MULTIPLE sclerosis (MS) is an autoimmune neurological condition diagnosed in 3.5 to 6.6 people per 100,000 of the population each year — equivalent to between 1,800 and 3,400 people in England and Wales.

It is mostly diagnosed between the ages of 20 and 40 years and there are roughly three times as many women with MS than men. On average, men present with symptoms one to two years later than women, but are more likely to have the progressive disease at onset (see later).2

Causes and risk factors

Although it is not yet certain why people develop MS, research suggests a combination of factors is involved. MS is not directly inherited but there does appear to be a genetic component (possibly a combination of certain genes) which makes people more susceptible. Relatives of someone diagnosed with MS have a slightly higher risk of developing the disease (see later).2

MS is characterised by repeated episodes of inflammation of the nervous tissue in the brain and spinal cord, causing loss of the insulating myelin sheath.

Symptoms

Common early signs of MS are:

- Visual problems, such as optic neuritis (loss of vision in one eye, eye pain, impaired colour vision) and diplopia (double vision).
- Balance problems and dizziness
- Bladder problems (storage and emptying)

Other symptoms include fatigue (both physical and mental), spasticity, gait problems, tremor, reduced co-ordination (ataxia), vertigo, limb weakness, numbness and pins and needles.

Pharmacists might also come across Lhermitte’s and Uhthoff’s phenomena. Lhermitte’s phenomenon describes sudden painless but unpleasant electric shock-like discharges that occur in cervical cord demyelination, due to non-synaptic (ephaptic) transmission of impulses. Flexion of the neck causes these symptoms to be felt in the trunk or limbs. In Uhthoff’s phenomenon demyelinated nerves have become unusually temperature sensitive and some patients develop symptoms of neurological dysfunction which
occur only when their body temperature is raised. MS can also affect memory, thinking and emotions.

**Diagnosis**
Diagnosis involves referral to a neurologist, who will take into account medical history, examinations and a number of investigations, including magnetic resonance imaging (to identify areas of sclerosis within the brain or spinal cord), lumbar puncture (to test for abnormalities of cerebrospinal fluid) and evoked potentials (to measure the time taken for nerves to respond to electrical stimulation). A positive diagnosis can take time and tests are not always conclusive.

**Prognosis and progression**
MS is characterised by repeated episodes of inflammation of the nervous tissue in the brain and spinal cord, causing loss of the insulating myelin sheath. This inflammation is caused by activated leukocytes infiltrating the blood brain barrier, resulting in areas of hardening (sclerosis) along the neurones, which blocks signal transmission to and from the brain and spinal cord. This leads to a variety of dysfunctions, depending on the sites and sizes of demyelinated plaques, and explains why people with MS can experience different symptoms at different times.

In the earlier stages of MS, the central nervous system can sometimes repair the damaged myelin or use different pathways for signals. This is why episodes of symptoms can be followed by periods when symptoms improve or disappear altogether. In some people there is simply a slow increase in symptoms.

Recognised terms for describing different patterns of MS are:
- Relapsing and remitting
- Secondary progressive
- Primary progressive
- Benign

In relapsing and remitting MS (RRMS) periods of good health (remission) are followed by sudden symptoms (relapses). Most (80 per cent) of people have this type of MS at disease onset. Secondary progressive MS (SPMS) follows on from RRMS. There are gradually more or worsening symptoms with fewer remissions. About 50 per cent of those with RRMS develop SPMS during the first 10 years of their illness.

In primary progressive MS (PPMS) symptoms gradually develop and worsen over time and are more or less continuous. Between 10 and 15 per cent of patients have this type of MS, and are diagnosed retrospectively.

In benign MS mild relapses are followed by long periods of remission with little or no decline in function. Life expectancy in most patients with MS can be normal or almost normal but, for many, symptoms can be debilitating. In addition, disability predisposes to respiratory and urinary tract infections, and pressure sores.

**Disease management**
Although there is no cure for MS, there are positive roles for healthcare professionals. These include making the correct diagnosis, trying to reduce disease progression, and trying to help patients experience as few symptoms and functional problems as possible.

