Myasthenia gravis (MG) is the most common autoimmune neuromuscular disorder. It is associated with painless, and variable, muscle weakness and fatigue that can cause considerable disability.

MG affects around 100–150 people per million of population. In the UK around three people per 100,000 develop MG each year. It has a bimodal distribution, affecting around twice as many young women as young men, but this gender imbalance is reversed in older patients. The average age of onset is around 35 years for women and 50 years for men.

Although MG is rare it is important that pharmacists have an understanding of the condition and its treatment because of the potential for drug-drug and drug-disease interactions. Information about MG for patients and healthcare professionals is available from the Myasthenia Gravis Association, and its website (www.mga-charity.org) is a useful resource for anyone involved in the management of patients with MG.

**Clinical features**
MG can present with an abrupt onset of symptoms or insidiously over weeks or years, with progressive weakness of affected muscle groups. The disease course is highly variable and, although most patients will respond to treatment, often this can take many months. Symptoms of MG can be exacerbated by several factors, outlined in the accompanying article (p287).

Depending on the muscle groups affected, patients with MG can present with ocular symptoms, specific muscle weakness that fluctuates throughout the day and from day to day, or difficulty chewing and swallowing. Affected muscles can be subdivided broadly into extraocular, skeletal and bulbar (see below).

Muscles under control of the autonomic nervous system (those involving muscarinic acetylcholine [ACh] receptors) — which are responsible for, for example, cardiac, digestive and urinary function — are not affected by MG. Sensory deficits, and absent or increased tendon reflexes, are not features of MG so the presence of these features suggests an alternative or concomitant neurologic diagnosis.

**Ocular muscles** The muscles surrounding the eye (extraocular muscles) are affected in over 85% of patients.
with MG, for many patients this will be the initial or only muscle group affected. These muscles are thought to be vulnerable to fatigue because they have relatively small motor units and fire at high frequency. Extraocular muscles can also be more susceptible to autoimmune injury caused by ACh receptor antibodies.

Ocular MG presents with ptosis (drooping of the upper or lower eyelids) or diplopia (double vision with vertical or horizontal displacement), both of which can be disabling. In some instances a patient's optician will be the first person to suggest a diagnosis of MG.

Around 80% of patients who present with ocular MG will go on to develop generalised MG, with most progressing within two years. For those in whom symptoms remain purely ocular for more than two years, progression to generalised MG is uncommon, occurring in less than 10% of patients.

Skeletal muscles Skeletal muscle weakness can affect any muscle group and will impact on a patient's ability to perform day-to-day activities. Proximal muscles (those closer to the centre of the body), such as those involved in sitting upright, breathing or rising from a chair, are more commonly and profoundly affected. MG can also affect a patient's ability to drive (see Box 1).

Muscle weakness typically worsens over the course of the day and patients with generalised MG should be advised on strategies to minimise fatigue. Early and ongoing support from a physiotherapist or occupational therapist can have a considerable impact on a patient's ability to manage their condition.

Although MG is typified by painless fatigue, the condition can lead to strain on other muscle groups causing aches.

Bulbar muscles The bulbar muscles are those controlled by the lower brain stem (medulla). These muscles are responsible for actions such as chewing, swallowing, speech and breathing control. Up to 20% of patients with MG have prominent bulbar dysfunction early in their condition.

Swallowing disorders are an issue in around a third of MG patients and it is common for these symptoms to worsen towards the end of a meal. As well as the discomfort associated with chewing difficulties, and the unpleasant sensation of food sticking in the throat, these patients are at risk of aspiration. This can cause coughing, a sensation of choking and, if food or secretions make their way into the lower airways, aspiration pneumonia.

All patients with MG should be advised to maintain appropriate and adequate nutritional intake; dietitians and speech and language therapists are well placed to provide information around such issues. During MG exacerbations, swallowing can become particularly difficult and the risk of aspiration often necessitates the placement of a nasogastric feeding tube. Patients with a nasogastric tube will need a complete review of their medicines to allow dosing by this route.

Patients with bulbar symptoms often have strained or nasal speech. Because MG can also cause weak facial movements and difficulty smiling (which often looks like the patient is scowling or snarling), there is potential for communication difficulties and misinterpretation of both verbal and non-verbal cues.

Respiratory dysfunction can lead to inadequate ventilation and respiratory failure. If respiration is impaired, particularly during an MG exacerbation, pulse oximetry and regular measurement of forced vital capacity (FVC) can be used to monitor respiratory function and the need for ventilatory support.

Pathophysiology

ACh is the key neurotransmitter at the interface between presynaptic motor neurons and receptors on postsynaptic muscle membranes.

Once an action potential reaches the presynaptic endplate of a motor neuron, voltage-gated calcium channels open. The influx of calcium ions brings vesicles containing ACh close to the presynaptic membrane and triggers release of the ACh into the synaptic cleft.
Thymomas are present in around 10–15% of patients compressing or invading surrounding organs or tissues. Thymomas can cause symptoms by slow growing and benign, but they can become malignant thymus. Known as thymomas, these tumours are generally

**Role of the thymus**

The thymus is a specialised immune organ located between the heart and sternum that has an important role in adaptive immunity and development of T cells.

