a backup power supply which will continue to drive the concentrator for a minimum of 8 h should the mains supply fail.
5. Provided patients receive the required duration of therapy each day, beneficial effects on life expectancy, exercise tolerance and mental capacity can be anticipated.

Case 26.2

Mrs VL, a 58-year-old lady, has been brought into hospital by ambulance having been struggling with dyspnoea and significantly reduced exercise tolerance for several days. You review her chart and medical notes on the hospital admissions ward. The working diagnosis is an infective exacerbation of COPD. The patient presents with:
Thick green sputum which the patient reports is usually clear/white.
O_2 saturation of 82% on 28% oxygen delivered via a Venturi mask
Arterial blood gases (ABG):
pH 7.33 (7.35–7.45)
pO_2 7.24 kPa (10.7 kPa)
pCO_2 7.1 kPa (4.7–6.0 kPa)
Bicarbonate 46 mmol/L (22–26 mmol/L)
D-dimer negative
Drug history:
Salbutamol 2.5 mg via a nebuliser four times a day
Symbicort® 200/6 2 puffs twice a day
Tiotropium 18 µcg daily
Furosemide 40 mg twice a day
Ramipril 5 mg daily
Alendronate 70 mg weekly on Saturdays
Adcal D3 2 tablets daily
Mrs VL is commenced on:
Salbutamol 5 mg via a nebuliser 4 hourly
Ipratropium bromide 500 µcg via a nebuliser 6 hourly
Prednisolone 30 mg daily
Co-amoxiclav 1.2 g i.v. three times a day
Doxycycline 200 mg stat then 100 mg od thereafter.

Questions

1. Explain the arterial blood gas profile.
2. What is the significance of the negative D-dimer result?

3. If she does not respond to initial therapy, what might it be appropriate to change or introduce?

Answers

1. The low pO_2 indicates significant hypoxia. A slightly low pH and slightly elevated pCO_2 suggest a respiratory acidosis. The high bicarbonate level indicates that this acid/base disturbance is compensated at this level. The bicarbonate is likely to have accumulated over a relatively prolonged period.
2. A negative D-dimer is a strong indicator that Mrs VL's dyspnoea is not as a result of a pulmonary embolism. Although a raised D-dimer is not a reliable means of confirming thromboembolic disease (low specificity – frequent false positives), it is far more reliable in excluding such conditions where the result falls within the normal range (high sensitivity – rare false negatives). It is important to exclude conditions such as pulmonary embolism or acute left ventricular failure when patients with COPD present with increased shortness of breath to avoid missed diagnoses.
3. The concentration of oxygen could be increased to 35%. Mrs VL may be at risk of developing hypercapnia as a result of her COPD, and so her arterial blood gases should be rechecked 30–60 min after the change in her oxygen therapy. Particular attention should be made to any increase in the carbon dioxide concentration. If Mrs VL's respiratory rate exceeds 30 breaths/min while using a Venturi mask, the oxygen flow rate should be increased by 50%. The target for oxygen therapy is to achieve a saturation of 88–92%.

   Inadequate response to nebulised bronchodilators is an indication where intravenous aminophylline should be considered. A loading dose of 5 mg/kg over at least 20 min followed by a continuous infusion of 500 µcg/kg/h can be administered. Levels should be checked within the first 24 h of therapy.

   There is no evidence that use of mucolytics at this acute stage will be of benefit.

Case 26.3

Mrs SS is a 61-year-old retired factory worker who has been recently diagnosed with COPD after admission to hospital. She was discharged a few days ago having been started on a nicotine patch, 14 mg every 24 h. She asks you for advice on the best way to give up smoking as she has tried several times in the past and failed to quit. She smokes around 25 cigarettes a day and has been smoking since she was 17. She has a history of oesophageal reflux and also has epilepsy.

Questions

1. Why is it important for Mrs SS to give up smoking?
2. How many pack-years has she smoked?
3. What aspects should be discussed when helping someone to stop smoking?
   When you question Mrs SS about her previous attempts to stop smoking, she confides that her husband smokes in the house and she finds it difficult not to smoke when he does. She has tried nicotine gum but finds it difficult to use with her dentures. Her current patch does not seem to be helping, it has reduced her craving but not eliminated it, especially when she wakes up in the morning.
4. Is the current management of Mrs SS appropriate?
5. What non-pharmacological support should be offered to Mrs SS?

Answers

1. Stopping smoking is the single most important way of affecting a patient's outcome at all stages of COPD. Giving up smoking will slow down the gradual decline in FEV_1 that is seen in smokers.
2. $$\text{Total pack years} = \frac{\text{Number of cigarettes smoked per day}}{20} \times \text{number of years of smoking}$$

   Mrs SS has smoked approximately 55 pack-years.
3. There are five key steps in helping a smoker to stop smoking, the 'five As':

   - *Ask* about tobacco use. This should include an assessment of the degree of addiction
   - *Advise* to quit
   - *Assess* willingness to make an attempt
   - *Assist* in quit attempt
   - *Arrange* follow-up.

   Motivation from the patient is the key to giving up smoking but is related to the degree of dependence on tobacco. Heavy smokers may exhibit low motivation to quit as they lack confidence in their ability to do so.
4. Nicotine replacement patches are considered to be most suitable for people who smoke regularly through the day but a 21- to 25-mg patch would have been a more appropriate starting dose for someone smoking 20 or more cigarettes a day. Two of the most common side effects are insomnia or vivid dreams, if these occur the patch can either be removed before bedtime or a 16-h patch used. A suitable alternative would be the short-acting gum, lozenge or nasal spray. Mrs SS would require the 4-mg gum and should be encouraged to use the 8- to 12-pieces of gum a day to provide approximately 20 mg of absorbed nicotine per day. As the nasal spray is most useful for people who smoke 20 or more cigarettes per day, this may be the preferred formulation.
   Mrs SS may benefit from a combination of products. Although this practice is not specifically recommended by product manufacturers, it is considered suitable in highly dependent patients, or in those who have had unsuccessful quit attempts using a single nicotine replacement therapy preparation. If breakthrough cravings are felt despite a background patch then the addition of short-acting dosage forms may be used as 'rescue' medication.
   A date on which to quit smoking should be set. Nicotine replacement therapy should be prescribed in blocks of 2 weeks. Mrs SS should be seen and helped regularly throughout this process, before and after her quit date. The duration of nicotine replacement therapy in people who maintain an abstinence is usually 8–12 weeks, depending on the product, followed by a dose reduction.
   Another option would be to try varenicline. This may be more effective in achieving continuous abstinence (National Institute for Health and Clinical Excellence, 2007) than either nicotine replacement therapy or bupropion. Varenicline should be started 1–2 weeks before Mrs SS's quit date and is continued for a total of 12 weeks, although an additional 12 weeks' therapy may be required. Bupropion is contraindicated as this may increase Mrs SS's risk of seizures.
5. It is thought that around 3% of smokers quit every year on their own but that percentage increases when they are given simple advice whilst encouraging the quit attempt. Several non-pharmacological strategies exist to help:

   - Written self-help material.
   - Counselling and behavioural therapy. These aim to motivate the smoker and help with the skills and strategies required to cope with nicotine withdrawal, psychological pressures to smoke and situations of temptation to smoke.

In all cases, pharmacological therapy should also be offered as appropriate.

Several NHS, patient and charitable organisations can provide help and support to people wishing to stop smoking. Information can be obtained from the followed web sites:

http://smokefree.nhs.uk/
http://www.quit.org.uk/
http://www.patient.co.uk/health/Smoking-Tips-to-Help-you-Stop.htm

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27 Insomnia

S. Bleakley and M. Sie

Key points

- Hypnotic drugs do not cure insomnia but can provide useful short-term symptomatic treatment.
- Before starting medication, the primary cause of insomnia should be investigated and treated appropriately where possible.
- Hypnotic drugs should only be used short-term (2–4 weeks); long-term regular use leads to tolerance, dependence and other adverse effects.
- Sleep hygiene, relaxation techniques and psychological methods are more appropriate than hypnotics as long-term treatment for patients with insomnia.
- Non-benzodiazepine hypnotics such as zopiclone, zolpidem and zaleplon have similar pharmacological and adverse effects to benzodiazepines, offer few advantages and are more expensive.
- A melatonin preparation is available for primary insomnia. Its place in therapy is yet to be determined but it does not cause tolerance or dependence.

Definitions and epidemiology

Insomnia refers to difficulty in either falling asleep, remaining asleep or feeling refreshed from sleep. Complaints of poor sleep increase with increasing age and are twice as common in women as in men (Sateia and Nowell, 2004). Thus, by the age of 50, a quarter of the population are dissatisfied with their sleep, the proportion rising to 30–40% (two-thirds of them women) among individuals over 65 years.

Pathophysiology

Insomnia reflects a disturbance of arousal and/or sleep systems in the brain. These systems are functionally interrelated and their activity determines the degree and type of alertness during wakefulness and the depth and quality of sleep.

Sleep systems

The phenomenon of sleep is actively induced and maintained by neural mechanisms in several brain areas, including the lower brainstem, pons and parts of the limbic system. These mechanisms have reciprocal inhibitory connections with arousal systems, so that the activation of sleep systems inhibits waking and vice versa. Normal sleep includes two distinct levels of consciousness, orthodox sleep and paradoxical sleep, which are promoted from separate neural centres.

Orthodox sleep normally takes up about 75% of sleeping time. It is somewhat arbitrarily divided into four stages (1–4) which merge into each other, forming a continuum of decreasing cortical and behavioural arousal (see Fig. 27.1). Stages 3 and 4 represent the deepest phase of sleep and are also termed slow-wave sleep (SWS).

Paradoxical sleep, rapid eye movement (REM) sleep, normally takes up about 25% of sleeping time and has quite different characteristics to non-rapid eye movement (NREM) sleep. The EEG shows unsynchronised fast activity similar to that found in the alert conscious state and the eyes show rapid jerky movements. Peripheral autonomic activity is increased during REM sleep and there is an increased output of catecholamines and free fatty acids. Vivid dreams and nightmares most often occur during REM sleep, although brief frightening dreams (hypnagogic hallucinations) can occur in orthodox sleep, especially at the transition between sleeping and waking. Normally, stage 4 sleep occurs primarily in the first few hours of the night, while REM sleep is most prominent towards the morning. Brief awakenings during the night are normal. Both SWS and REM sleep are thought to be essential for brain function and both show a rebound after a period of deprivation, usually at the expense of lighter (stage 1 and 2) sleep which appears to be expendable. Many drugs can affect the different stages of sleep.

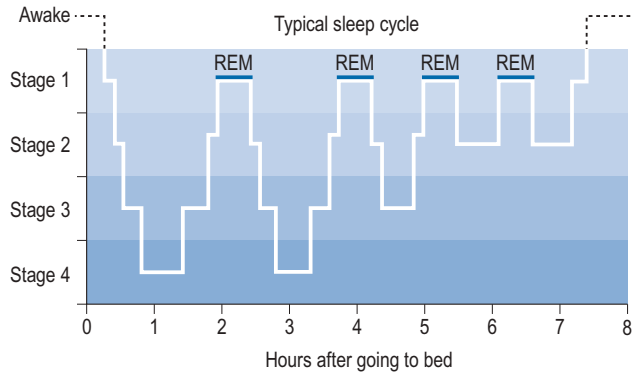

Fig. 27.1 The five stages of sleep. REM, rapid eye movement.

Benzodiazepines suppress stages 3 and 4 of sleep, but only cause a slight decrease in REM sleep. Z-hypnotics shorten stage 1 of sleep and prolong stage 2 of sleep but have little effect on stages 3, 4 and REM sleep. Chloral derivatives do not affect sleep architecture.

Aetiology and clinical manifestations

Insomnia may be caused by any factor which increases activity in arousal systems or decreases activity in sleep systems. Many causes act on both systems (Morin, 2003). Increased sensory stimulation activates arousal systems, resulting in difficulty in falling asleep. Common causes include chronic pain, gastric reflux, uncontrolled asthma and external stimuli such as noise, bright lights and extremes of temperature. Anxiety may also delay sleep onset as a result of increased emotional arousal.

Drugs are an important cause of insomnia. Difficulty in falling asleep may result directly from the action of stimulants, including caffeine, nicotine, theophylline, sympathomimetic amines, some antidepressants, levothyroxine and antimuscarinics. Some illicit substances, cocaine, amphetamines and anabolic steroids can also cause insomnia. Drug withdrawal after chronic use of central nervous system depressants, including hypnotics, anxiolytics and alcohol, commonly causes rebound insomnia with delayed or interrupted sleep, increased REM sleep and nightmares. With rapidly metabolised drugs, such as alcohol or short acting benzodiazepines, this rebound may occur in the latter part of the night, resulting in early waking. Certain drugs, including antipsychotics, tricyclic antidepressants and propranolol, may occasionally cause nightmares.

Difficulty in staying asleep is characteristic of depression. Patients typically complain of early waking but sleep records show frequent awakenings, early onset of REM sleep and reduced NREM sleep. Alteration of sleep stages, increased dreaming and nightmares may also occur in schizophrenia, while recurring nightmares are a feature of post-traumatic stress disorder (PTSD). Interference with circadian rhythms, as in shift work or rapid travel across time zones, can cause difficulty in falling asleep or early waking.

Frequent arousals from sleep are associated with myoclonus, 'restless legs syndrome', muscle cramps, bruxism (tooth grinding), head banging and sleep apnoea syndromes. Reversal of the sleep pattern, with a tendency for poor nocturnal sleep but a need for daytime naps, is common in the elderly, in whom it may be associated with cerebrovascular disease or dementia. In general, decreased duration of sleep has been shown to increase the risk of obesity (Kripke et al., 2002) and hypertension (Gangwisch et al., 2006). Sleep disturbances in the elderly are also associated with increased falls, cognitive decline and a higher rate of mortality (Cochen et al., 2009). There is growing concern that daytime sleepiness resulting from insomnia increases the risk of industrial, traffic and other accidents.

Investigations and differential diagnosis

Many patients complaining of insomnia overestimate their sleep requirements. Although most people sleep for 7–8 h daily, some healthy subjects require as little as 3 h of sleep and sleep requirements decline with age. Such 'physiological insomnia' does not usually cause daytime fatigue, although the elderly may take daytime naps. If insomnia is causing distress, primary causes such as pain, drugs which disturb sleep, psychiatric disturbance including anxiety and depression and organic causes such as sleep apnoea should be identified and treated before hypnotic therapy is prescribed.

Treatment

Non-drug therapies

Explanation of sleep requirements, attention to sleep hygiene (see Box 27.1), reduction in caffeine or alcohol intake and the use of analgesics where indicated may obviate the need for hypnotics (Anon, 2004). Medications that cause insomnia should also be avoided if possible. Psychological techniques such as relaxation therapy and cognitive behavioural therapy (CBT) are also helpful (Kierlin, 2008). However, studies comparing psychological approaches to hypnotics are scarce (Riemann and Perlis, 2009).

Hypnotic drugs

Hypnotic drugs provide only symptomatic treatment for insomnia. Although often efficacious in the short-term, they do little to alter the underlying cause which should be sought and treated where possible. About 20 million prescriptions for hypnotics are issued each year in the UK and these drugs can improve the quality of life if used rationally.

Box 27.1 Principles of typical advice for good sleep hygiene (Anon, 2004)

- Have a good bed time routine, go to bed and get up at the same time every day and avoid daytime naps.
- Avoid stimulants such as caffeine, nicotine, chocolate and alcohol 6 h before bedtime.
- Take regular exercise during the day, but avoid strenuous exercise within 4 h of bedtime.
- Avoid large meals close to bedtime.
- Associate bed with sleep. Do not watch TV or listen to music when retiring to bed.
- The bedroom should be a quiet, relaxing place to sleep; make sure the room is not too hot or too cold.
- If after 30 min you cannot get off to sleep, then get up. Leave the bedroom and try to do something else, return to bed when sleepy. This can be repeated as often as necessary until you are asleep.

The ideal hypnotic would

- gently suppress brain arousal systems while activating systems that promote deep and satisfying sleep,
- have a rapid onset of action with a duration of less than 8 h,
- have no hangover effect the next day,
- not induce tolerance or dependence if used long-term,
- not cause withdrawal effects when stopped,
- not depress respiration,
- be safe for use in the elderly patient.

Unfortunately, no such hypnotic exists; most available hypnotics are general central nervous system depressants which inhibit both arousal and sleep mechanisms. Thus, they do not induce normal sleep and often have adverse effects, including daytime sedation ('hangover') and rebound insomnia on withdrawal. They are unsuitable for long-term use because of the development of tolerance and dependence.

Benzodiazepines

By far the most commonly prescribed hypnotics are the benzodiazepines. A number of different benzodiazepines are available (see Table 27.1). These drugs differ considerably in potency (equivalent dosage) and in rate of elimination but only slightly in clinical effects. All benzodiazepines have sedative/hypnotic, anxiolytic, amnesic, muscular relaxant and anticonvulsant actions with minor differences in the relative potency of these effects.

Pharmacokinetics

Most benzodiazepines marketed as hypnotics are well absorbed and rapidly penetrate the brain, producing hypnotic effects within half an hour after oral administration. Rates of elimination vary, however, with elimination half-lives from 6 to 100 h (see Table 27.1). These drugs undergo hepatic metabolism via oxidation or conjugation and some form pharmacologically active metabolites with even longer elimination half-lives. Oxidation of benzodiazepines is decreased in the elderly, in patients with hepatic impairment and in the presence of some drugs, including alcohol.