**Treating symptoms**
Acute episodes vary in nature and severity, and may not always require treatment. The National Institute for Health and Clinical Excellence recommends treatment when the episode causes distress or an increased limitation of activities.

Relapses are thought to follow demyelination and corticosteroids (eg, methylprednisolone 500mg–1g od intravenously or 500mg–2g od orally, for three to five days) are the treatment of choice.

Methylprednisolone, a synthetic glucocorticoid, is a potent anti-inflammatory. Its exact action in MS is unclear but it is thought to act by immunosuppression1 or by reducing fluid accumulation around the site of nerve damage, or both.

Many studies have shown that steroids are effective in speeding recovery from relapse but that they make no difference either to the degree of recovery or to the long-term progression of the disease. A Cochrane review compared oral and intravenous corticosteroid treatments in people with MS and found no major differences in clinical outcomes of efficacy and safety.

In the short-term, the side effects of steroids are usually minor and transient, but patients should be warned that they may experience indigestion, psychiatric symptoms such as mood changes (especially at high doses), an altered sleep pattern, increased appetite and a metallic taste in the mouth. Special care is needed for patients with diabetes, and for those with previous gastric problems, who may need gastroprotection.

Long-term treatment should normally be avoided due to side effects of weight gain, acne,

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**NICE recommends that courses of steroids be limited to a maximum of three times a year**

Famprytra tablets (fampridine) were given conditional approval from the European Commission in 2011 to improve walking in adults with MS and walking disability defined as a score of 4 to 7 on the expanded disability status scale, where a score of 0 denotes normal neurological examination and a score of 10 denotes death due to MS (4 indicates significant disability but self sufficient and 7 indicates that the patient is mostly restricted to a wheelchair).

According to the Multiple Sclerosis Society, up to 40,000 people with MS in the UK experience problems with walking and it was predicted that this drug had the potential to improve greatly the independence and quality of life for many.

Fampridine is a potassium channel blocker that is thought to restore conduction in demyelinated axons — it reduces the ionic current through the channels so prolongs repolarisation and enhances action potential formation. The 10mg modified release tablets are taken morning and evening without food. The initial prescription should be limited to two weeks and treatment discontinued if no improvement is seen. A timed walking test is recommended for evaluation.

**Trials**
In phase III clinical trials, between 34 and 42 per cent of patients responded to treatment compared with placebo (7.8 per cent and 9.3 per cent, respectively). These patients increased their walking speed by around 25 per cent within weeks.

Side effects of fampridine include increased risk of seizures, insomnia, anxiety, dizziness and tremor.

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**PANEL 1: FAMPRIDINE**

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cataracts, osteoporosis, deterioration of the head of the thigh bone and diabetes. NICE recommends that courses of steroids be limited to a maximum of three times a year.

There are also several options available to treat complications commonly associated with MS such as fatigue, bladder and bowel problems, weakness, spasticity and spasms, and swallowing difficulties. These include intrathecal baclofen and cannabidiol extract (Sativex®) for spasticity (see Resources) and fampipride (Fampyra®) for improved walking ability, which was launched in the UK in October 2011 (see Panel 1).

Maintaining remission

People with RRMS, and those with SPMS may be prescribed disease modifying drugs (DMDs) with the aim of maintaining remission. There are several available DMDs, including interferon beta, natalizumab and azathioprine, but many are only prescribable for patients who meet certain criteria.

There is no proven disease modifying treatment for PPMS - symptomatic treatment is the main approach.

Interferon beta and glatiramer

Interferon beta and glatiramer acetate are currently the first-line choices for maintaining remission. However, only patients with RRMS or SPMS where relapses are the key feature and who meet the criteria developed by the Association of British Neurologists (ABN) are eligible for treatment (under a risk sharing scheme; see Panel 2).