Tumours can arise from the epithelial cells in the thymus. Known as thymomas, these tumours are generally slow growing and benign, but they can become malignant and metastasise. Thymomas can cause symptoms by compressing or invading surrounding organs or tissues. Thymomas are present in around 10–15% of patients with MG. Most of these patients are diagnosed between the ages of 40 and 60 years. There is an equal male-to-female distribution.

All patients diagnosed with MG should undergo chest computed tomography scan, or magnetic resonance imaging, to rule out this condition. The management of thymoma is beyond the scope of this series.

Early-onset MG with AChR antibodies is often associated with an enlarged thymus. In late-onset MG the thymus is typically atrophic.

**Diagnosis**

Symptoms of MG are often mild and can overlap with those of other conditions, which can mean that diagnosing MG is a difficult or lengthy process. Generally, patients are classified as having ocular or generalised MG, based on their symptoms.

Diagnosis can often be based on clinical evaluation alone. Rapidly evolving ptosis during upward gaze, eye drifting during sustained lateral or vertical gaze and profound dysarthria are among the classic symptoms of MG.

Patients with clinical features of MG should have blood tests to look for AChR antibodies. This is a gold-standard test that is specific for MG, and false positives are rare. If the results of the AChR antibody test are negative then the presence of MuSK antibodies should be assessed. If either assay is positive then no further investigations to confirm the diagnosis are generally required. It is worth noting that the serum levels of both antibodies vary between patients, and levels do not reflect the degree of weakness.

If patients are seronegative, which is more common for ocular MG, or if it is unreasonable to await results then additional tests can be used to confirm the diagnosis (see Box 2, p286).

Thyroid function should also be assessed during diagnosis as dysfunction is common in patients with MG and can exacerbate myasthenic weakness. It is useful to repeat thyroid function tests during exacerbations.

**Myasthenic crisis**

Myasthenic crisis is a neurological emergency in which impaired respiration can prompt the need for intensive care and ventilatory support. Myasthenic crisis affects 10–15% of MG patients, usually with two to three years of diagnosis, and is more likely in patients with MuSK antibodies. Occasionally patients present in crisis at the onset of MG.

Increasing muscle weakness and double vision can often precede a myasthenic crisis; quieter breath sounds, reduced chest expansion, tachycardia and increased blood pressure indicate imminent deterioration. Generally, a patient’s ventilation-perfusion ratio is well maintained, and oxygen saturation and blood gases are normal, until late in the crisis.

FVC is a useful predictor of impending respiratory failure, and an FVC of less than 1L (or 15ml/kg) indicates the need for critical care and respiratory support.

**Cholinergic crisis**

Cholinergic crisis can be mistaken for myasthenic crisis, since it also causes muscle weakness and respiratory failure. Generally, cholinergic crisis is only associated with excessive doses of anticholinesterases and is rare with contemporary management of MG (see accompanying article, p287).
Classic symptoms of cholinergic crisis include salivation, lacrimation, diarrhoea, urinary incontinence, bradycardia, miosis and bronchospasm. These are not symptoms of myasthenic crisis.

**Box 2: Diagnostic tests**

In cases where a diagnosis of myasthenia gravis (MG) is not definite, despite a clinical assessment of symptoms and results of serological tests, the following can be used to aid diagnosis:

**Electrophysiological investigations**

Electrodes are placed adjacent to a muscle and repeatedly stimulated so the action potential of the muscles can be measured. A decreasing response to stimulation indicates a defect (this is more likely in proximal or facial muscles). This test can yield both false positive and false negative results; accurate results rely on the operator’s skill and experience.

**Ice test**

The ice test involves placing, on the eyelids of patients affected by ptosis, an ice pack for two minutes; improvement in ocular symptoms after the ice pack is removed is indicative of MG. Improvement is more likely if ptosis is partial rather than complete (ie, eyelids are partially rather than completely closed).

**Edrophonium test**

Edrophonium, a rapid-acting cholinesterase inhibitor, can be used to diagnose MG (known as the Tensilon test). The drug is administered intravenously (2mg followed by a further 8mg if no adverse effects are experienced) and, if it induces a rapid, profound and short-lived improvement in muscle strength, this supports a diagnosis of MG (however, false positives occur in around 10% of people undergoing the test). The test can be repeated after 45 minutes if necessary.

Due to the risk of bradycardia and heart block, cardiac monitoring, resuscitation facilities and expertise, and a prepared dose of atropine should be available during the test. Other serious adverse effects include arrhythmia, respiratory failure or seizures. Edrophonium can also cause abdominal cramps, lacrimation and twitching of the eyelids. Rarely it can induce bowel evacuation.

**References**