Pharmacokinetic characteristics are important in selecting a hypnotic drug. A rapid onset of action combined with a medium duration of action (elimination half-life about 6–8 h) is usually desirable. Too short a duration of action may lead to, or fail to control, early morning waking, while a long duration of action (e.g. nitrazepam) may produce residual effects

Table 27.1 Overview of the medication used for insomnia

Drug	Usual dose at night (adult) (mg)	Half life in adults (h)	Licensed indication	Tolerance	Dependence
Benzodiazepines					
Diazepam	2–5	24–36	Insomnia (short-term use)	Yes	Yes
Loprazolam	1	11	Insomnia (short-term use)	Yes	Yes
Lorazepam	1	12–16	Insomnia (short-term use)	Yes	Yes
Lormetazepam	0.5–1.5	10	Insomnia (short-term use)	Yes	Yes
Nitrazepam	5–10	18–36	Insomnia (short-term use)	Yes	Yes
Temazepam	10–20	5–11	Insomnia (short-term use)	Yes	Yes
Z-Hypnotics					
Zaleplon	10	2	Insomnia (short-term use up to 2 weeks)	Yes	Yes
Zolpidem	5–10	2–3	Insomnia (short-term use up to 4 weeks)	Yes	Yes
Zopiclone	3.75–7.5	3.5–6	Insomnia (short-term use up to 4 weeks)	Yes	Yes
Chloral and Derivatives (rarely used)					
Cloral Betaine	707	Unclear	Insomnia (short-term use)	Yes	Yes
Clomethiazole					
Clomethiazole	192–384	4–5	Severe insomnia in elderly (short-term use)	Yes	Yes
Antihistamines					
Promethazine	25–50	10–19	Night sedation and insomnia (short-term use)	Yes	No
Melatonin					
Melatonin Circadin® Unlicensed products also available	2	3.5–4	Insomnia in adults over 55 years (short-term use)	No	No

the next day and may lead to accumulation if the drug is used regularly. However, frequency of use and dosage are also important. For example, diazepam (5–10 mg) produces few residual effects when used occasionally, despite its slow elimination, although chronic use impairs daytime performance. Large doses of short acting drugs may produce hangover effects, while small doses of longer acting drugs may cause little or no hangover.

Mechanism of action

Most of the effects of benzodiazepines result from their interaction with specific binding sites associated with postsynaptic $GABA_A$ receptors in the brain. All benzodiazepines bind to these sites, although with varying degrees of affinity, and potentiate the inhibitory actions of GABA at these sites.

$GABA_A$ receptors are multi-molecular complexes (see Figs. 27.2 and 27.3) that control a chloride ion channel and contain specific binding sites for GABA, benzodiazepines and several other drugs, including many non-benzodiazepine hypnotics and some anticonvulsant drugs (Haefely, 1990). The various effects of benzodiazepines (hypnotic, anxiolytic, anticonvulsant, amnesic, muscle relaxant) result from GABA potentiation in specific brain sites and at different types of $GABA_A$ receptor. There are multiple subtypes of $GABA_A$ receptor which may contain different combinations of at least 18 sub-units (including α_{1-6}, β_{1-3}, γ_{1-3} and others) and the subtypes are differentially distributed in the brain.

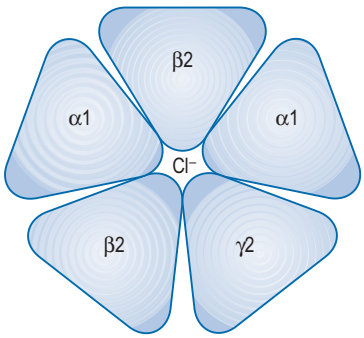

Fig. 27.2 *The $GABA_A$ receptor and sub-units.* The $GABA_A$ receptor is a heteropentameric glycoprotein. A total of five distinct polypeptide sub-units have been cloned to date; α, β, γ, d and r, and multiple isoforms of these sub-units are reported in the literature. Different confirmations of the $GABA_A$ receptor are found throughout the brain, and the most common mammalian arrangements of sub-units is $(\alpha1)_2(\beta2)_2(\gamma1)$. The specific sub-units in the $GABA_A$ receptor confer functional diversity on the receptor. For example, the γ sub-unit needs to be co-expressed with the α and β sub-units to observe the potentiation of the $GABA_A$ receptor by benzodiazepines.

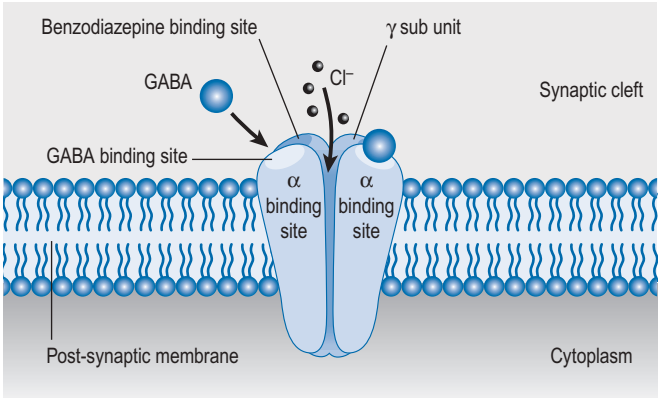

Fig. 27.3 *Schematic representation of the $GABA_A$ receptor.* GABA is the major inhibitory neurotransmitter in the central nervous system. The $GABA_A$ receptor is composed of five sub-units – two α, two β and one γ sub-unit. Two molecules of GABA activate the receptor by binding to the α sub-units. Once activated the receptor allows the passage of negatively charged ions (Cl–) into the cytoplasm, which results in hyper-polarisation and the inhibition of neurotransmission. Source: www.CNSforum.com.

Benzodiazepines bind to three or more subtypes and it appears that their combination with α_2-containing subtypes mediates their anxiolytic effects, α_1-containing subtypes their sedative and amnesic effects, and α_1 as well as α_2 and α_5 their anticonvulsant effects (Rudolph et al., 2001).

Zopiclone

In 1988, zopiclone, a cyclopyrrolone, was the first non-benzodiazepine to be approved for the treatment of insomnia in the European market. Although classed as a non-benzodiazepine, it still binds to benzodiazepine receptors but is said to be more selective for the α_1 subtype. It has hypnotic effects similar to benzodiazepines and carries a similar potential for adverse effects including tolerance, dependence and abstinence effects on withdrawal. Psychiatric reactions, including hallucinations, behavioural disturbances and nightmares, have been reported to occur shortly after the first dose. Other common adverse reactions include a bitter taste, a dry mouth and difficulty arising in the morning (Zammit, 2009). This drug appears to have no particular advantages over benzodiazepines, although it may cause less alteration of sleep stages and does not have the controlled drug requirements of the benzodiazepines. Eszopiclone the S- (+) isomer of zopiclone is available in the USA but there are no current plans to launch in the UK. What advantage, if any, the isomer incurs over zopiclone is unclear.

Zolpidem

Zolpidem is an imidazopyridine that binds preferentially to the α_1 benzodiazepine receptor sub-unit thought to mediate hypnotic effects. It is an effective hypnotic with only weak anticonvulsant and muscle relaxant properties. As it has a

short elimination half-life (2 h) hangover effects are rare but rebound effects may occur in the later part of the night, causing early morning waking and daytime anxiety. High doses have been reported to cause brief psychotic episodes, tolerance and withdrawal effects. Anecdotal case reports (mainly from the USA) have associated zolpidem with complex sleep related behaviours. These have included 'sleep-driving', making phone calls, preparing food and eating while asleep. The majority of these cases also involved ingestion of alcohol and should be interpreted with caution because they are not replicated in the wider medical literature (Zammit, 2009). A controlled release version of zolpidem (zolpidem-CR) is available in some countries.

Zaleplon

Zaleplon is a pyrazolopyrimidine which, like zolpidem, binds selectively to the α_1 benzodiazepine receptor. It is an effective hypnotic, has a very short elimination half-life (1 h) and appears to cause minimal residual effects on psychomotor or cognitive function after 5 h. There is little evidence of tolerance or withdrawal effects in short-term use and the drug appears suitable for use in the elderly (Doble et al., 2004).

All the 'Z-hypnotics' are recommended for short-term use only (2–4 weeks) and are more expensive than benzodiazepines. There is no compelling evidence to distinguish them from the shorter acting benzodiazepine hypnotics (National Institute of Health and Clinical Excellence, 2004). Patients who do not respond to either a benzodiazepine or z-hypnotic should not be prescribed the other.

Melatonin

Melatonin is a naturally occurring hormone, produced by the pineal gland, which regulates the circadian rhythm of sleep. It begins to be released once it becomes dark, and continues to be released until the first light of day. Melatonin release decreases with age which may in-part explain why older adults require less sleep. Melatonin supplementation promotes sleep initiation and helps to reset the circadian clock allowing uninterrupted sleep. It has also been shown to improve next day functioning. Contrary to most other hypnotics melatonin shows no abuse or tolerance potential and appears to have no next day sedation problems. Prolonged release melatonin (Circadin®) was launched in June 2008 and is available at a dose of 2 mg at night for up to 3 weeks. It is licensed as monotherapy in primary insomnia for adults over 55 years old. Whilst the adverse effect profile looks advantageous there are currently no trials comparing melatonin against psychological or other hypnotic treatments. Circadin® is also much more expensive than other currently prescribed hypnotics (Anon, 2009).

Other hypnotic drugs

The risk of adverse effects, including dependence and dangerous respiratory depression in overdose, generally outweighs the potential benefits of the older hypnotics, chloral derivatives, clomethiazole and barbiturate. Therefore, these drugs are best avoided. Antidepressants with sedative properties, such as amitriptyline, mirtazapine, trazodone and agomelatine may be helpful if sleep disturbance is secondary to depression. Sedative antihistamines, such as promethazine, diphenhydramine and chlorphenamine, which can be purchased over-the-counter, have mild-to-moderate hypnotic efficacy but commonly produce hangover effects and rebound insomnia can occur after prolonged use (Anon, 2004).

Potential adverse effects of hypnotic use

Tolerance and dependence

Tolerance to the hypnotic effects of benzodiazepines and probably z-hypnotics develops rapidly and may lead to dosage escalation. Nevertheless, poor sleepers may report continued efficacy and the drugs are often used long-term because of difficulties on withdrawal.

Rebound insomnia

Rebound insomnia, in which sleep is poorer than before drug treatment, is common on withdrawal of benzodiazepines. Sleep latency (time to onset of sleep) is prolonged, intra-sleep wakenings become more frequent and REM sleep duration and intensity are increased, with vivid dreams or nightmares which may add to frequent awakenings. These symptoms are most marked when the drugs have been taken in high doses or for long periods, but can occur after only a week of low dose administration. They are prominent with moderately, rapidly eliminated benzodiazepines (temazepam, lorazepam) and may last for many weeks. With slowly eliminated benzodiazepines (diazepam), SWS and REM sleep may remain depressed for some weeks and then slowly return to the baseline, sometimes without a rebound effect. Tolerance and rebound effects are reflections of a complex homeostatic response to regular drug use, involving desensitisation, uncoupling and internalisation of certain GABA/benzodiazepine receptors and sensitisation of receptors for excitatory neurotransmitters (Allison and Pratt, 2003). These changes encourage continued hypnotic usage and contribute to the development of drug dependence.

Oversedation and hangover effects

Many benzodiazepines used as hypnotics can give rise to a subjective 'hangover' effect and after most of them, even those with short elimination half-lives, psychomotor performance, including driving ability and memory, may be impaired on the following day. Over sedation is most likely with slowly eliminated benzodiazepines, especially if used chronically, and is most marked in the elderly in whom drowsiness, incoordination and ataxia, leading to falls and fractures, and acute confusional states may result even from small doses. Chronic use can

cause considerable cognitive impairment, sometimes suggesting dementia. Paradoxical excitement may occasionally occur.

Some benzodiazepines in hypnotic doses may decrease alveolar ventilation and depress the respiratory response to hypercapnia, increasing the risk of cerebral hypoxia, especially in the elderly and in patients with chronic respiratory disease.

Drug interactions

Benzodiazepines have additive effects with other central nervous system depressants. Combinations of benzodiazepines with alcohol, other hypnotics, sedative tricyclic antidepressants, antihistamines or opioids can cause marked sedation and may lead to accidents or severe respiratory depression.

Rational drug treatment of insomnia

A hypnotic drug may be indicated for insomnia when it is severe, disabling, unresponsive to other measures or likely to be temporary. In choosing an appropriate agent, individual variables relating to the patient and to the drug need to be considered (see Table 27.1).

Patient care

Type of insomnia

The duration of insomnia is important in deciding on a hypnotic regimen. Transient insomnia may be caused by changes of routine such as overnight travel, change in time zone, alteration of shift work or temporary admission to hospital. In these circumstances, a hypnotic with a rapid onset, medium duration of action and few residual effects could be used on one or two occasions.

Short-term insomnia may result from temporary environmental stress. In this case, a hypnotic may occasionally be indicated but should be prescribed in low dosage for 1 or 2 weeks only, preferably intermittently, on alternate nights or one night in three.

Chronic insomnia presents a much greater therapeutic problem. It is usually secondary to other conditions (organic or psychiatric) at which treatment should initially be aimed. In selected cases, a hypnotic may be helpful but it is recommended that such drugs should be prescribed at the minimal effective dosage and administered intermittently (one night in three) or temporarily (not more than 2 or 3 weeks). Occasionally it is necessary to repeat short, intermittent courses at intervals of a few months.

The elderly

The elderly are especially vulnerable both to insomnia and to adverse effects from hypnotic drugs. They may have reduced metabolism of some drugs and may be at risk of cumulative effects. They are also more susceptible than younger people to central nervous system depression, including cognitive impairment and ataxia (which may lead to falls and fractures). They are sensitive to respiratory depression, prone to sleep apnoea and other sleep disorders and are more likely to have 'sociological', psychiatric and somatic illnesses which both disturb sleep and may be aggravated by hypnotics. For some of these elderly patients, hypnotics can improve the quality of life but the dosage should be adjusted (usually half the recommended adult dose) and hypnotics with long elimination half-lives or active metabolites should be avoided.

A considerable number of elderly patients give a history of regular hypnotic use going back for 20 or 30 years. In many of these patients, gradual reduction of hypnotic dosage or even withdrawal may be indicated and can be carried out successfully, resulting in improved cognition and general health with no impairment of sleep or escalation of other symptoms (Curran et al., 2003).

The young

Traditional benzodiazepine-like are generally contraindicated for children. Where sedation is required, sedative antihistamines or melatonin are usually recommended.

Disease states

Hypnotics are contraindicated in patients with acute pulmonary insufficiency, significant respiratory depression, obstructive sleep apnoea or severe hepatic impairment. In patients with chronic pain or terminal conditions, suitable analgesics including non-steroidal anti-inflammatory agents or opiates, sometimes combined with neuroleptics, usually provide satisfactory sedation. In such patients, the possibility of drug dependence becomes a less important issue and regular use of hypnotics with a medium duration of action should not be denied if they provide symptomatic relief of insomnia.

Choice of drug

There is little difference in hypnotic efficacy between most of the available agents. The main factors to consider in the rational choice of a hypnotic regimen are duration of action and the risk of adverse effects, especially over sedation and the development of tolerance and dependence. Cost may also be a factor when prescribing melatonin.

Rate of elimination

Slowly eliminated drugs should be avoided because of the risk of over sedation and hangover effects. Very short acting drugs such as zaleplon carry the risk of late night rebound insomnia and daytime anxiety. Drugs with a medium elimination half-life (6–8 h) appear to have the most suitable profile for hypnotic use. These may include temazepam and loprazolam, as these are the drugs of first choice in most situations where hypnotics are indicated. Zopiclone is a

reasonable second choice and sedative antihistamine such as promethazine is a safe third choice. These are useful in children, although sedative antihistamine may produce daytime drowsiness.

Duration and timing of administration

To prevent the development of tolerance and dependence, the maximum duration of treatment should be limited to 2 or 3 weeks and treatment should, where possible, be intermittent (one night in two or three). Dosage should be tapered slowly if hypnotics have been taken regularly for more than a few weeks. Doses should be taken 20 min before retiring in order to allow dissolution in the stomach and absorption to commence before the patient lies down in bed.

Case studies

Case 27.1

Mr PH, aged 24, was hospitalised for 3 months after a serious motorcycle injury followed by painful complications. While in hospital he developed panic attacks and insomnia. He received no psychological support but was prescribed temazepam, initially in 20 mg doses but later increased to 60 mg because of continued insomnia. After discharge from hospital Mr PH continued to receive temazepam from his primary care doctor and the dosage was increased over a period of years until he was taking 80 mg temazepam each night and 40–80 mg during the day. At the age of 30, Mr PH was removed from the practice list of his doctor after he altered a prescription. He later attended several different primary care doctors, obtaining multiple temazepam prescriptions. When he could no longer satisfy his need from prescriptions he took to obtaining temazepam on the street, taking large and irregular doses by mouth. All this time, his anxiety levels increased. His behaviour became chaotic and he was twice imprisoned for credit card fraud but he was able to obtain temazepam and other drugs from his co-prisoners. When last heard of, Mr PH, aged 35, was again buying temazepam illicitly, as well as other addictive drugs, had started injecting intravenously and was involved in a court case for obtaining money under false pretences.

Question

How could this tragedy have been prevented?

Answer

Mr PH's downfall could have been averted at several stages.

- The hospital staff should not have allowed the temazepam dosage to escalate and should have provided psychological/psychiatric help for what was probably PTSD or panic disorder.
- An antidepressant drug could have been prescribed, along with psychological measures, instead of prolonged treatment with excessive doses of temazepam.
- On discharge from hospital, Mr PH's doctor should have been warned of his temazepam intake and a slow withdrawal schedule suggested.
- The series of primary care doctors who gave Mr PH prescriptions should have been aware that he was likely to obtain illicit supplies and should have referred him to a withdrawal clinic or drugs unit.