Interferons belong to the family of cytokines (naturally occurring proteins) which mediate antiviral, antiproliferative and immunomodulatory activities. Interferon beta has been shown to possess both antiviral and immunomodulatory properties. The mechanism by which it exerts its actions in multiple sclerosis are not clearly understood. However, it is known that the biological response-modifying properties of interferon beta are mediated through its interactions with specific cell receptors found on the surface of human cells. It also enhances the suppressor activity of peripheral blood mononuclear cells.

There are two forms of interferon beta — interferon beta-1a (Avonex and Rebif) and interferon beta-1b (Betaferon, Extavia). They are deemed equivalent with no difference in efficacy. The difference is in how they are manufactured.

The mechanism(s) by which glatiramer acetate (Copaxone) exerts its effects in patients with MS are not fully elucidated, but the drug is thought to modify immune processes currently believed to be responsible for the pathogenesis of the disease.

It is well established that interferon beta and glatiramer reduce both the number and severity of relapses and formation of new lesions. However, it is less clear what effect they have on long-term progression of disability and whether they prolong the time to SPMS. Interferon beta consistently reduces relapses by about a third over two years in patients with RRMS or SPMS. Five-year data indicate that patients treated with interferon beta-1b have 75 per cent fewer brain lesions on MRI scans compared with placebo. Early treatment with interferon beta-1a or -1b has been found to reduce the proportion of patients going on to develop MS from around half in those receiving placebo to around a third in those receiving active treatment.

Glatiramer acetate has been shown to delay progression to “clinically definite MS” in patients with “clinically isolated syndrome” for up to three years. The proportion of patients who converted to clinically defined MS was 43 per cent in the placebo group compared with 25 per cent in the glatiramer group.

Product choice is affected by patient preference, which is influenced by frequency and ease of injection. All except Avonex are administered by subcutaneous injection. Avonex is administered weekly, Rebif three times a week, Betaferon and Extavia on alternate days and glatiramer daily. Rebif and Betaferon have auto-injector devices.

The most commonly reported side effects with interferon beta are flu-like symptoms such as myalgia, fever, chills, sweating, lack of strength (asthenia), headache and nausea. With glatiramer, injection site reactions are seen within minutes in around 70 per cent of patients and around 31 per cent of patients experience one or more of the following: vasodilation, chest pain, dyspnoea, palpitations and tachycardia.

Natalizumab

Natalizumab (Tysabri®), a monoclonal antibody, is currently seen as the gold standard for preventing relapses. After two years treatment 67 per cent of patients were relapse free compared with 41 per cent given placebo.

Natalizumab is a selective adhesion molecule inhibitor and binds to the α4-subunit of human integrins, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. Disruption of molecular interactions prevents transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue. A further mechanism of action may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α4-expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. As such, natalizumab may act to suppress inflammatory activity present at the disease site, and inhibit further recruitment of immune cells into inflamed tissues.

Natalizumab is recommended by NICE as an option for the treatment of rapidly evolving severe RRMS (two or more disabling relapses in a year and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with previous MRI). It is administered by intravenous infusion at a dose of 300mg every 28 days. Use of natalizumab may be associated with infections, urticaria, headache, dizziness,
vomiting, nausea, arthritis, infusion reactions and hypersensitivity reactions. The drug has also been associated with an increased risk of progressive multifocal leukoencephalopathy (PML).7 This is characterised by progressive inflammation of the white matter in the brain at multiple locations. PML has similar symptoms to those of an MS relapse and a mortality of up to 50 per cent. For this reason natalizumab is not a first-line therapy in practice.

At the time of reapproval of the drug in 2006, the incidence of PML was one in 1,000. over 17.9 months’ treatment.8 Since then, three risk factors have emerged, which are cumulative exposure to natalizumab, previous cytotoxic or immunosuppressive therapy and history of John Cunningham (JC) virus infection.

Mitoxantrone Mitoxantrone is a DNA-reactive agent. Although its mechanism of action has not been determined, it has a cytotoxic effect on proliferating and non-proliferating cultured human cells. It is approved in the US to treat SPMS and worsening and progressive RRMS. In the UK it is not licensed for MS but is prescribed off-label, being reserved for severe recurrent relapses. Mitoxantrone is administered by IV infusion and various trials show benefits. However, it is a cytotoxic and serious side effects include life threatening reactions and cardiac toxicity. It also has a maximum lifetime dose, preventing it being used as a long-term DMD.