Case 27.2

Mrs AK, a recently widowed lady aged 65, had difficulty sleeping after her bereavement. She was prescribed nitrazepam in a bedtime dose of 5 mg, which was very effective and was continued for over 4 weeks. Mrs AK lived alone but was visited occasionally by her daughter. On a visit 2 weeks after the nitrazepam was started, Mrs AK seemed calm and said that she was sleeping well but the daughter noticed her mother was unsteady on her feet. A week later the daughter visited again and found her mother lying on the bedroom floor, in pain and unable to move. She said that she had lost her balance on getting out of bed. An ambulance was called and it was found in hospital that Mrs AK had broken her hip.

Question

Should the doctor have prescribed nitrazepam for this lady?

Answers

- Long acting benzodiazepines should be avoided in the elderly. The elimination half-life of nitrazepam is 15–38 h and the recommended dose for the elderly is 2.5–5 mg. Temazepam, loprazolam or lormetazepam would have been a better choice but for short-term use only (preferably only 2 weeks).
- The elderly are particularly prone to ataxia and light-headedness with benzodiazepines and this can lead to falls and fractures.
- Benzodiazepines are not recommended, except acutely, for bereavement. Their amnesic effects may interfere with subsequent psychological adjustment.

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28 Anxiety disorders

S. Bleakley and D. Baldwin

Key points

- Benzodiazepines should only be used short-term (2–4 weeks) as long-term regular use can lead to tolerance, dependence and other adverse effects.
- If benzodiazepines are indicated, the smallest effective dose should be used along with intermittent dosing where possible. Start with small doses, increase if necessary. Use half the adult dose in elderly patients.
- Psychological therapies (talking therapies) are generally considered first-line treatments in all anxiety disorders because they may provide a longer lasting response and lower relapse rates than pharmacotherapy.
- Some antidepressants are appropriate long-term treatment for anxiety disorders.
- Selective serotonin reuptake inhibitors (SSRIs) are the recommended antidepressants in anxiety disorders but can worsen symptoms at the beginning of treatment and, therefore, should be initiated at half the usual dose used.

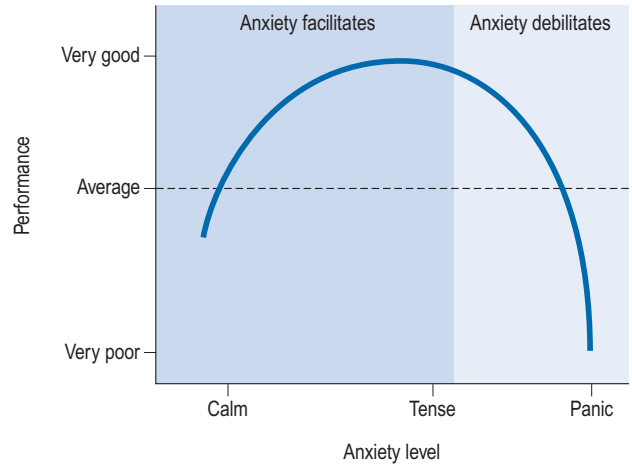

Fig. 28.1 The Yerks Dodson curve.

Definitions and epidemiology

Anxiety is a normal, protective, psychological response to an unpleasant or threatening situation. Mild to moderate anxiety can improve performance and ensure appropriate action is taken. However, excessive or prolonged symptoms can be disabling, lead to severe distress and cause much impairment to social functioning. Figure 28.1 shows that as anxiety levels increase performance/actions increase. However, as the anxiety level increases beyond acceptable or tolerated levels, the performance declines.

The term 'anxiety disorder' encompasses a variety of complaints which can either exist on their own or in conjunction with another psychiatric or physical illness. Symptoms of anxiety vary but generally present with a combination of psychological, physical and behavioural symptoms (Fig. 28.2). Some of these symptoms are common to many anxiety disorders while others are distinctive to a particular disorder. Anxiety disorders are broadly divided into generalised anxiety disorder (GAD), panic disorder, social phobia, specific phobias, post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD), see Table 28.1. Patient testimonials are presented in Box 28.1. Approximately two-thirds of sufferers of an anxiety disorder will have another psychiatric illness. This is most commonly depression and often successful treatment of

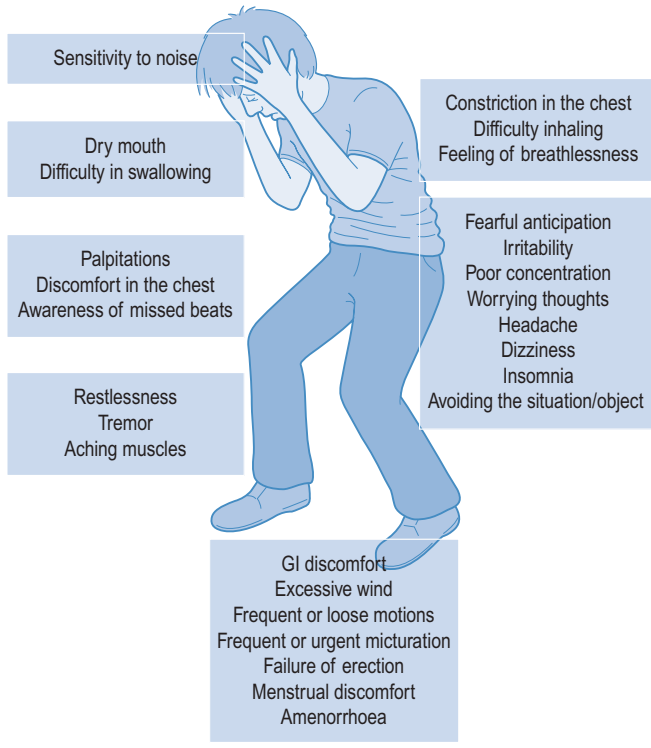

Fig. 28.2 The symptoms of anxiety.

Table 28.1 A brief description of the common anxiety disorders

Symptoms common to all anxiety disorders	Fear or worry, sleep disturbances, concentration problems, dry mouth, sweating, palpitations, GI discomfort, restlessness, shortness of breath, avoidance behaviour
Generalised anxiety disorder (GAD)	Persistent (free floating), excessive and inappropriate anxiety on most days for at least 6 months. The anxiety is not restricted to a specific situation
Panic disorder (with or without agoraphobia)	Recurrent, unexplained surges of severe anxiety (panic attack). Most patients develop a fear of repeat attacks or the implications of an attack. Often seen in agoraphobia (fear in places or situations from which escape might be difficult)
Social phobia (or social anxiety disorder)	A marked, persistent and unreasonable fear of being observed, embarrassed or humiliated in a social or performance situation (e.g. public speaking or eating in front of others)
Specific phobia	Marked and persistent fear that is excessive or unrealistic, precipitated by the presence (or anticipation) of a specific object or situation (e.g. flying, spiders). Sufferers avoid the feared object/subject or endure it with intense anxiety
Post-traumatic stress disorder (PTSD)	Can occur after an exposure to a traumatic event which involved actual or threatened death, or serious injury or threats to the physical integrity of self or others. The person responds with intense fear, helplessness or horror. Sufferers can re-experience symptoms (flashbacks) and avoid situations associated with the trauma. Usually occurs within 6 months of the traumatic event
Obsessive-compulsive disorder (OCD)	Persistent thoughts, impulses or images (obsessions) that are intrusive and cause distress. The person attempts to get rid of these obsessions by completing repetitive time-consuming purposeful behaviours or actions (compulsions). Common obsessions include contamination while the compulsion may be repetitive washing or cleaning

Box 28.1 Patient testimonies (NICE, 2005a,b)

Symptoms described by a sufferer of post-traumatic stress disorder:

> I would feel angry at the way the crash happened and that there was nothing I could do to stop it or help. I was physically exhausted, but was finding it hard to sleep. As soon as the bedroom light went out at night a light would come on in my head and all I could do was lie there and think. When I would eventually fall asleep, I would wake up with nightmares of the crash. I could not get away from it. It was all I could think about in the day and all I would dream about at night.

Thoughts from a sufferer of obsessive-compulsive disorder:

> I've just arrived home from work. Tired and tense, I'm convinced my hands are contaminated with some hazardous substance and my primary concern now is to ensure that I don't spread that contamination to anything that I, or others, may subsequently touch. I will wash my hands, but first I will need to put a hand in my pocket to get my door keys, contaminating these, the pocket's other contents, and everything else I touch on my way to the sink. It will be late evening before I will have completed the whole decontamination ritual.

A slow recovery described by a post-traumatic stress disorder and panic attack sufferer:

> Slowly I gained ground and as each new insight came I was able to see my symptoms diminish. The panic attacks tapered off, the intensity of the flashbacks dwindled, and my irritable bowel began to loosen some of its hold on me. I was able to breathe again.

an underlying depression will significantly improve the symptoms of anxiety. Many patients will also present with more than one anxiety disorder at the same time which can further complicate treatment. Anxiety disorders are the most commonly reported mental illness and as a whole have a lifetime prevalence of 21% (Baldwin et al., 2005) with specific phobias the most commonly reported.

For all anxiety disorders together the overall female to male ratio is 2:1. The age of onset of most anxiety disorders is in young adulthood (20s and 30s), although the maximum prevalence of generalised anxiety and agoraphobia in the general population is in the 50–64 year age group.

Pathophysiology

Anxiety occurs when there is a disturbance of the arousal systems in the brain. Arousal is maintained by at least three interconnected systems: a general arousal system, an 'emotional' arousal system and an endocrine/autonomic arousal system (Fig. 28.3). The general arousal system, mediated by the brainstem reticular formation, thalamic nuclei and basal forebrain bundle, serves to link the cerebral cortex with incoming sensory stimuli and provides a tonic influence on cortical reactivity or alertness. Excessive activity in this system, due to internal or external stresses, can lead to a state of hyperarousal as seen in anxiety. Emotional aspects of arousal, such as fear and anxiety, are contributed by the limbic system which also serves to focus attention on selected aspects of the environment. There is evidence that increased activity in certain limbic pathways is associated with anxiety and panic attacks.

These arousal systems activate somatic responses to arousal, such as increased muscle tone, increased sympathetic activity and increased output of anterior and posterior pituitary hormones. Inappropriate increases in autonomic activity are

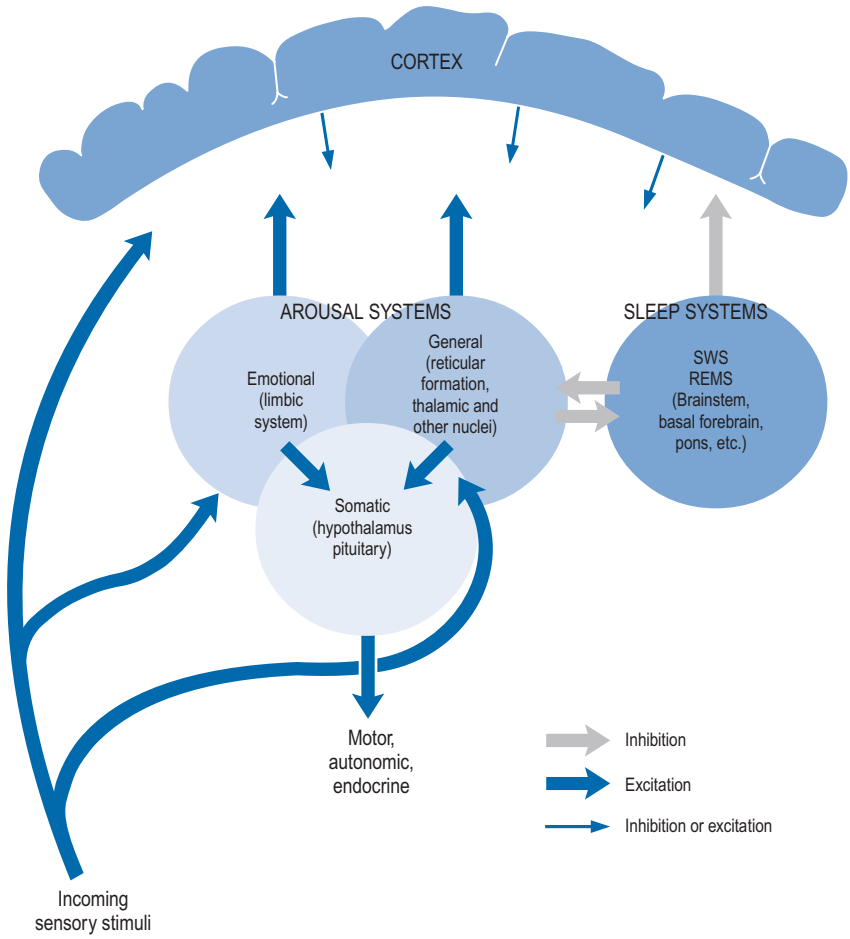

Fig. 28.3 Diagram of arousal and sleep systems. Arousal systems receive environmental and internal stimuli, cause cortical activation and mediate motor, autonomic and endocrine responses to arousal. Reciprocally connected sleep systems generate slow-wave sleep (SWS) and rapid eye movement sleep (REMS). Either system can be excited or inhibited by cognitive activity generated in the cortex.

often associated with anxiety states; the resulting symptoms (palpitations, sweating, tremor, etc.) may initiate a vicious circle that increases the anxiety.

Several neurotransmitters have been implicated in the arousal systems. Acetylcholine is the main transmitter maintaining general arousal but there is evidence that heightened emotional arousal is particularly associated with noradrenergic and serotonergic activity. Drugs which antagonise such activity have anxiolytic effects. In addition, the inhibitory neurotransmitter γ-aminobutyric acid (GABA) exerts an inhibitory control on other transmitter pathways and increased GABA activity may have a protective effect against excessive stress reactions. Many drugs which increase GABA activity, such as the benzodiazepines, are potent anxiolytics.

Aetiology and clinical manifestations

Anxiety is commonly precipitated by stress but vulnerability to stress appears to be linked to genetic factors such as trait anxiety. Many patients presenting for the first time with anxiety symptoms have a long history of high anxiety levels going back to childhood. Anxiety may also be induced by central stimulant drugs (caffeine, amphetamines), withdrawal from chronic use of central nervous system depressant drugs (alcohol, hypnotics, anxiolytics) and metabolic disturbances (hyperventilation, hypoglycaemia, thyrotoxicosis). It may form part of a depressive disorder and may occur in temporal lobe lesions and in rare hormone-secreting tumours such as phaeochromocytoma or carcinoid syndrome.

Apart from the psychological symptoms of apprehension and fear, somatic symptoms may be prominent in anxiety and include palpitations, chest pain, shortness of breath, dizziness, dysphagia, gastro-intestinal disturbances, loss of libido, headaches and tremor. Panic attacks are experienced as storms of increased autonomic activity combined with a fear of imminent death or loss of control. If panic becomes associated with a particular environment, commonly a crowded place with no easy escape route, the patient may actively avoid similar situations and eventually become agoraphobic. When anxiety is precipitated by a specific cause then behaviour can become altered to ensure the sufferer avoids the cause. This avoidance behaviour can maintain the often irrational fear and strengthen the desire to avoid the threat.

Investigations and differential diagnosis

In patients presenting with symptoms and clinical signs of anxiety, it is important to exclude organic causes such as thyrotoxicosis, excessive use of stimulant drugs such as caffeine and the possibility of alcoholism or withdrawal effects from benzodiazepines. However, unnecessary investigations should generally be avoided if possible. Extensive gastroenterological, cardiological and neurological tests may increase anxiety by reinforcing the patient's fear of a serious underlying physical disease.

Treatment

Treatment for anxiety disorders often requires multiple approaches. The patient may need short-term treatment with an anxiolytic, such as a benzodiazepine, to help reduce the immediate symptoms combined with psychological therapies and an antidepressant for longer term treatment and prevention of symptoms returning.

Psychotherapy

Psychological therapies (talking therapies) are generally considered first-line treatments in all anxiety disorders because they may provide a longer lasting response and lower relapse rates than pharmacotherapy. Psychotherapy, however, is less available, more demanding and takes longer time to work than pharmacotherapy. If the patient is unable to tolerate the anxiety or associated distress, then medicines are often used before psychotherapy or while awaiting psychotherapy. The ideal treatment should be tailored to the individual and may involve a combination of both psychotherapy and pharmacotherapy. The type of treatment should depend on symptoms, type of anxiety disorder, speed of response required, long-term goals and patient preference.

The specific psychotherapy with the most supporting evidence in anxiety disorders is cognitive behavioural therapy (CBT). Cognitive behaviour therapy focuses on the 'here and now' and explores how the individual feels about themselves and others and how behaviour is related to these thoughts. Through individual therapy or group work the patient and therapist identify and question maladaptive thoughts and help develop an alternative perspective. Individual goals and strategies are developed and evaluated with patients encouraged to practise what they have learned between sessions. Therapy usually lasts for around 60–90 minutes every week for 8–16 weeks, or longer in more resistant cases. Cognitive behavioural therapists are usually health professionals such as mental health nurses, psychologists, general practitioners, social workers, counsellors or occupational therapists who have undertaken specific training and supervision.

In PTSD, CBT is trauma focused, with the therapist helping the patient confront their traumatic memory and people or objects associated with this trauma. At the same time, patients are taught skills to help them cope with the emotional or physical response of this trauma. One such skill includes relaxation training which may involve systematically relaxing major muscle groups in a way that decreases anxiety. Another psychotherapy sometimes recommended in PTSD is eye movement desensitisation and reprocessing (EMDR). This involves briefly recounting the trauma or objects associated with the trauma to the therapist who will then simultaneously initiate another stimulus, for example, moving a finger continuously in front of the patient's eyes or hand tapping. Over time it enables the patient to focus on alternative thoughts when associations with the trauma occur. A single session of debriefing following a traumatic event is not thought effective to prevent PTSD and, therefore, not recommended.

In OCD, CBT includes exposure and response prevention (ERP). This involves the therapist and the patient repeatedly facing the fears, beginning with the easiest situations and progressing until all the fears have been faced. At the same time the person must not perform any rituals or checks.

Specific phobias are also almost exclusively treated using exposure techniques and most patients will respond to this treatment. Only a very few will require additional drug therapy.

Other psychotherapies, although occasionally tried, have a poorer evidence base than CBT and are, therefore, not usually recommended. Self-help is one alternative technique which is recommended (NICE, 2007) for GAD and panic disorder. It involves using materials either alone or in part under professional guidance to learn skills to help cope with the anxiety. The materials such as books, tapes or computer packages can be accessed at home and in the patients' own time. Some self-help material, however, is of poor quality, so it is probably best used in those who have mild symptoms and who do not need more intensive treatments.

Pharmacotherapy

Benzodiazepines

Benzodiazepines are commonly prescribed to provide immediate relief of the symptoms of severe anxiety. A number of different benzodiazepines are available (Table 28.2). These drugs differ considerably in potency (equivalent dosage) and in rate of elimination but only slightly in clinical effects. All benzodiazepines have sedative/hypnotic, anxiolytic, amnesic, muscular relaxant and anticonvulsant actions with minor differences in the relative potency of these effects.

Pharmacokinetics. Most benzodiazepines are well absorbed and rapidly penetrate the brain, producing an effect within half an hour after oral administration. Rates of elimination vary; however, with elimination half-lives from 8 to 35 h (see Table 28.2). The drugs undergo hepatic metabolism via oxidation or conjugation and some form pharmacologically active metabolites with even longer elimination half-lives. Oxidation of benzodiazepines is decreased in the elderly, in patients with hepatic impairment and in the presence of some drugs, including alcohol. Benzodiazepines are metabolised through the cytochrome P450 3A4/3 enzyme system in the liver, so

Table 28.2 Profile of selected benzodiazepines (Bazire, 2009; Taylor et al., 2009)

Drug	Usual daily dose (mg)	Half-life hours (range)	Equivalent dose to diazepam 10 mg
Alprazolam	0.5–1.5	13 (12–15)	Unknown
Chlordiazepoxide	30	12 (6–30)	30 mg
Clonazepam	2–4	35 (20–60)	1–2 mg
Diazepam	5–30	32 (21–50)	–
Lorazepam	1–4	12 (8–25)	1 mg
Oxazepam	30	8 (5–15)	30 mg
Temazepam	10–20	8 (5–11)	20 mg

significant enzyme inducers (such as carbamazepine) may reduce levels while enzyme inhibitors (e.g. erythromycin) may increase levels (Bazire, 2009).

Mechanism of action. Most of the effects of benzodiazepines result from their interaction with specific binding sites associated with postsynaptic $GABA_A$ receptors in the brain. All benzodiazepines bind to these sites, although with varying degrees of affinity, and potentiate the inhibitory actions of GABA at these sites. GABA is the most important inhibitory neurotransmitter in the central nervous system (CNS). Neuronal activity in the CNS is regulated by the balance between GABA inhibitory activity and excitatory neurotransmitters such as glutamate. If the balance swings towards more GABA activity, sedation, ataxia and amnesia occur. Conversely, when GABA is reduced arousal, anxiety and restlessness occur. $GABA_A$ receptors are multimolecular complexes that control a chloride ion channel and contain specific binding sites for GABA, benzodiazepines and several other drugs, including many non-benzodiazepine hypnotics and some anticonvulsant drugs (Haefely, 1990) (Fig. 28.4). The various effects of benzodiazepines (hypnotic, anxiolytic, anticonvulsant, amnesic, myo-relaxant) result from GABA potentiation in specific brain sites and at different $GABA_A$ receptor types. There are multiple subtypes of $GABA_A$ receptor which may contain different combinations of at least 17 subunits (including α_{1-6}, β_{1-3}, γ_{1-3} and others) and the subtypes are differentially distributed in the brain (Christmas et al., 2008). Benzodiazepines bind to two or more subtypes and it appears that combination with α_2-containing subtypes mediates their anxiolytic effects and α_1-containing subtypes their sedative and amnesic effects. There is some evidence that patients with anxiety disorders

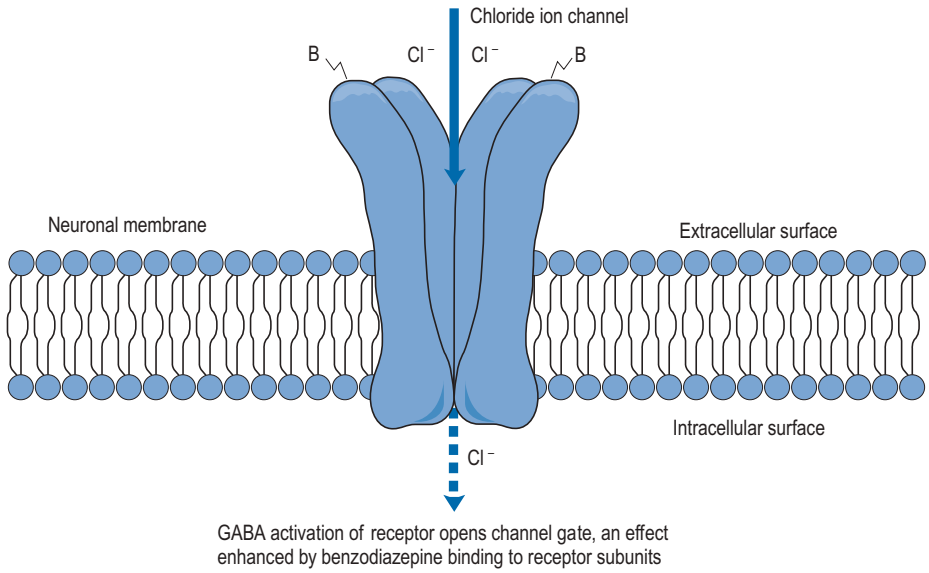

Fig. 28.4 Schematic diagram of the $GABA_A$ receptor. This consists of five subunits arranged around a central chloride ion channel (one subunit has been removed in the diagram to reveal the ion channel, shown in the closed position). Some of the subunits have binding sites for benzodiazepines (B) and other hypnotics and anticonvulsants. Activation of the receptor by GABA opens the chloride channel, allowing chloride ions (Cl^-) to enter the cell, resulting in hyperpolarisation (inhibition) of the neurone. Occupation of the benzodiazepine site, along with GABA, potentiates the inhibitory actions of GABA.

have reduced numbers of benzodiazepine receptors in key brain areas that regulate anxiety responses (Roy-Byrne, 2005). Secondary suppression of noradrenergic and/or serotonergic and other excitatory systems may also be of importance in relation to the anxiolytic effects of benzodiazepines.

Role in treating anxiety. The benzodiazepines have been used for over 40 years in the treatment of anxiety and can provide rapid symptomatic relief from acute anxiety states. Concerns over dependence and tolerance restrict use to short-term use only. Many clinical trials have shown short-term efficacy in patients with anxiety disorders, although the efficacy shown is in part dependent on the year of publication of the study. Older randomised controlled trials appear to show a larger effect than more recent ones (Martin et al., 2007). Anxiolytic effects have also been reported in normal volunteers with high trait anxiety and in patients with anticipatory anxiety before surgery. However, in subjects with low trait anxiety and in non-stressful conditions, benzodiazepines may paradoxically increase anxiety and impair psychomotor performance.

Although useful for many anxiety disorders, benzodiazepines are not generally recommended for those with panic disorder as the long-term outcome is poor (NICE, 2007). Some patients report worse panic attacks after the benzodiazepines are stopped. Benzodiazepines are also useful at the start of SSRI treatment in OCD and as hypnotics in PTSD (NICE, 2005a,b). They should, however, be used at the lowest effective dose prescribed intermittently where possible and used for no longer than 2–4 weeks.

Choice of benzodiazepine in anxiety. The choice of benzodiazepine depends largely on pharmacokinetic characteristics. Potent benzodiazepines such as lorazepam and alprazolam (Table 28.2) have been widely used for anxiety disorders but are probably inappropriate. Both are rapidly eliminated and need to be taken several times a day. Declining blood concentrations may lead to interdose anxiety as the anxiolytic effect of each tablet wears off. The high potency of lorazepam (~10 times that of diazepam), and the fact that it is available only in 1 and 2.5 mg tablet strengths, has often led to excessive dosage. Similarly, alprazolam (~20 times more potent than diazepam) has often been used in excessive dosage, particularly in the USA. Such doses lead to adverse effects, a high probability of dependence and difficulties in withdrawal.

A slowly eliminated benzodiazepine such as diazepam is more appropriate in most cases. Diazepam has a rapid onset of action and its slow elimination ensures a steady blood concentration. Clonazepam, although long acting, is more potent than diazepam and in practice is often difficult to withdraw from. It is only indicated for epilepsy in the UK, but is commonly used as an anxiolytic.

Parenteral administration of lorazepam or diazepam may occasionally be indicated for severely agitated psychiatric patients.

Adverse effects. Adverse effects include drowsiness, lightheadedness, confusion, ataxia, amnesia, a paradoxical increase in aggression, an increased risk of falls and fractures in the elderly and an increased risk of road traffic accidents. They are also widely acknowledged as addictive and cause tolerance after more than 2–4 weeks of continuous use (Taylor et al., 2009). Respiratory depression is rare, but possible following high oral doses or parenteral use. Flumazenil, a benzodiazepine receptor antagonist, can reverse the effects of severe reactions but requires repeated dosing and close monitoring because of its short half-life.

Psychomotor and cognitive impairment. Although oversedation is not usually a problem in anxious patients, there is evidence that long-term use of benzodiazepines results in psychomotor impairment and has adverse effects on memory. Many patients on long-term benzodiazepines complain of poor memory and incidents of shoplifting have been attributed to memory lapses caused by benzodiazepine use. In elderly patients, the amnesic effects may falsely suggest the development of dementia. There is some evidence that benzodiazepines also inhibit the learning of alternative stress-coping strategies, such as behavioural treatments for agoraphobia. Additive effects with other CNS depressants including alcohol occur and may contribute to road traffic and other accidents.

Disinhibition, paradoxical effects. Occasionally, benzodiazepines produce paradoxical stimulant effects. These effects are most marked in anxious subjects and include excitement, increased anxiety, irritability and outbursts of rage. Violent behaviour has sometimes been attributed to disinhibition by benzodiazepines. This behaviour is normally suppressed by social restraints, fear or anxiety. Increased day-time anxiety can also occur with rapidly eliminated benzodiazepines and may be a withdrawal effect.

Affective reactions. Chronic use of benzodiazepines can aggravate depression, may sometimes provoke suicide attempts in impulsive patients, and can cause depression in patients with no previous history of depressive disorder. Aggravation of depression is a particular risk in anxious patients who often have mixed anxiety/depression. Benzodiazepines are taken alone or in combination with other drugs in 40% of self-poisoning incidents. Although relatively non-toxic in overdose, they can cause fatalities as a result of drug interactions and in those with respiratory disease.

Some patients on long-term benzodiazepines complain of 'emotional anaesthesia' with inability to experience either pleasure or distress. However, in some patients, benzodiazepines induce euphoria and they are occasionally used as drugs of abuse.

Dependence. The greatest drawback of chronic benzodiazepine use is the development of drug dependence. It is generally agreed that the regular use of therapeutic doses of benzodiazepines as hypnotics or anxiolytics for more than a few weeks (2–4 weeks) can give rise to dependence, with withdrawal symptoms on cessation of drug use in over 40% of patients. It is estimated that there are about 1 million long-term benzodiazepine users in the UK and many of these are likely to be dependent. People with substance misuse histories, anxious or 'passive-dependent' personalities seem to be most vulnerable to dependence and withdrawal symptoms. Such individuals make up a large proportion of anxious patients in psychiatric practice, are often described as suffering from 'chronic anxiety' and are the type of patient for whom benzodiazepines are most likely to be prescribed.

Such patients often continue to take benzodiazepines for many years because attempts at dosage reduction or drug withdrawal result in abstinence symptoms, which they are unable to tolerate. Nevertheless, these patients continue to suffer from anxiety symptoms despite continued benzodiazepine use, possibly because they have become tolerant to the anxiolytic effects and may also suffer from other adverse effects of long-term benzodiazepine use such as depression or psychomotor impairment.

Abuse. In the last 15 years, there has been much concern about benzodiazepine abuse. Some patients escalate their prescribed dosage and may obtain prescriptions from several doctors. These tend to be anxious patients with 'passive-dependent' personalities who may have a history of alcohol misuse; they often combine large doses of benzodiazepines with excessive alcohol consumption. In addition, a high proportion (30–90%) of illicit recreational drug abusers also use benzodiazepines and some take them as euphoriants in their own right. Recreational use of most benzodiazepines has been reported in various countries; in the UK, temazepam is most commonly abused. Exceedingly large doses (over 1 g) may be taken and sometimes injected intravenously. Benzodiazepines became easily available due to widespread prescribing which favoured their entrance into the illicit drug scene. Abusers become dependent and suffer the same adverse effects and withdrawal symptoms as prescribed dose users.

Benzodiazepine withdrawal. Many patients on long-term benzodiazepines seek help with drug withdrawal. Clinical experience shows that withdrawal is feasible in most patients if carried out with care. Abrupt withdrawal in dependent subjects is dangerous and can induce acute anxiety, psychosis or convulsions. However, gradual withdrawal, coupled where necessary with psychological treatments, can be successful in the majority of patients. The duration of withdrawal should be tailored to individual needs and may last many months. Dosage reductions may be of the order of 1–2 mg of diazepam per month. Even with slow dosage reduction, a variety of withdrawal symptoms may be experienced, including increased anxiety, insomnia, hypersensitivity to sensory stimuli, perceptual distortions, paraesthesia, muscle twitching, depression and many others (Box 28.2). These may last for many weeks, though diminishing in intensity, but occasionally the withdrawal syndrome is protracted for a year or more. Transfer to diazepam, because of its slow elimination and availability as a liquid and in low dosage forms, may be indicated for patients taking other benzodiazepines. Useful guidelines for benzodiazepine withdrawal are given in the British National Formulary and detailed withdrawal schedules are also available (Lader et al., 2009).

The eventual outcome does not appear to be influenced by dosage, type of benzodiazepine, duration of use, personality disorder, psychiatric history, age, severity of withdrawal symptoms or rate of withdrawal. Hence, benzodiazepine withdrawal is worth attempting in patients who are motivated to stop and most patients report that they feel better after withdrawal than when they were taking the benzodiazepine. Community pharmacists may be ideally suited to advise doctors and patients on the management of benzodiazepine withdrawal. Leading a benzodiazepine withdrawal clinic may also be a useful role for pharmacist or nurse prescribers.

Box 28.2 Some common benzodiazepine withdrawal symptoms

Symptoms common to anxiety states	Symptoms relatively specific to benzodiazepine withdrawal
Anxiety, panic	Perceptual distortions, sense of movement
Agoraphobia	Depersonalisation, derealisation
Insomnia, nightmares	Hallucinations
Depression, dysphoria	Distortion of body image
Excitability, restlessness	Tingling, numbness, altered sensation
Poor memory and concentration	Skin prickling (formication)
Dizziness, light-headedness	Sensory hypersensitivity
Weakness, 'jelly legs'	Muscle twitches, jerks
Tremor	Tinnitus
Muscle pain, stiffness	Psychosis[a]
Sweating, night sweats	Confusion, delirium[a]
Palpitations	Convulsions[a]
Blurred or double vision	
Gastro-intestinal and urinary symptoms	

[a]Usually only on rapid or abrupt withdrawal from high doses.

Drug interactions. In addition to the pharmacokinetic interactions listed earlier, benzodiazepines have additive effects with other CNS depressants. Combinations of benzodiazepines with alcohol, other hypnotics, sedative tricyclic antidepressants (TCAs), antihistamines or opioids can cause marked sedation and may lead to accidents, collapse or severe respiratory depression.

Pregnancy and lactation. The regular use of benzodiazepines is not recommended in pregnancy since the drugs are concentrated in fetal tissue where hepatic metabolism is minimal. They have been associated with an increased risk of oral clefts following first trimester exposure, a low birth weight, neonatal depression, feeding difficulties and withdrawal symptoms if given in late pregnancy. They also enter breast milk and may cause sedation, lethargy and weight loss in the infant. Long-acting benzodiazepines should particularly be avoided during lactation because of the potential for the infant to accumulate the drug. Short- to medium-acting benzodiazepines are occasionally used with enhanced monitoring of the infant.

Antidepressant drugs

Antidepressants can provide a long-term treatment option for those with an anxiety disorder. They are generally recommended for those who are unable to commit to or have not responded to psychological therapies. In addition, antidepressants are considered first-line treatment option either alone or in combination with CBT in patients suffering from OCD with moderate or severe impairment (NICE, 2005a). The number needed to treat (NNT) to see one benefit with antidepressants is around five in PTSD and GAD (NICE, 2005b, 2007).

The response rate to antidepressants in anxiety is often lower and takes longer than that seen in depression. Initial worsening of symptoms can occur and high therapeutic doses are often required to improve response (Baldwin et al., 2005).