Mitoxantrone was previously used in patients with frequent and severe relapses who were failing on or who did not qualify for interferon or glatiramer treatment but since the development of natalizumab it is rarely used.

Azathioprine The immunosuppressant azathioprine has been used in MS to try to prevent relapses and slow disease progression. A Cochrane review in 2007 showed benefits on relapses and disease progression, although the usual side effects associated with the drug’s use (ie, gastrointestinal disturbances, bone marrow suppression and hepatic toxicity) were also found. It has now mainly been superseded by newer drugs for first-line use which also have more evidence of efficacy in MS.

**Fingolimod** Fingolimod (Gilenya ▼) is a sphingosine-1-phosphate receptor modulator, which works by exhausting lymphocytes in the lymph nodes, preventing them reaching the central nervous system and causing damage. Launched in April 2011 to treat RRMS in those for whom interferon beta has failed, it is an oral disease modifying treatment (one 500μg capsule daily) that has been shown to be more effective than both glatiramer and interferon beta, although it is not as effective as natalizumab.9,10 Fingolimod received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency and is approved for use in the US but it was rejected by NICE for cost efficiency, despite savings from not requiring hospital admission for administration.

Fingolimod was covered in a *New product focus* article (see Resources) but it is currently the subject of a European Medicines Agency safety review and a verdict expected next month. In the meantime cardiovascular monitoring should be increased *(PJ, 28 January 2012, p101).*

**No longer in use** Cladribine, a purine nucleoside analogue, affects the behaviour and proliferation of white blood cells, particularly lymphocytes, which are thought to be involved with the development of MS. However, NICE says that it should not be used and the drug was refused a marketing authorisation by the CHMP. Intravenous immunoglobulin (IVIg) treatment has also been used for MS but, in 2008, the Department of Health produced demand management guidelines restricting its use to particular conditions. Multiple sclerosis is now listed as a condition for which IVIg is not appropriate.

**Resources**

- **Muscle spasms and stiffness** are common symptoms of MS. A CPD article looks at this symptom and current treatments (www.pjonline.com/cpd/dealing_with_the_symptom_of_spasticity). Between 30 and 40 per cent of people with MS experience difficulties with swallowing at some time. A CPD article “How to help if a patient can’t swallow” is available at www.pjonline.com/cpd.
- **Fingolimod** is discussed in “Gilenya: an alternative to MS injections?”, available at www.pjonline.com.

**Future therapies** There are over 600 trials registered with the US National Institutes of Health relating to investigations in MS, many of them involving drugs not yet licensed for use in MS. These include monoclonal antibodies (eg, alemtuzumab [MABThera], daclizumab [Zenapax] and rituximab [MABThera]) and several oral agents, including:

- **Teriflunomide** (an immunosuppressant that reversibly inhibits dihydroorotate dehydrogenase, a key enzyme involved in de novo pyrimidine synthesis)
- **Laquinimod** (an immunomodulator)
- **Dimethyl fumarate** (an antipsorotic)

The development of oral agents is exciting because they offer a more acceptable route of administration.

**Complementary therapies** There is some evidence that reflexology, massage, tai chi, magnetic field therapy, neural therapy, fish oils, and the combination of some forms of complementary therapies (known as multimodal therapy) may be helpful for people with MS in terms of their general sense of wellbeing.11 In addition, patients can be advised that linoleic acid 17–23g/day may reduce progression of disability. Rich sources of linoleic acid include sunflower, corn, soya and safflower oils.3

**Signposting**

- **Both the Multiple Sclerosis Society** (www.mssociety.org.uk) and the Multiple Sclerosis Trust (www.mstrust.org.uk) provide information and support for anyone affected by MS.

- A document “Multiple sclerosis: understanding NICE guidance — information for people with multiple sclerosis, their families and carers, and the public” is available at www.nice.org.uk.

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