Selective serotonin reuptake inhibitors. The selective serotonin reuptake inhibitors (SSRIs) have a broad anxiolytic effect and are considered the first drug options in GAD, panic disorder, social phobia, PTSD and OCD (NICE, 2005a,b, 2007; Baldwin et al., 2005). Individual SSRIs have varying licensed indications across the anxiety disorders but this does not necessarily mean others have no supporting evidence. Where more than one SSRI is licensed in a particular disorder it is not possible to conclude which SSRI would be more effective because of the lack of direct head to head trials. The SSRIs do differ in their interaction potential, side effect profile and ease of discontinuation. Initial worsening of symptoms is common when starting an SSRI in anxiety, so beginning with half the dose than that used in depression is recommended as is reassuring the patient that this is usually only experienced for the first few weeks of treatment. In view of these concerns, the NICE (2007) guidelines for GAD and panic disorder recommend that patients are reviewed every 2 weeks for the first 6 weeks of treatment to monitor for efficacy and tolerability.

Tricyclic antidepressants. Certain TCAs such as clomipramine, imipramine and amitriptyline are efficacious in some anxiety disorders. They are, however, associated with a greater burden of adverse reactions such as anticholinergic effects, hypotension and weight gain. Of particular concern is the TCAs' cardiac toxicity in overdose which relegates their use to second line following the failure of an SSRI. They should be avoided in any patient at risk of suicide or those with an underlying cardiac disease. TCAs commonly cause sedation which occasionally can prove useful in anxiety disorders. Clomipramine may also be slightly more effective in OCD compared with SSRIs.

Monoamine-oxidase inhibitors. The monoamine-oxidase inhibitors (MAOIs) are rarely used in practice because of their potential interactions with other medicines and tyramine in the diet. Moclobemide is a reversible MAOI, so causes fewer problematic interactions. Phenelzine and moclobemide are occasionally used by specialists in social phobia following the failure of an SSRI. Phenelzine is also recommended as a third-line treatment option in PTSD (NICE, 2005b).

Other antidepressants. The selective and noradrenaline reuptake inhibitor (SNRI) venlafaxine has some evidence to support its use in almost all the anxiety disorders, but it is only licensed for use in GAD and social phobia at a dose of 75 mg/day in the extended release form. Discontinuation symptoms are common following venlafaxine withdrawal and can be experienced after missing a single dose. Patients prescribed venlafaxine should be reminded of the importance of a slow withdrawal (over at least 4 weeks) when discontinuation is necessary. Venlafaxine can increase blood pressure at higher doses and so is contraindicated in patients with a very high risk of cardiac ventricular arrhythmia or uncontrolled hypertension. Duloxetine, another SNRI, is also licensed in GAD and can similarly increase blood pressure.

Mirtazapine, an α_2-adrenoreceptor antagonist, is recommended as an option for PTSD if patients do not wish to participate in trauma focused CBT (NICE, 2005b). Mirtazapine has a lower incidence of nausea, vomiting and sexual dysfunction than the SSRIs but can commonly cause weight gain and sedation.

No other antidepressants are routinely recommended for anxiety disorders, although some such as agomelatine are under clinical trials in anxiety to investigate potential future uses. To reduce the risk of symptoms returning patients should be advised to continue the antidepressant for at least 6 months following improvement of symptoms in GAD and panic disorder and for 12 months in PTSD, OCD and social phobia (NICE, 2005a, 2007; Baldwin et al., 2005). Those with an enduring and recurrent illness, however, may continue for many years, depending on the risk of relapse and severity of symptoms.

For a complete review of the antidepressants, including adverse effects and interactions, see Chapter 29.

Other medications occasionally used in anxiety

Hydroxyzine, a sedating antihistamine, is licensed for the short-term treatment of anxiety in adults at a dose of 50–100 mg four times a day. The clinical evidence only supports its use in GAD (for up to 4 weeks) if sedation is required. NICE supports the use of a sedating antihistamine in the immediate management of GAD but state they should not be used in panic disorders (NICE, 2007).

Antipsychotics have limited evidence and a high side effect burden when used in anxiety disorders. The first-generation (typical) antipsychotics are associated with movement disorders such as akathisia and tardive dyskinesia and so are rarely used in anxiety. The second-generation (atypical) antipsychotics are less likely to cause movement disorders but can have other physical health concerns. The majority of the evidence only supports antipsychotics (specifically risperidone and quetiapine) in combination with an SSRI in OCD in those who have failed to respond to the SSRI alone. Olanzapine augmentation has also been used in PTSD and social phobia.

Pregabalin is licensed for GAD and has shown an anxiolytic effect over placebo after 1 week in adults or 2 weeks in the elderly (Montgomery et al., 2008). Two short-term studies (4 and 6 weeks) suggest that pregabalin 400–600 mg/day is as effective but better tolerated than venlafaxine 75 mg/day XL or lorazepam 6 mg/day. Pregabalin, however, commonly causes dizziness, somnolence and nausea and is more expensive than other medication options in GAD and should be limited to specialist use only after other treatments have failed.

Buspirone, a $5HT_{1A}$ partial agonist, is licensed for short-term use in anxiety. It is not a benzodiazepine and so does not treat or prevent benzodiazepine withdrawal problems. In GAD, buspirone and other azapirones are superior to placebo in short-term studies (4–9 weeks) but less effective or acceptable than benzodiazepines (Chessick et al., 2006). NICE have said the evidence for buspirone in GAD is equivocal and, therefore, presumably not recommended (NICE, 2007). There is no evidence supporting buspirone in other anxiety disorders.

Table 28.3 Overview of the recommended drug treatments in anxiety

	Generalised anxiety disorder (GAD)	Panic disorder	Social phobia (social anxiety disorder)	Obsessive-compulsive disorder (OCD)	Post-traumatic stress disorder (PTSD)
Immediate management/ short-term treatment	Benzodiazepines (2–4 weeks only) Hydroxyzine	Benzodiazepines not recommended by NICE	Benzodiazepines (2–4 weeks only)	Benzodiazepines (only to counter initial worsening of symptoms with SSRIs)	Hypnotics may be considered for short-term use for insomnia
First-line pharmacotherapy[a]	SSRI Escitalopram Paroxetine Sertraline	SSRI Citalopram Escitalopram Paroxetine	SSRI Escitalopram Paroxetine	SSRI Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline	SSRI Paroxetine Sertraline
Other drug treatments with some supporting evidence	Buspirone Duloxetine Imipramine Pregabalin[c] Venlafaxine	Clomipramine[b] Imipramine[b] Mirtazapine Moclobemide Venlafaxine	Moclobemide[c] Phenelzine[c] Venlafaxine	Clomipramine Augmentation with quetiapine or risperidone[c]	Amitriptyline[c] Augmentation with olanzapine or risperidone[c] Imipramine Mirtazapine[b] Phenelzine[c] Venlafaxine

[a]The licensed SSRI is indicated but other SSRIs may also be beneficial.
[b]Unlicensed but recommended by NICE (2005a,b, 2007).
[c]Usually prescribed by mental health specialists only.

Propranolol and oxprenolol are both licensed for anxiety symptoms but are probably only useful for physical symptoms such as palpitations, tremor, sweating and shortness of breath. β-Blockers do not have sufficient evidence to support their inclusion in NICE guidelines but intriguingly small pilot studies indicate that giving an immediate course of propranolol following a traumatic event may prevent emerging PTSD (Pitman et al., 2002; Vaiva et al., 2003).

An overview of the recommended drug treatments in anxiety is provided in Table 28.3.

Case studies

Case 28.1

Mrs DW is a 32-year-old with a 10-year history of 'emotional problems'. These have largely been dealt with by her primary care doctor who has prescribed low dose TCAs for the last 3 years. Mrs DW's life is severely restricted by a number of rituals which she obsessively carries out. They include washing of sinks, baths and toilets, disinfection of kitchen surfaces, and vacuuming. These activities occupy up to 8 hours a day.

Current prescribed medication:
Diazepam 10 mg three times a day
Amitriptyline 25 mg twice a day
Both have been prescribed for 3 years

Mrs DW is concerned about possible addiction to her medication, as previous attempts to stop it have been unsuccessful. In addition, both she and her family feel that more can be achieved and are willing to work at solving the problems faced by Mrs DW.

Questions

1. Is this appropriate therapy for OCD and if not what would be a better first choice?
2. Suggest possible drug therapies for Mrs DW and indicate for how long they should be continued?
3. Providing an alternative therapy is commenced, recommend an appropriate scheme for withdrawal of the diazepam.

Answers

1. Benzodiazepines are not recommended in OCD. First choice is cognitive behaviour therapy or an SSRI.
2. Potential drug treatments include high dose SSRIs or clomipramine. Augmentation strategies (e.g. antipsychotics) would also be a possibility. Treatment may need to be continued for a year before a dose reduction is tried.
3. As Mrs DW is on a dose of 30 mg diazepam daily, it would be appropriate to consider reducing the diazepam by 2 mg/day every 1–2 weeks until 20 mg/day dose is reached. Further reductions may need to be 1 mg every 1–2 weeks until stopped. Longer intervals between dose reduction may be necessary as the dose reduces towards zero. Patient may wish to adopt faster withdrawal and accept the consequences. All patients should be monitored for increased anxiety, restlessness, agitation, etc., and may need slow withdrawal.

Case 28.2

Mrs AB, a previously well 30-year-old woman, had been treated with paroxetine 40 mg daily for anxiety/depression which had been precipitated by a traumatic marriage break-up. After taking paroxetine for 18 months, Mrs AB's problems had

mainly resolved and she was feeling well. She decided that she no longer needed the drug and stopped taking it. Within 3 days her anxiety/depression returned with insomnia and nightmares. Her mood lowered and she became irritable and found herself weeping for no reason. A week later she returned to her doctor complaining of these symptoms as well as depersonalisation and strange electric shock sensations. The doctor thought the original depression had returned and reinstated paroxetine which cleared up her symptoms within a few days.

Questions

1. What alternative explanation could there be for Mrs AB's symptoms and what other decision could the doctor have made?
2. What would be a suitable withdrawal schedule for her paroxetine?

Answers

1. All antidepressants can cause a discontinuation reaction. Mrs AB's symptoms were typical of SSRI withdrawal. This occurs most commonly with paroxetine, perhaps partly due to its rapid rate of elimination (half-life 21 h in chronic users).
2. In this previously well lady no longer under marital stress, the doctor, after reinstating paroxetine, could have supplied a gradual tapering schedule of drug withdrawal, that is, reducing the dose by 10 mg/week, aiming to withdrawal in 4 weeks.

Case 28.3

Mr SB is a 22-year-old soldier. He has recently returned from his second active tour where he was injured by a roadside bomb. Two of his squad were killed in the same blast and, although his physical injuries healed quickly, he has persistent and intense episodes of panic and flashbacks. He is especially aroused at night and has great difficulty getting to sleep. An initial prescription of an SSRI has proved ineffective and he is currently on the waiting list for psychological therapies.

Question

1. What alternative drug treatment may be appropriate?

Answer

1. A sedating antidepressant such as mirtazapine or amitriptyline may be appropriate, ensuring adequate duration of therapy and effective dose. A short cause of a benzodiazepine may prove useful but for no longer than 2–4 weeks. Alternatively, augmenting the antidepressant with a sedating antipsychotic such as olanzapine may be useful. For prolonged symptom treatment and relapse prevention it is likely that the patient will need to fully engage with psychological therapies.

Case 28.4

Ms AC is a 32-year-old personal assistant to a director of a leading investment company. She has recently been promoted to this role and is now expected to entertain potential clients by dining out with the director at local restaurants. She has always preferred eating alone in the comfort of her own home and the thought of eating in public while promoting the business fills her with dread, which brings on palpitations and shortness of breath.

Questions

1. What drug therapy is available which may provide some immediate relief of her anxiety symptoms?
2. What would be an appropriate choice of treatment for long-term control and prevention of symptoms?

Answers

1. β-Blockers such as propranolol may help with the shortness of breath and palpitations but will not treat the fear and dread. Benzodiazepines may be appropriate but may affect her performance and cause other adverse reactions.
2. For long-term control, a course of cognitive behavioural therapy including exposure techniques is appropriate or treatment with an SSRI such as escitalopram.

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Further reading

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Useful resources

The British Association for Behavioural and Cognitive Psychotherapies has a list of therapists, training resources and general information for the public.
www.babcp.com
Anxiety UK: a national charity for anyone affected by an anxiety disorder.
www.anxietyuk.org.uk
No Panic: a national charity offering support for suffers of panic attacks, phobias, Obsessive Compulsive Disorder and Generalised Anxiety Disorder.
www.nopanic.org.uk

29 Affective disorders

J. P. Pratt

Key points

- Diagnosis should be made using standardised criteria, for example, DSM IV, ICD 10.
- Target symptoms should be recorded and response to treatment monitored against these symptoms.
- In patients with depression of mild severity, non-pharmacological strategies should be considered as first-line intervention.
- The evidence base for determining the use of a particular antidepressant in an individual patient does not exist. For most patients, when an antidepressant is indicated, a generic SSRI should be considered as a first-line treatment option.
- Currently, all antidepressants are considered equally effective but differ in their side effect profile, toxicity in overdose, need for dose titration and monitoring.
- In the absence of a previous response or contraindication, antidepressant choice should be guided by evidence-based clinical guidelines and the clinician and the patient's perception of the risks and benefits of available options. Resource implications should not be ignored.
- Emerging evidence and a greater understanding of the clinical application of pharmacogenomics may increase the ability to individualise treatments in the future.
- Comprehensive assessment, accurate diagnosis, adequate duration of pharmacotherapy and involvement of the patient in the treatment regimen are the cornerstones of effective management of affective disorders.
- Valproate, antipsychotics and benzodiazepines, sometimes in combination, are the treatments of choice in acute mania.
- Either lithium, valproate or specific antipsychotics may be considered to be the first-line prophylactic agent of choice in bipolar I disorder.

This chapter focuses on affective disorders in adults. The issues of affective disorders in children and adolescents are more complex and beyond the scope of this section.

The central feature of an affective disorder is an alteration in mood. The most common presentation is that of a low mood or depression. Less commonly, the mood may become high or elated, as in mania.

Classification

Depression

The term 'depression' can in itself be misleading. Everyone in the normal course of daily life will experience alterations in mood. Depressed mood in this context does not represent a disorder or illness; in fact, lowered mood as a response to the ups and downs of living is considered normal and termed sadness or unhappiness. Sometimes clinical depression may present in a mild form, so it is important to differentiate this from normal unhappiness.

Mania

If the mood becomes elated or irritable this may be a symptom of mania. The term 'mania' is used to describe severe cases, frequently associated with psychotic symptoms. Hypomania describes a less severe form of the disorder. In clinical practice, this distinction often becomes blurred, with hypomania being seen as patients develop, or recover from, mania.

Bipolar and unipolar disorders

If a patient develops one or more severe episodes of a mood disorder which includes a manic episode, the condition may be termed a bipolar disorder. The existence of repeated manic episodes alone is sufficient to be termed a bipolar disorder. The disorder can be further categorised as bipolar I, where full-blown episodes of mania occur, and bipolar II, where depressive episodes are interspersed with less severe hypomanic episodes. The term 'manic-depressive' is now outdated. Rapid cycling describes the existence of four or more episodes within a year. Unipolar mood disorder is used to describe single episodes of depression.

Epidemiology

Differences in diagnosis, particularly of depression, make it difficult to estimate the true incidence of affective disorders. The lifetime risk of developing a bipolar I disorder is said to be about 1% (0.3–1.5%). An accurate estimate for the more broadly defined bipolar II disorder is more difficult and it may be much more common, with studies suggesting a lifetime prevalence of between 0.2% and 10.9%. The incidence of bipolar I is generally reported to be the same for both men and women, whereas some studies suggest that bipolar II may be slightly more common in women. By comparison, the overall incidence of depression is much higher and there does appear to be a significant difference between the sexes. Studies from America and Europe, using standard assessment tools, found a lifetime prevalence of between 16% and 17%,

with a 6-month prevalence of about 6%. Higher rates are consistently found in women but social, economic and ethnic factors are also likely to be influential. Although depression may occur at any age, including early childhood, it is estimated that the average age of onset of depression is in the mid-20s. Some earlier studies found the incidence and prevalence of depression in women peaking at the age of 35–45 years. In bipolar disorder, an earlier age of onset is suggested, perhaps in late adolescence, with most people experiencing their first episodes before 30 years of age.

Aetiology

Like most psychiatric disorders, the causes of affective disorders remain unknown. In depression, it is likely that genetic, hormonal, biochemical, environmental and social factors all have some role in determining an individual's susceptibility to developing the disorder, with major life events sometimes, but not always, acting as a precipitant for a particular episode. Although pharmacological treatments are clearly effective, there is no simple relationship between biochemical abnormalities and affective disorders.

Genetic causes

In depression, one theory suggests that a variant of the gene responsible for encoding the serotonin transporter protein could account for early childhood experiences being translated into an increased risk of depression through stress sensitivity in adulthood. In bipolar disorder, some genetic linkage has been proposed, but a precise marker remains elusive.

The incidence of affective disorder in first-degree relatives of someone with severe depression may be about 20%, which is almost three times the risk for relatives in control groups. Comparisons of the risk of affective disorder in the children of both parents with an affective disorder show a four times greater risk, and the risk is doubled in children with one parent with an affective disorder. Studies looking at twins have found fairly strong evidence for a genetic factor. Evidence of a genetic link has also been found in studies of children from parents with affective disorder who were adopted by healthy parents. A higher incidence of affective disorder was found in the biological parents of adopted children with affective disorder than in the adoptive parents.

Environmental factors

Although environmental stresses can often be identified prior to an episode of mania or depression, a causal relationship between a major event in someone's life and the development of an affective disorder has not been firmly established. It may be that life events described as 'threatening' are more likely to be associated with depression. The lack of prospective studies makes it difficult to interpret data linking early life events, such as loss of a parent, to the development of an affective disorder. The fact that specific environmental stresses have not been identified should not lead to the conclusion that the environment or lifestyle is irrelevant to the course or development of affective disorders. Employment, higher socio-economic status and the existence of a close and confiding relationship have been consistently noted to offer some protection against the development of an episode.

Biochemical factors

In its simplistic form, the biochemical theory of depression postulates a deficiency of neurotransmitter amines in certain areas of the brain. This theory has been developed to suggest that receptor sensitivity changes may be important. Alternative propositions suggest a central role of acetylcholine arising from dysregulation of the cholinergic and noradrenergic neurotransmitter systems. Although many neurotransmitters may be implicated, the theory focuses on an involvement of the neurotransmitters noradrenaline (norepinephrine), serotonin (5-hydroxytryptamine) and dopamine. This theory emerged from the findings that both monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants appeared to increase neurotransmitter amines, particularly noradrenaline (norepinephrine), at important sites in the brain. When it was found that reserpine, previously used as an antihypertensive, caused both a depletion of neurotransmitter and also induced depression, this was taken as an apparent confirmation of the theory.

Although less attention has been paid to dopaminergic activity, some studies have found reduced activity in depressed patients, and an overactivity has been postulated in mania.

The concept of noradrenergic (norepinephrinergic) and serotonergic forms of depression has not gained widespread support, and there is no justification in measuring the activity of neurotransmitters such as noradrenaline (norepinephrine) or serotonin metabolites in routine clinical practice.

Endocrine factors

The endocrine system, particularly the hypothalamic-pituitary-adrenal (HPA) axis and the hypothalamic-pituitary-thyroid (HPT) axis, is felt to be implicated in the development of affective disorders. Some endocrine disorders such as hypothyroidism and Cushing's syndrome have also been associated with changes in mood. People with depression have been found to have increased cortisol levels, which also supported the proposition that mood disorders may be linked to dysfunction within the HPA axis. This led to the development of a dexamethasone suppression test for depression in the 1970s. The relationship between cortisol and symptoms of depression is complex which severely limits the clinical utility of such a test.

Physical illness and side effects of medication

Disorders of mood, particularly depression, have been associated with several types of medication and a number of physical illnesses (Box 29.1). Depression can affect the outcome in people with a range of physical problems. An increase in death rates has been found in those patients with co-morbid depression.

Box 29.1 Drugs and physical illnesses implicated in disorders of mood

Drugs
Analgesics
Antidepressants
Antihypertensives
Anticonvulsants
Opiate withdrawal
Amfetamine withdrawal
Benzodiazepine withdrawal
Antipsychotics
Benzodiazepines
Antiparkinsonism agents
Steroids
Oral contraceptives

Physical illness
Viral illness
Carcinoma
Neurological disorders
Diabetes
Multiple sclerosis
Thyroid disease
Addison's disease
Systemic lupus erythematosus
Pernicious anaemia

Box 29.2 ICD 10 diagnostic criteria for bipolar affective disorder (WHO, 1992)

Characterised by repeated (at least two) episodes in which the patient's mood and activity levels are significantly disturbed. This disturbance consisting on some occasions of an elevation in mood and increased energy and activity (mania or hypomania), and on others of a lowering of mood and decreased energy and activity (depression).

Manic episodes usually begin abruptly and last for between 2 weeks and 4–6 months (median 4 months). Depression tends to last longer (median about 6 months). Episodes of both kinds often follow stressful life events or other mental trauma, but the presence of such stress is not essential for the diagnosis.

Clinical manifestations

Depression

A low mood is the central feature of depression. This is often accompanied by a loss of interest or pleasure in normally enjoyable activities. Thinking is pessimistic and in some cases suicidal. A depressed person may complain they have little or no energy. In severe cases, psychotic symptoms such as mood congruent hallucination or delusion may be present. Anxiety or agitation frequently accompany the disorder, and the so-called biological features of sleep disturbances, weight loss and loss of appetite are often present. Depressed people typically complain of somatic symptoms, particularly gastric problems, and non-specific aches are common. Sexual drive is often reduced, and some people may lose interest in sex altogether. In some cases, the biological symptoms are reversed and excessive eating and sleeping may occur. In contrast to agitation, psychomotor retardation may be a presenting feature.

Bipolar disorder

Standardised diagnostic criteria vary. For an ICD 10 diagnosis of bipolar disorder, at least two mood episodes must occur, one of which must be manic or hypomanic (Box 29.2). According to DSM IV, at least one episode of mania must have occurred for a diagnosis of bipolar I disorder to be made; depression may also occur, but it is not essential.

Mania

In mania, the mood is described as elated or irritable and the accompanying overactivity is usually unproductive. Disinhibition may result in excessive spending sprees, inappropriate sexual activity and other high-risk behaviours. Driving may be particularly dangerous. Manic people may describe their thoughts as racing, with ideas rapidly changing from one topic to another. Speech may be very rapid with frequent punning and rhyming. Ideas may become grandiose with patients embarking on fantastic projects which lead nowhere and inevitably are left incomplete and disjointed. Clothing is usually flamboyant, and if make-up is worn it is usually excessive and involves bright colours.

Severity

The severity of the disorder may vary from mild through moderate to severe. In most circumstances, it would be inappropriate for people with mild forms of the disorders to be seen by specialist services and treated with pharmacotherapy. In the absence of a risk of serious self-harm, people with less severe forms of the disorder should be treated by the primary health care team. Guidelines advise that a stepwise approach is taken on the management of depression, with increasing evidence supporting the fact that antidepressant therapy is more likely to be effective in the more severe episodes (NICE, 2009).

If left untreated, it is important to remember that affective disorders carry a risk of mortality. In addition to suicidal attempts by someone who is depressed, the lack of self-care and physical exhaustion resulting from mania may be life-threatening. The social and financial consequences can have a devastating effect on both the patient with mania or hypomania and their family. Depression may also contribute to exacerbation of physical problems such as increased pain and worsening outcomes from cardiac disease (Nicholson et al., 2006).

Investigations

There are no universally accepted biochemical or genetic tests which will confirm the presence of an affective disorder. Various rating scales have been developed that may help to

demonstrate the severity of depressive disorder or distinguish a predominantly anxious patient from a depressed patient. Within the limits of our current understanding of the technology, biochemical or genetic tests are unlikely to be helpful in determining the treatment plan or management of affective disorders.

In the UK, mental and behavioural disorders are commonly classified using the *International Classification of Diseases*, ICD 10 (WHO, 1992).The American Psychiatric Association has developed a precise system of diagnosis, based on the description of symptoms in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM IV TR), now in its revised, fourth edition (American Psychiatric Association, 2000).

A systematic approach to the diagnosis of affective disorders is important when considering the effectiveness of medication. Most new clinical trials for antidepressants or antipsychotics require a DSM diagnosis as an entry criterion. In the UK, the ICD 10 classification is commonly used, with the severity of depression determined by the presence of the number of symptoms (see Boxes 29.2 and 29.3). More recently, use of the symptom count as a single factor upon which to base treatment decisions has been cautioned against (NICE, 2009). Account should also be taken of the extent of impairment and disability associated with depression.

National guidelines provide a sound framework for the management of depression (NICE, 2009) and bipolar disorder (NICE, 2006). It is important that people with depression are identified. A simple screening process for the presence of depression could involve asking the patient two questions about their mood and interest. For example, the patient could be asked 'During the last month, have you often been bothered by feeling down, depressed or hopeless?' and 'During the last month, have you often been bothered by having little interest or pleasure in doing things?'. If the answer to either question is 'no', it is unlikely the patient will be considered to have a depressive disorder. Patients who answer 'yes' warrant further investigation.

Identification of target symptoms may be useful in evaluating the response to treatment. In routine clinical practice, antidepressant medication should not generally be used to treat patients with mild depression. Non-pharmacological strategies are preferable in this group.

Box 29.3 ICD 10 diagnostic criteria for a depressive episode (WHO, 1992)

Usual symptoms

Depressed mood, loss of interest and enjoyment, and reduced energy leading to increased fatiguability and diminished activity

Common symptoms

Reduced concentration and attention
Reduced self-esteem and self-confidence
Ideas of guilt and unworthiness (even in a mild type of episode)
Bleak and pessimistic views of the future
Ideas or acts of self-harm or suicide
Disturbed sleep
Diminished appetite

In a depressive episode, the mood varies little from day to day and is often unresponsive to circumstances, yet may show characteristic diurnal variation as the day goes on. The clinical picture shows marked individual variations, and atypical presentations are particularly common in adolescence. In some cases, anxiety, distress and motor agitation may be more prominent at times than the depression.

For depressive episodes of all grades of severity, a duration of 2 weeks is usually required for diagnosis, but shorter periods may be reasonable if symptoms are unusually severe and of rapid onset.

Mild depressive episode: For at least 2 weeks, at least two of the usual symptoms of a depressive episode plus at least two of the common symptoms listed above.

An individual with a mild depressive episode is usually distressed by the symptoms and has some difficulty in continuing with ordinary work and social activities, but will probably not cease to function completely.

Moderate depressive episode: For at least 2 weeks, at least two or three of the usual symptoms of a depressive episode plus at least three (preferably four) of the common symptoms listed above.

An individual with moderately severe depressive episode will have these symptoms to a marked degree, but this is not essential if a particularly wide variety of symptoms is present overall. They will usually have considerable difficulties in continuing with social, work or domestic activities.

Severe depressive episode: For at least 2 weeks, all three of the usual symptoms of a depressive episode plus at least four of the common symptoms listed above, some of which should be of severe intensity.

An individual with severe depressive episode may be unable or unwilling to describe many symptoms in detail, but an overall grading of severe may still be justified. They will usually show considerable distress or agitation, unless retardation is a marked feature. Loss of self-esteem or feelings of uselessness or guilt are likely to be prominent. Suicide is a distinct danger, particularly in severe cases.

Rating scales

Various rating scales can be used to assist with the assessment of the severity of the disorder. Two of the more commonly used rating scales are the Beck Depression Inventory and the Hamilton Depression Rating Scale.

Beck Depression Inventory

This is a self-reporting scale looking at 21 depressive symptoms. The subject is asked to read a series of statements and mark on a scale of 1–4 how severe their symptoms are. The higher the score, the more severely depressed a person may be.

Hamilton Depression Rating Scale

This rating scale is used by a health care professional at the end of an interview to rate the severity of depression.

Treatment

The aim of treatment is to prevent harm and to relieve distress or to be prophylactic. It is important to differentiate symptoms of the disorder from the premorbid personality. In general, the drugs which are used to control the symptoms of mania are not specifically antimanic. These agents are also used to treat other disorders. This means the diagnosis will primarily influence the way in which these drugs are used rather than the choice of drug per se. Clinicians should be aware of the licensed indication of treatments, so that any 'off label' use is done knowingly and in line with current best practice.

In the treatment of depression, all the antidepressants currently available in the UK may be considered to be equally effective. There is increasing evidence that patients with more severe episodes of depression are more likely to respond to antidepressant drugs, as opposed to placebo, than those with less severe forms of the disorder (Fournier et al., 2010). There is also some evidence to suggest that sertraline and escitalopram may have a more favourably risk/benefit profile than some other antidepressants (Cipriani et al., 2009). However, it is unclear if the magnitude of the difference between these drugs is sufficient to direct treatment choice for most depressed patients.

There are some generalisations which may help individualise the choice of antidepressant. Females may have a poorer tolerance of migraine than males and tricyclic antidepressants are less well tolerated and more likely to be toxic in overdose than the selective serotonin reuptake inhibitors (SSRIs). Patients may prefer one drug over another based on their past experience of benefit or side effects. Overall, the major difference between antidepressant agents is in their side effect profile and toxicity in overdose. There can also be significant variations in the costs of different agents.

Treatment of depression

In moderate and severe depression, pharmacological intervention is important, but this should never be considered in isolation from the social, cultural and environmental influences on the patient. Non-pharmacological therapies are effective and in mild depression they are considered preferable to drug treatment. Non-drug treatments and antidepressant medication are not mutually exclusive and in some cases it is preferable to use both in combination.

Drug treatment

Despite the availability of many new antidepressants, the therapeutic effectiveness of these agents has changed little since the discovery of the antidepressant properties of drugs used to prevent migraine in the late 1950s. Further research may reveal differences between antidepressants. Advances in the clinical utility of pharmacogenomics may, in time, provide clinicians with a tool to individualise pharmacotherapy. Overall, the SSRI antidepressants appear to be better tolerated than tricyclics and their safety profile in overdose should be an important consideration for use.

A strong response to placebo is found in most of the studies of antidepressants. Tolerability is, therefore, an important factor in the choice of drug; patients who are unable to tolerate the side effects of antidepressants are likely to discontinue these drugs. Antidepressants should be taken in adequate doses for some 4–6 weeks, and up to 12 weeks in older people, to achieve a full response. Following a single episode of depression, treatment should be continued for 6 months, at the same dose at which the patient achieved remission, before attempting withdrawal. In patients experiencing multiple episodes of depression, treatment should be continued for longer periods (2 years).

Withdrawal of antidepressants should normally be undertaken gradually. Following abrupt discontinuation, patients may experience symptoms of withdrawal that include gastro-intestinal symptoms, together with headache, giddiness, sweating, shaking and insomnia. In addition, extrapyramidal reactions may be associated with abrupt withdrawal from some of the SSRI antidepressants. Following successful treatment, antidepressants should be gradually reduced over a period of 4 weeks. This period should be increased if patients experience problems, or where medication has been given for extended periods.

Generally, the long half-life of fluoxetine enables the drug to be stopped without the need for tapering from the standard antidepressant dose of 20 mg. Patients taking MAOIs may experience psychomotor agitation following discontinuation.

As patients do not experience the craving typically associated with drugs of addiction, most health care professionals do not class antidepressants as addictive. Patients should be warned that there is a risk of problems with abrupt discontinuation, but use of emotive words like addiction or dependence is best avoided. In moderate or severe depression, the balance of risks and benefits is usually in favour of using antidepressants. Occasionally, some patients report that they have become dependent on their antidepressants and feel unable to stop taking them. These concerns should not be dismissed lightly, but the focus of discussion with the patient should be on the overall risks and benefits of the treatment in the context of their individual circumstances.

As discussed earlier, there is no strong evidence for the existence of a particular biochemical subtype of depression. However, some patients do respond better to particular antidepressants. This has led to the widely held view that previous response to treatment is a strong indication to use that particular drug in the treatment of a future episode.

In addition to previous response, the other important considerations to take into account when selecting an antidepressant are side effects, contraindications, toxicity in overdose, patient preference and clinician familiarity.

Generally speaking, the older drugs have a poorer side effect (Barbui et al., 2001; Geddes et al., 2002) and toxicity profile than the more recently introduced agents. Traditionally, the antidepressant drugs are categorised by their chemical structure, for example, tricyclic, or their predominant pharmacological action, for example, MAOI, SSRI.

Tricyclic antidepressants. A greater understanding of the pharmacology of antidepressants has given much support to the so-called biochemical theory of depression. Although substantial data on the pharmacological effects of the tricyclic antidepressants exist, it is still not clear how the drugs relieve the symptoms of depression. This is an important point often overlooked when discussing the issue with patients. The notion that depression is a simple lack of, or imbalance of, chemicals has little basis in fact. It merely provides a useful framework from which to discuss the benefits and harms of antidepressants.

It was thought originally that the primary effect of these drugs was related to their ability to block the reuptake of noradrenaline (norepinephrine) and/or 5HT following their release and action as neurotransmitters. As this effect occurs some weeks before the antidepressant response, clearly this is not the whole story. Following chronic administration, further biochemical changes take place, particularly with pre- and postsynaptic receptor sensitivity. Reduction of presynaptic α_2-inhibitory receptor sensitivity occurs, and this increases the production of noradrenaline (norepinephrine). Other effects which may be relevant include an increase in α_1 and β_1 receptor sensitivity. It is now felt that these receptor changes in the cerebral cortex and hippocampus may be more relevant to the antidepressant response than simple reuptake inhibition.

There are a number of tricyclic antidepressants in current clinical use. The basic chemical structures of these compounds are similar but there are differences between them. All the tricyclic antidepressants block the reuptake of noradrenaline (norepinephrine) and 5HT to a greater or lesser degree. In view of the risks associated with cardiac abnormalities, an ECG is advised prior to initiating treatment with this group of drugs.

Imipramine. The antidepressant effect of imipramine was demonstrated around 50 years ago and it has been widely prescribed in subsequent years. Although imipramine is less sedating than other tricyclic drugs, some patients may still experience problems. As well as cardiovascular problems, significant antimuscarinic effects such as dry mouth, blurred vision and constipation occur. Females tend to tolerate imipramine less well than males. At one time it was felt to be important that the drug should be prescribed at the full therapeutic dose. Recent analysis of clinical trials suggests this is not the case. If patients respond to lower doses, there is no rationale for increasing the dose further. Tolerance may develop to some of the unpleasant side effects, and this may be facilitated by starting with a lower dose of the drug and gradually increasing the dose over a week.

In addition to the unpleasant side effect profile, imipramine is toxic following overdose. Considering that the drug is used to treat a disorder which involves suicide, this relative lack of safety is an important disadvantage. As with all tricyclics, imipramine should only be used in circumstances where cardiac tolerability can be assured and intentional overdose can be prevented. Imipramine is metabolised by demethylation to an active metabolite, desipramine. Both the parent drug and its metabolite have long half-lives, of 9–20 and 10–35 h, respectively, that permit single daily dosing.

Amitriptyline. Also developed in the late 1950s, amitriptyline has a similar poor side effect and toxicity profile to imipramine but is more sedative. Additional sedative properties are sometimes considered an advantage in selected patients. The widespread use of low doses of amitriptyline commonly relate to its use in the management of pain, rather than depressive disorders. Like imipramine, the drug and its active metabolite (nortriptyline) have long half-lives, of 9–46 and 18–56 h, respectively. The dose range is similar to imipramine.

Clomipramine. This was one of the first antidepressants found to be a potent 5HT reuptake inhibitor. Some clinicians believed that the drug was more effective than other antidepressants, but little evidence exists to support this anecdotal view. However, the effects on 5HT may explain the benefit of this drug in the management of obsessive-compulsive disorder.

Data from a fatal toxicity index (Buckley and McManus, 2002) show clomipramine to have a lower than expected toxicity index. It is unlikely that clomipramine is inherently less toxic than other antidepressants, so this finding could be accounted for by other factors, such as the relatively high rate of prescribing in non-depressive states.

Dosulepin. Guidelines for the management of depression (NICE, 2009) advise that dosulepin should not be prescribed because of the risks associated with cardiac problems and toxicity in overdose compared to other available treatments.

Doxepin. Doxepin has similar effects and side effects to the traditional tricyclics. Limited evidence suggests that it may have fewer cardiac effects in patients with pre-existing cardiac disease than other traditional tricyclics. However, direct comparisons do not exist and a newer, alternative agent should be considered in preference to doxepin in patients with cardiac disease.

Lofepramine. Although desipramine is a metabolite of lofepramine, the latter should not be considered purely as a prodrug. Important differences exist between lofepramine and the other traditional tricyclics. Antimuscarinic effects do occur with lofepramine, but these are less severe than with other tricyclics. In addition, despite being metabolised to desipramine, lofepramine is significantly safer in overdose than the traditional agents. This may be due to lofepramine antagonising the cardiac effects of desipramine. Lofepramine does not have a significant sedative effect, which may be an advantage in some patients, but in others the lack of sedation may be seen as a disadvantage. Some patients may complain of an alerting effect from lofepramine, particularly if the majority of the dose is given at bedtime. Despite a few reports of hepatic problems, given the favourable side effect profile and low toxicity in overdose, lofepramine may be considered as a reasonable option if an SSRI is ineffective or not tolerated.

Nortriptyline. Nortriptyline is the major metabolite of amitriptyline, but appears to have little effect on blood pressure. Nortriptyline shares many of the properties of the traditional tricyclic antidepressants.

Trimipramine. This is a particularly sedative tricyclic antidepressant with few differences from the rest of the traditional tricyclics.

Monoamine oxidase inhibitors. Two types of MAOI are available: the traditional MAOIs, which are both non-selective and irreversible, and moclobemide, which is a selective reversible inhibitor of monoamine oxidase type A (RIMA). In clinical

practice, the traditional MAOIs are not widely prescribed. If patients are able to tolerate adequate doses, they are effective antidepressants, particularly in patients with atypical symptoms of depression. Due to the potential for drug and food interactions, MAOIs should be reserved for use in situations where a first-line SSRI antidepressant has failed. The potential for MAOIs to interact with other drugs and tyramine-containing foods has been well known since the 1960s. It is important that patients are made aware of the dietary restrictions and potential for serious drug interactions. These can be found in standard texts such as the British National Formulary.

Although the inhibitory effect of these drugs on monoamine oxidase is well understood, as with other antidepressants it is still not clear exactly how the MAOIs exert their antidepressant effect. MAOIs inhibit the enzymes responsible for the oxidation of noradrenaline (norepinephrine), 5HT and other biogenic amines. Two forms of monoamine oxidase have been found to exist, MAO-A and MAO-B. The traditional MAOIs are all non-selective and inhibit both forms of the enzyme.

Inhibition of MAO-A is thought to be responsible for the antidepressant effects. It is also responsible for metabolising tyramine and producing the cheese interaction. Moclobemide is an antidepressant that acts as a reversible inhibitor of MAO-A. As tyramine is metabolised by both forms of the enzyme, if tyramine-containing foods are consumed, tyramine is metabolised by MAO-B enzymes as well as being able to reverse the inhibition of MAO-A. Unless very large quantities of tyramine are ingested, this appears to prevent the typical hypertensive reaction seen with conventional MAOIs and tyramine-containing foods.

Traditional MAOIs. The traditional MAOIs and moclobemide have little anticholinergic effect. Nevertheless, some patients do experience dry mouth, constipation and urinary retention. In contrast to the hypertension which follows the interaction of tyramine-rich foods with the traditional MAOIs, these drugs are liable to cause postural hypotension as a side effect. This side effect may be particularly problematic with phenelzine and may prevent adequate dosages being achieved.

Tranylcypromine. Tranylcypromine has a structure that closely resembles amfetamine. It has a significant stimulant effect, and because of this could be more likely to give rise to problems around dependence. Unlike the other MAOIs, it does not irreversibly inhibit monoamine oxidase, which is said to recover some 5 days after withdrawal of the drug. Even so, the precautions associated with the MAOIs must still be continued for 2 weeks after discontinuing the drug. Due to the amfetamine-like alerting effect of tranylcypromine, the last dose should not be given after about 3 p.m. The risk of severe interaction is also said to be greater with tranylcypromine than with other MAOIs.

Phenelzine. Phenelzine has a hydrazine structure and because hydrazines have been associated with hepatocellular jaundice, it is recommended that phenelzine should be avoided in patients with hepatic impairment or abnormal liver function tests.

Reversible inhibitors of monoamine oxidase. Although moclobemide is an effective antidepressant, with less propensity for interactions with tyramine-rich foods, caution should still be exercised as other drug interactions do occur. It could be considered, after a suitable wash-out period, as an option if a first- or second-line SSRI is ineffective.

Selective serotonin reuptake inhibitors. These agents were developed in an attempt to reduce some of the problems associated with the tricyclic antidepressants. Overall, the SSRIs are better tolerated by most patients and coupled with the fact that they are considerably less toxic in overdose; this means that they should be the first-line choice for the pharmacological management of moderate or severe depression (NICE, 2009). As generic versions of the drugs are available, the financial impact of using SSRIs first line has reduced in recent years. The SSRIs have a broadly similar range of side effects, but there are variations in the intensity or duration. The degree of specificity for serotonin reuptake differs between the SSRIs, but this does not correlate with clinical efficacy. If given in adequate doses for an adequate period of time, all the drugs in this class appear to be equally effective.

They do not appear to be significantly more or less effective than traditional tricyclics. They are, however, better tolerated than tricyclics and importantly much less toxic if taken in overdose. There are differences between SSRI's effect on the cytochrome P450 isoenzyme system. This may also be an important factor to consider when individualising treatment.

Fluvoxamine. Although patients experience few antimuscarinic side effects, other problems related to serotonergic enhancement such as nausea, headache and nervousness have been reported.

Fluoxetine. The main difference between fluoxetine and the other SSRIs is the long half-lives of both the parent drug and its primary active metabolite, desmethylfluoxetine. In the initial stages of treatment, some patients may experience a greater feeling of nervousness with fluoxetine than with the other SSRIs, but in most cases tolerance to this develops. The long half-life of fluoxetine and its major metabolite is a problem if severe side effects develop. In other situations, the long half-life means that the risks of discontinuation syndrome is reduced. Formulations of fluoxetine that can be taken on a weekly basis are available in some parts of the world.

Paroxetine. Although all the SSRIs have been reported to cause extrapyramidal-type movements, paroxetine appears to be more commonly implicated. The problem may be particularly severe following abrupt discontinuation of high doses.

Sertraline. Like the other SSRIs, sertraline is an effective antidepressant. Although doses of up to 200 mg have been used, doses of 150 mg and above should not be given for longer than 8 weeks.

Citalopram. The efficacy and side effect profile of citalopram appear similar to the other agents but, like sertraline, the reduced propensity for interactions with drugs metabolised by the cyctochrome P450 2D6 isoenzyme may be an advantage in some cases.

Escitalopram. Escitalopram is thought to be the active *S* enantiomer of citalopram, which is a racemic mixture of *R*- and *S*-citalopram. The use of escitalopram has been advocated on the basis that the *R* enantiomer has no antidepressant effect, and may even counteract some of the antidepressant effects of the *S* enantiomer of escitalopram.

Lithium. Lithium does have antidepressant properties but will be discussed in more detail in the antimanic section.

Other drugs

Trazodone. In vitro, trazodone appears to operate as a mixed serotonin agonist/antagonist, but clinically it is thought to operate as a serotonin agonist. Trazodone is much safer than the tricyclics following overdose but causes pronounced sedative and hypotensive effects in some patients. Priapism has also been noted as a rare but distressing side effect. This is probably due to its potent α-receptor blocking properties.

Mianserin. Mianserin was one of the first antidepressants to demonstrate an improved toxicity profile following overdose. Like many of the newer drugs, it has fewer antimuscarinic side effects than the traditional tricyclics. One drawback in using mianserin is the need for monthly blood counts during the first 3 months of treatment, due to a high reported incidence of blood dyscrasias, particularly in the elderly. Mianserin is no longer widely prescribed in the UK.

Venlafaxine. Venlafaxine was reported to be the first in a new class of antidepressants, the serotonin-noradrenaline reuptake inhibitors (SNRIs). These antidepressants were developed in an attempt to improve efficacy over the standard agents. As the name suggests, they prevent the reuptake of both serotonin and noradrenaline (norepinephrine), a mechanism they have in common with the tricyclic antidepressants. It was hoped this would result in a drug with similar efficacy to the tricyclics in more severe cases but without the antimuscarinic, cardiac or toxic effects of the older drugs. Guidelines for depression (NICE, 2009) highlight the relative poor tolerability and increased risks of toxicity compared to the SSRIs. In view of this, venlafaxine is not recommended as a first-line treatment for patients with moderate or severe depression.

Duloxetine. Like venlafaxine, duloxetine is an SNRI. It weakly inhibits dopamine reuptake and may be less well tolerated than SSRIs. Given the relative benefit/tolerability profile, the drug is considered to be a second-line treatment option.

Reboxetine. Reboxetine is a specific noradrenergic (norepinephrinergic) reuptake inhibitor (NARI). Response rates appear similar to other antidepressants. This casts further doubt on the existence of particular subtypes of depression likely to respond to particular antidepressants. Patients experiencing problems with serotonergic-related side effects may benefit from a switch to reboxetine.

Mirtazapine. Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA). It enhances both noradrenergic (norepinephrinergic) and $5HT_1$ serotonergic transmission. Specific $5HT_1$ neurotransmission is achieved as the drug also acts as a $5HT_2$ and $5HT_3$ antagonist. The receptor-specific effects of mirtazapine may explain some reduction in sexual dysfunction and nausea compared to other SSRIs. Despite this novel pharmacology, mirtazapine appears little different from other antidepressants in terms of efficacy.

Agomelatine. Agomelatine is structurally related to melatonin, it gained regulatory approval for use as an antidepressant in Europe in 2009. It is thought to act as an agonist at melatonin MT_1 and MT_2 and antagonist at $5HT_{2c}$ (Kasper and Hamon, 2009). In contrast to other antidepressants, it has no effect on monoamine uptake systems. Liver function tests are required prior to commencement and at intervals during treatment as rare cases of hepatic dysfunction have been reported. As yet there is insufficient evidence to comment on the place of this drug in the management of depression, but its relatively high cost may limit its use within the UK.

Choice of antidepressant. Whilst it has been suggested (Cipriani et al., 2009) that sertraline and escitalopram should be considered first-choice antidepressants for the majority of patients, it is unclear whether this will be translated into routine practice. The severity of the disorder, patient preference and previous experience should also play a part as they are also likely to affect outcome. In some areas, cost has become a critical factor in choice. For most people with moderate-to-severe depression, unless otherwise contraindicated, the use of a generic SSRI as the first-line choice is appropriate. Previous response, tolerance and the likelihood of drug interactions should also be considered.

In clinical practice, the identification of patients at high risk of suicide is difficult, and all patients with severe depression should be considered at risk of self-harm. The quantities of medication supplied to these patients should be carefully monitored.

Other treatments

Non-drug treatments. In addition to drug treatment, it is important to consider the patient's wider social, cultural and environmental circumstances. Although most patients with moderate to severe symptoms of depression will be offered pharmacological treatment, all patients and their close family should be offered help and support to cope with depression. Specific non-pharmacological interventions such as cognitive behaviour therapy (CBT) can be as effective as drug treatments. For people with more severe symptoms of depression, a combination of antidepressants and CBT is recommended. For mild-to-moderate forms of depression or persistent subthreshold symptoms, then non-drug strategies based on the principals of CBT should be considered as the first-line treatment (NICE, 2009).

The basis of CBT was developed over 50 years ago and subsequently refined into a specific therapy in the 1970s. This type of treatment helps patients to address their unhelpful thoughts and actions associated with depression. Over a series of up to 20 sessions the CBT therapist works with the patient either alone or in groups, to replace negative or self-critical thoughts and actions with more positive and helpful ones. CBT is not a 'quick fix' solution to depression, patients are often given 'homework' between sessions to try and put their positive actions into place. Interpersonal psychotherapy (IPT) is another form of psychotherapy which may help patients overcome symptoms of depression. This type of therapy aims to improve the patient's social functioning by linking their mood with interpersonal contacts so that their depressive mood and relationships can simultaneously improve.

Electroconvulsive therapy. Electroconvulsive therapy (ECT) would only be considered after referral to a psychiatrist. Although it is said to have a faster onset of action, its effects

are fairly short-lived and antidepressants are normally required to prevent relapse. Although the treatment itself is considered safe, there are risks from the anaesthetic agent, and some patients suffer short-term memory loss following treatment.

St John's wort (*Hypericum perforatum*). Extracts of hypericum have been shown to be as effective as standard antidepressants in the management of major depression (Linde et al., 2008). In England and Wales, prescribers are advised against prescribing hypericum because of uncertainty about appropriate doses and persistence of effect. Problems can also be caused due to the variation in the nature of preparations available and the potential for serious interactions with other drugs.

Treatment of mania

Valproate semisodium (divalproate) is licensed in the UK as a specific treatment for mania associated with bipolar disorder. Other antipsychotics, including lithium and benzodiazepines, may also have a role in the management of mania. There appears to be insufficient evidence to differentiate between the various antipsychotics licensed for use in the acute management of mania and as a consequence the side effect profile, tolerability, previous experience and patient preference should all be considered when selecting the agent to use. Short-term adjunctive treatment with a benzodiazepine may be also be required.

Lithium may be used as an antimanic agent but it takes longer than other agents to produce its full effect and few would consider lithium as their agent of choice for acute antimanic treatment. However, it remains a drug of choice for long-term use to prevent recurrence or relapse. Valproate, certain antipsychotics, carbamazepine and lamotrigine (off-label use) may also be considered for this indication. In the future, further evidence or new technologies may emerge that permit better individualisation of treatment.

When used prophylactically the antimanic agents are commonly referred to as mood stabilisers.

If an episode of mania occurs in patients taking antidepressants, the antidepressant should be withdrawn. If mania occurs in patients already taking an antimanic agent for prophylaxis, attention should be given to maximising the dose and, if necessary, adding a second agent.

Valproate semisodium

This is a 1:1 molar combination of sodium valproate and valproic acid. Following administration, valproate ion is released and subsequently absorbed. The therapeutic differences between sodium valproate and valproate semisodium have not been established. However, the latter is the only form of valproate licensed for the acute treatment of mania. The mechanism of action in mania is unclear but may be related to increased levels of GABA. The antimanic effects of valproate are seen within 3 days, but the full benefit of treatment may not be apparent for up to 3 weeks. Dose should be rapidly titrated to between 1000 and 2000 mg per day. Routine valproate serum levels are not necessary, but levels between 50 and 100 mg/L have been reported to be associated with optimal response in some patients. Although the risks of liver damage are greater in young children, liver function tests should be performed prior to initiation of therapy and periodically thereafter in all patients. In addition, the patient must be instructed to report any problems, such as unexplained bruising, that may indicate abnormalities in coagulation. Although valproate is well established as a prophylactic treatment to prevent relapse, this is an off-label use and should not be used in patients likely to become pregnant because of its teratogenic potential.

Antipsychotics

All the antipsychotics share a common effect of blocking dopamine D_2 postsynaptic receptors to some degree. Most of the newer antipsychotics, for example olanzapine, risperidone, quetiapine and aripiprazole, are licensed for use in the management of acute mania and prevention of new manic episodes.

Concerns about the side effect profiles of antipsychotic drugs often limit use, but in reality individual patients vary in their concern for and susceptibility to different side effects. Therefore, it is important that treatment choices are individualised and patients monitored regularly for side effects. Haloperidol, in an appropriate dose, is still commonly prescribed as part of the acute management of mania. It is less sedating than other antipsychotics which means it may occasionally be necessary to control severe behaviour disturbances with additional sedatives such as lorazepam, either orally or by injection. When a single agent is not considered to be effective, consideration should be given to augmenting the antipsychotic with valproate. Dose and duration of treatment are important considerations when treating acute mania. The dose of antipsychotic should be reviewed as the patient improves and where necessary consideration given to switching to an alternative prophylactic agent or continuing treatment to prevent relapse.

Lithium

Although lithium is effective in the acute management of mania, other treatments are generally preferred. This is due to the delay in response and variability of physical exertion and fluid intake which may compromise the safe use of lithium. In the acute situation, lithium may take up to 10–14 days to exert an effect. Dose is adjusted to achieve a target serum lithium concentration of 0.8–1 mmol/L for the management of acute episodes of mania, and for patients who have previously or have subsyndromal symptoms.

Antipsychotics or valproate semisodium, either alone or in combination, along with benzodiazepines should be considered the first-line treatment in the acute phase of mania.

Following an acute episode, lithium is a well-established treatment that may be considered as a first-line option for prophylaxis (Baldessarini and Tondo, 2000). Continuation therapy with a prophylactic mood stabiliser should be considered in all bipolar patients who have had two or more

acute episodes within 2–4 years. It may also be reasonable to consider prophylaxis in any patient following a severe manic episode. As treatment is long term, the cooperation of the patient is essential and so a thorough explanation of the risks and benefits of the treatment is vital.

Before lithium treatment is initiated, an assessment of the patient's physical state is essential. Thyroid, renal and cardiac function should all be within normal limits. It is, however, still possible to use lithium, with caution, in patients with mild-to-moderate renal failure or cardiovascular impairment. Any thyroid deficiency should be corrected before lithium treatment is commenced. Patients should be informed of the need for monitoring and cautioned about the consequences of dehydration and risks of drug interactions.

Serum levels. There is a narrow therapeutic window for lithium serum levels and variation in the reference ranges reported. Some of this variation can be accounted for by variation in dose schedules. In the main, 12-h (post-dose) levels above 1.2 mmol/L are considered to be toxic and levels below 0.4 mmol/L are not considered to be effective. In adults, if lithium serum levels are kept in the range 0.4–0.8 mmol/L, then lithium is usually well tolerated with minimal side effects. Levels at or above 0.7 mmol/L are reported as being more effective than lower doses.

For most patients the range of 0.4–0.8 mmol/L is appropriate for prophylaxis, but if lithium is used to control the acute phase, levels may need to be around 1.0 mmol/L. To accurately interpret lithium levels, it is important that the correct schedule is followed and to establish consistent results, the 12-h standard serum lithium protocol has been devised. This means that lithium levels should be taken in the morning as near as possible to 12 h after the last dose of lithium.

As the absorption and bioavailability of lithium may vary from brand to brand, it is important that patients do not inadvertently change brands or dosage forms without levels being checked. Lithium not only has a narrow therapeutic range but is particularly toxic in overdose. Common side effects reported by patients are gastro-intestinal disturbances, tremor, thirst, polyuria, weight gain and lethargy. In addition to complaints of side effects, some patients prefer to remain untreated as they feel lithium 'damps down' their creativity and they miss the slight 'highs' that occur as part of their illness.

Patients taking a prophylactic mood stabiliser may occasionally stop taking their medication when they feel they no longer need it, or want to see if they can overcome the disorder without the need for drugs. Patients commonly have several trials on a mood stabiliser before they accept that the balance of risks and benefits is usually in favour of longer term treatment. There is a significant risk of relapse if lithium is discontinued abruptly.

Other anticonvulsants

Carbamazepine is generally considered as a second-line prophylactic treatment, when first-line therapy is either not tolerated or is ineffective. Emerging evidence continues to support the use of lamotrigine as an alternative in patients with bipolar depression (Geddes et al., 2009).

Treatment combinations

In patients who cannot be controlled on a single mood stabiliser, consideration should be given to combining treatments. Although not entirely without risks, all the above drugs have been used in various combinations in resistant cases.

Patient care

In the acute phase of an affective disorder, a patient will have little or no insight into his or her condition. This often makes it difficult to prescribe medication following an informed discussion on the risks and benefits of treatment. Depressed patients may say they are not worth treating; most manic patients will find it impossible to engage in meaningful dialogue, or they may insist they do not need medication and consistently refuse treatment. Thus, in the initial stages of treatment, some patients are treated against their will. As patients respond to treatment, it is crucial that the benefits and risks of treatment are explained. This may need to be repeated and backed up by written information. Engaging the patient and including them in the choice of treatment not only supports their basic human rights but is also likely to lead to a better therapeutic outcome. The discussion should also allow the patient to record their preference for future treatment. This may include drug regimens they would prefer to receive should they relapse as well as medication they would find objectionable.

During the acute phase of their illness, patients may often forget what they have been told about their medication. It is, therefore, important to regularly offer information or reassurance about medication, even if the patient is reported to have fully discussed the actions and effects with a health care professional.

Many patients are frightened by the notion of taking medication that will affect their mind. Taking an antidepressant is often felt to be a sign of failure or weakness by the patient as well as their family and friends. This often leads people to try and deal with their depression without medication. This is fine for the milder forms of the disorder and is sometimes referred to as 'watchful waiting'. In more severe cases, such an approach could have life-threatening consequences for the patient.

Patients should always be offered the opportunity of discussing their medication. The use of patient information leaflets and the involvement of the family or close friends may help patients understand the risks and benefits of their treatment. Many of the drugs used in the treatment of affective disorders have the potential to interact with other drugs that have been prescribed or purchased. Some of these are summarised in Table 29.1.

Common therapeutic problems in the management of affective disorder are outlined in Table 29.2.

Table 29.1 Examples of important drug interactions with drugs used in the management of affective disorders

Antidepressant	Interacting drug	Effect
Tricyclics	Adrenaline (epinephrine) and other directly acting sympathomimetics	Greatly enhances effect. Dangerous acting sympathomimetics
	Alcohol	Enhanced sedation
	Antiarrhythmics	Risk of ventricular arrhythmias
	Anticonvulsants	Lowered seizure threshold and possible lowered tricyclic levels
	MAOIs	Severe hypertension
	Fluoxetine	Increased tricyclic serum levels
SSRIs	Anticoagulants	Enhanced effects
	MAOIs	Dangerous
	Lithium	Possible serotonin syndrome
MAOIs	Alcohol, fermented beverages, tyramine-rich foods	Hypertensive crisis
	Antihypertensives	Increased effect
	Anticonvulsants	Lowered seizure threshold
	Levodopa	Hypertensive crisis
	Sympathomimetics	Hypertensive crisis
Antipsychotics	Anaesthetic agents	Hypotension
	Anticonvulsants	Lowered seizure threshold
	Antiarrhythmics	Risk of ventricular arrhythmias
	Astemizole and terfenadine	Risk of ventricular arrhythmias
Lithium	Non-steroidal anti-inflammatory drugs (NSAIDs)	Enhanced lithium serum levels
	SSRIs	Possible serotonin syndrome
	Diuretics	Enhanced lithium serum levels particularly with thiazides
	Angiotensin-converting enzyme (ACE) inhibitors	Enhanced lithium serum levels
	Sumatriptan	Possible central nervous system toxicity
St John's wort	Induces cytochrome P450 enzymes, particularly 1A2, 2C9 and 3A4	
	Indinavir	Reduced serum concentration (avoid)
	Warfarin	Reduced anticoagulant effect (avoid)
	SSRIs	Increased serotonergic effect (avoid)
	Carbamazepine (and other anticonvulsants)	Reduced serum concentrations (avoid)
	Digoxin	Reduced serum concentration (avoid)
	Oestrogens and progestogens	Reduced contraceptive effect (avoid)
	Theophylline	Reduced serum concentration (avoid)
	Ciclosporin	Reduced serum concentration (avoid)

Table 29.2 Common therapeutic problems in the management of affective disorder

Problem	Possible solution
Antidepressants	
Treatment failure (30–40% of patients will not respond to first antidepressant)	Ensure adequate dose and duration of treatment Check adherence, engage the patient, develop therapeutic alliance Reassess response against target symptoms
Risk of self-harm	Reconfirm diagnosis and identify compounding factors, for example, high levels of alcohol consumption in unsupervised situations
Withdrawal reactions	Ensure gradual withdrawal
Relapse on discontinuation	Consider long-term treatment
Intolerance	Consider changing to a different class
Antimanic agents	
Treatment failure	Ensure adequate dose, check serum levels and adherence; consider drug combinations
Toxicity adverse effects	Determine dose by clinical response, guided by serum levels Ensure patient is well informed and able to recognise impending toxicity and adverse effects of treatment
Weight gain	Dietary advice; consider alternative pharmacotherapy
Lithium levels	Ensure serum levels are 12h post-dose, taken in the morning. Regular monitoring is important

Case studies

Case 29.1

Ms PS is a 17-year-old woman who presented to her primary care doctor with a 2-month history of difficulty in getting to sleep. She described herself as feeling generally unhappy. She had lost interest in socialising but was able to perform most of her usual daily routines. She sometimes felt as though she had little energy and was spending more time just watching the television.

Question

What diagnosis is likely to be given to Ms PS and what are the important factors to take into account when advising on treatment?

Answer

On further questioning by her primary care doctor, Ms PS does not reveal any ideas of self-harm. She is in a supportive relationship and, although she has some financial concerns, these are not excessive. It is likely that her depression is sub-threshold or of mild severity. Referral to specialist services is not appropriate. The patient should be given advice on sleep hygiene, including the removal of the television from her bedroom. A watching brief should be maintained and the patient asked to attend for a follow-up appointment within 2 weeks.

Antidepressants should not be prescribed. The risk/benefit balance is generally against prescribing antidepressants in people under 18 years of age. There is also little evidence to support the use of antidepressants in this case. More appropriate treatment options to consider would be a structured group exercise programme, guided self-help based on the principles of cognitive behavioural therapy or computerised cognitive behavioural therapy. The specific intervention should be guided by Ms PS's preferences.

Case 29.2

Mr DD is a 50-year-old unemployed man with a long-standing history of bipolar I disorder. He was admitted, as a voluntary patient, to an acute psychiatric ward by his community psychiatric nurse (CPN). The admission followed a short period of increasingly disturbed behaviour. Mr DD's daughter had contacted the CPN when she discovered that her father had just spent over £5000 on scientific instruments from an Internet auction site. Over the same period she had noticed that her father had lost interest in his self-care and become elated at the prospect of being on the verge of developing a special formula to solve the fuel crisis. On the ward Mr DD said he felt 'fine, fine all the time'. He told staff on the ward that he didn't need to be in hospital and it was keeping him away from his top secret mission. He also told ward staff that they could not keep him on the ward and insisted he was within his rights to go home. Mr DD's speech was sometimes very rapid, and it was sometimes difficult to understand what he was saying. His records showed that on his last admission he had been treated with haloperidol.

Question

What treatment is appropriate for Mr DD?

Answer

Before initiating treatment it is important to rule out any organic or physical causes for Mr DD's presentation. Following a thorough physical and psychiatric examination, it was established that Mr DD had been relatively well since commencing treatment with lithium almost 4 years previously.

It is important that symptoms of mania are brought under control. Haloperidol would be a suitable choice, in view of his previous response. However, a review of Mr DD's medication history revealed that he had experienced several acute dystonic reactions to haloperidol during previous admissions. His daughter also reported that her father had commented on how awful it felt being given haloperidol during his last admission. Mr DD was, therefore, given the option to discuss alternative antipsychotic treatment. He agreed to take olanzapine which was prescribed at a dose of 15 mg daily.

When Mr DD's manic symptoms are controlled, prophylactic treatment should be discussed with him. This should include a discussion about why he had discontinued lithium several months earlier. The opportunity should be taken to provide written information with the offer of a further discussion that should include his daughter.

Mr DD had stopped lithium as he felt he no longer needed it but after discussion was prepared to restart treatment. Renal, thyroid and cardiac function should be assessed, and if within normal limits, lithium carbonate 400 mg at night may be prescribed.

One week later a 12-h standard serum lithium level should be performed and the dose of lithium adjusted to achieve the same lithium levels as before (0.6 mmol/L).

The side effects and signs of impending toxicity from lithium should be explained to Mr DD and if possible his daughter. They should be given written information about the side effects, potential interactions, signs of toxicity and provided with a booklet to enable them to record the results of regular investigation. The arrangements for future prescribing and monitoring of lithium should be clarified so that Mr DD's care is not compromised by moving across organisational boundaries.

Case 29.3

Mrs FA is a 40-year-old designer. She was admitted to an acute psychiatric unit from the emergency department of the local hospital. She had taken an overdose of 32 co-codamol tablets when her husband told her he was going to leave her. On the ward she told staff she hated her life, and that everything was going wrong. She was angry that she had not been successful in killing herself as there was no point in living. She could see no hope for the future and had no interest in anything, not even eating.

Question

What course of action would you advise?

Answer

Mrs FA has a severe episode of depression. Antidepressant drug treatment should be initiated immediately. In line with guidelines for the management of depression, one of the SSRIs, for example, citalopram, should be considered as a suitable choice. Although Mrs FA may be reluctant to take medication, it should be explained that the drug does relieve the symptoms of depression. As soon as practical, the explanation should be followed up by discussing the importance of taking treatment for 4–6 weeks before the full benefit

is realised and the likely time course of antidepressant treatment being in the region of 6 months. Mrs FA should also be given the opportunity to discuss any concerns she may have about becoming dependent on the antidepressant as well as a general explanation about possible side effects.

Case 29.4

Mr MA is a 49-year-old unemployed man. He was admitted to a psychiatric unit at the request of the crisis intervention team. Mr MA had been prescribed fluoxetine 20 mg 2 months ago, and after no apparent response the prescriber in the crisis team had changed this to citalopram 4 weeks earlier. On admission he was noted to be withdrawn, lacking motivation and just gave 'yes' or 'no' in response to questioning. He reported no interests in his life, and it was noted that he had attempted to harm himself in the past. Two weeks after admission there was no significant improvement in his symptoms.

Question

What treatment options are appropriate for Mr MA?

Answer

Before considering a change in treatment, it should be confirmed that Mr MA has regularly taken his antidepressant medication. Serum levels are not generally available, or particularly helpful. Scrutiny of the medicine charts, discussion with nursing staff, relatives, key workers and the patient will enable a reasonable judgement to be reached. A dose increase could be considered if the patient had shown a limited response. In this case, the patient had received no apparent benefit and a change in treatment was warranted.

An in-depth review of his physical condition and previous medication should be undertaken. This should include discussion with the patient about any previous antidepressant treatment he had found to be particularly effective, or troublesome.

This review revealed that Mr MA had received several different antidepressants over the past 20 years. Three years ago he was treated with venlafaxine S/R 75 mg twice daily. The medical records confirmed Mr MA's view that this medication had helped him in the past, but on further questioning he stated that he had not taken medication for long after discharge from hospital as he did not want to get 'hooked' on it.

The importance of long-term treatment and the proposed treatment plan should be discussed with Mr MA. Particular issues to be addressed include an assessment of physical functioning including base line blood pressure and the need for ongoing periodic monitoring. In view of Mr MA's concerns about dependence, particular attention should be given to discussion around this issue. Based on Mr MA's agreement to the treatment plan, his previous response, the lack of any physical contraindication and the ability to organise ongoing, periodic blood pressure monitoring would be a reasonable treatment option.

Case 29.5

Ms YS is a 28-year-old student with a history of bipolar I disorder. She had recently moved to the area in the hope of continuing her studies. She was admitted to an acute psychiatric unit at the request of her key worker who reported that Ms YS had recently become increasingly elated and her partner was very concerned about the increased credit card bills she was incurring.

Whilst on the ward she attempted to develop sexual relationships with several young male patients.

Question

Describe the treatment options available for Ms YS.

Answer

There is insufficient information to determine whether or not Ms YS was being treated adequately with a prophylactic mood stabiliser. It is important to determine if the current episode was related to inadequate prophylactic treatment.

The current episode of hypomania must be treated. She is currently at risk through her promiscuity and the excessive use of her credit card. Both behaviours are likely to affect her ability to maintain a relationship with her partner.

As Ms YS was taking adequate contraceptive precautions and was adamant that she had no intention or desire to become pregnant, initially treatment with valproate semisodium should be considered. Olanzapine or another antipsychotic could also be considered, but Ms YS did not want to be treated with an antipsychotic. An assessment of liver function, prothrombin rate and full blood count should be performed prior to initiating therapy.

The patient should be informed of the important adverse effects of therapy. In particular, she should be advised to report any unexplained bruising and to avoid the use of salicylates. Treatment should be commenced at 250 mg three times daily and increased in accordance with response and tolerability. Benzodiazepines may also be considered as a short-term adjunct if additional sedation is required.

Following resolution of the acute episode, long-term prophylaxis must be considered. In this case, Ms YS had previously been treated with lithium, but had refused to continue as this had caused significant weight gain.

In view of the patient's refusal to consider lithium, prophylactic options include carbamazepine or valproate semisodium (valproate semisodium is not licensed for prophylactic use in the UK). Little hard evidence currently exists to guide the choice. It is important to take the patient's view into account. Even though valproate does not have a UK marketing authorisation for prophylaxis in bipolar disorder, on the basis of informed choice, prophylactic treatment with valproate was agreed with Ms YS.

Case 29.6

Ms AB is a 55-year-old unemployed lady with a long-standing history of depression. She has been treated with several antidepressants over the years and is currently under the care of the community mental health team.

The only treatment that appears to have had any effect on her depressive episodes has been dosulepin. She has taken several overdoses in the past and her psychiatrist is reluctant to prescribe this drug.

Question

What measures could be taken to enable Ms AB to be treated effectively?

Answer

Ms AB does not have treatment-resistant depression. She has been successfully treated with dosulepin in the past, but impulsively takes an overdose as a way of dealing with difficult circumstances even when she is not depressed.

Non-drug strategies by the mental health team should be directed at enabling Ms AB to find alternative ways of dealing with these difficulties.

In view of the obvious risk of fatality, alternative antidepressant treatment should be considered. Dosulepin could remain as an option for Ms AB due to her previous response to this drug and the lack of response to other antidepressants, but this would fall outside current guidance for the management of depression (NICE, 2009). Practical measures of controlling the quantities of medication should be introduced such as ensuring she only receives sufficient medication for 2 or 3 days treatment.

Communication between all those involved in the care of Ms AB is crucial. When individualizing the supply of medication in this way, all those involved must be alert to the possibility that the system of supply may break down. In this case, an apparently routine prescription for 1 month's supply of medication may have fatal consequences.

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