Multiple sclerosis information
for health and social care professionals

MS: an overview
Diagnosis
Types of MS
Prognosis
Clinical measures
A multidisciplinary approach to MS care
Self-management
Relapse and drug therapies
Relapse
Steroids
Disease modifying drug therapies
Symptoms, effects and management
Vision
Fatigue
Cognition
Depression
Women’s health
Bladder
Bowel
Sexuality
Mobility
Spasticity
Tremor
Pain
Communication and swallowing
Pressure ulcers
Advanced MS
Complementary and alternative medicine
Index
Relapse and drug therapies

Relapse

Section 2

Approximately 85% of people diagnosed with MS will have relapsing remitting MS. Relapsing remitting MS is characterised by a series of relapses (also referred to as an attack, a flare up, an episode or exacerbation), interspersed with periods of remission.

A relapse is defined as a sudden episode of symptoms or disability, in the absence of fever or infection, which lasts at least 24 hours, and is a neurological disturbance typical of MS\(^1\). A relapse must occur at least 30 days since the start of a previous episode.

Relapses occur spontaneously and are thought to be due to an episode of acute inflammation within the CNS. Frequency of relapses is very variable, some people will experience several in a year whilst others will be relapse free for many years. In one retrospective study in a population of 2,477 relapsing remitting patients, over three quarters experienced a five year relapse-free period\(^2\). On average, people will experience approximately 0.6 relapses per year with frequency gradually decreasing during the course of the condition\(^3\).

People with secondary progressive MS may also experience superimposed relapses and relapses have been reported in people with primary progressive MS\(^4\).

The symptoms experienced depend on the area of the brain or spinal cord affected. Typically, a relapse evolves over a few days, reaches a plateau, and then remits to a variable degree over a few weeks or months. Some relapses are relatively mild while others may cause more serious problems; most relapses do not require hospitalisation.

Relapses can have a significant impact not only on physical symptoms but also on social, financial and psychological well-being of those affected\(^5,6\). They may provoke fresh feelings of bereavement or fear. People may recover completely in episodes of remission or may have residual disability. Incomplete recovery has been found to range from 20 to 60% in different studies\(^7\).

Managing relapses

Different centres have different approaches to managing relapses. For many people, their MS nurse will be the first point of contact, for others it could be their neurologist or GP. Following diagnosis, an MS nurse or other health professional should explain the procedure to follow if the patient thinks they may be having a relapse.

A number of UK MS specialist centres have audited their relapse management services and developed protocols to ensure that anyone experiencing a relapse is assessed and offered appropriate treatment as soon as possible\(^8-11\).

A comparison of oral and intravenous corticosteroid treatments in MS shows that there are no major differences in clinical outcomes and both treatments appear to be equally effective and safe\(^13\).

In the short-term, the side effects of methylprednisolone are usually minor and transient, but may include:

- indigestion
- mood changes/mood swings
• altered sleep pattern
• increased appetite
• metallic taste
• flushing of the face.

Special care is needed for people who have diabetes, and for those with previous gastric problems who may need medication to protect the stomach. Long-term treatment should normally be avoided due to side effects including, weight gain, acne, cataracts, osteoporosis (thinning of the bones, particularly the head of the thigh bone), and diabetes.

Other treatments
There are many other management considerations apart from possible treatment with steroids. Depending on the symptoms, their severity and how they are affecting daily life, various adjustments and equipment may be necessary. For example, a mother with sensory symptoms in her hands might require help to care for her young baby and to cook. Someone experiencing problems with walking may benefit from a walking stick. It may be necessary to take time off work and/or temporarily reduce activities.

There is evidence that recovery from relapse is improved if neurorehabilitation is provided at the same time as steroids are prescribed14. When someone experiences a sudden increase in disability or dependence, the NICE Clinical Guideline12 recommends the individual should be:

• given support, as required and as soon as practical, both in terms of equipment and personal care
• referred to a specialist neurological rehabilitation service.

The urgency of the referral should be judged at the time, and this referral should be in parallel with any other medical treatment required.

Experiencing a relapse is often a very stressful time for both people with MS and their families who typically have a lot of unanswerable questions about when their symptoms will resolve, whether they will make a full recovery, the likelihood of further relapses or if the relapse is the start of a more progressive phase. At this time the need for reassurance is high. Health professionals sensitive to these issues can provide the communication and counselling skills needed.

Reducing the risk of relapses
Disease modifying therapies reduce the number and severity of relapses. See p24 Disease modifying drug therapies.

Life style issues may be important in reducing the risk of relapses. A well-balanced diet and regular exercise will promote good health and can help reduce the risk of relapse triggers such as infections. Strong evidence suggests that relapses can be triggered by infections, during the three month period after giving birth and stressful life events15. Vaccinations against influenza, hepatitis B and tetanus appear to be safe. Surgery, general and epidural anaesthesia and physical trauma are not associated with an increased risk of relapses.

References
Drug therapies

Significant advances have been made in the last fifteen years in developing drug therapies that offer real benefit to people who have MS. It is therefore important that whether a person is newly diagnosed, or has more advanced MS, they are managed by a neurologist with special interest in MS.

The aim of effective therapy is to reduce frequency and severity of relapses, prevent disability directly attributable to relapses, relieve symptoms, prevent or delay disability arising from disease progression and promote tissue repair to treat established progression. Drugs used in the treatment of MS can therefore be considered in three categories:

- treatment of relapse - steroids
- disease modification
- individual symptom relief (described in the sections on symptoms and symptomatic management).

Steroids

Steroids are the standard treatment for a relapse in MS and have been in use for about 50 years. The NICE guidelines\(^1\) state that any individual who experiences an acute episode (including optic neuritis) sufficient to cause distressing symptoms or an increased limitation on activities should be offered a course of high dose steroids to be started as soon as possible after the onset of the relapse. This should be either:

- IV methylprednisolone - 500mg-1g daily for 3-5 days or
- high-dose oral methylprednisolone - 500mg-2g daily for 3-5 days.

See page 22 Relapse.

Disease modifying drug therapies

Disease modifying therapies are used with a view to changing the long-term course of MS. The disease modifying drugs currently licensed for MS work by reducing the number and severity of relapses. As a result, they have only been found to be effective for people with relapsing remitting MS and for some people with secondary progressive MS who continue to relapse. As yet, there is no disease modifying treatment for progressive MS, due to the neurodegenerative process involved; treatment of which is thus based on the management of symptoms.

Disease modifying therapies licensed to treat MS

The table right describes the disease modifying therapies that are licensed in the UK for use in relapsing remitting MS, secondary progressive MS and clinically isolated syndrome.

The Association of British Neurologists (ABN) sets out the prescribing criteria for usage of disease modifying therapies and these are updated on a regular basis\(^1\).
## Disease modifying drug therapies

### Disease modifying treatments

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
<th>Administration</th>
<th>Dosage</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SELF-ADMINISTERED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>beta interferon 1a</td>
<td>Avonex</td>
<td>IM, once weekly</td>
<td>30μg</td>
<td>RRMS, SPMS, CIS</td>
</tr>
<tr>
<td>beta interferon 1a</td>
<td>Rebif</td>
<td>SC, three times per week</td>
<td>22μg or 44μg</td>
<td>RRMS, SPMS</td>
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<td>Betaferon</td>
<td>SC, alternate days</td>
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<td>RRMS, SPMS, CIS</td>
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<td>beta interferon 1b</td>
<td>Extavia</td>
<td>SC, alternate days</td>
<td>250μg</td>
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<td>glatiramer acetate</td>
<td>Copaxone</td>
<td>SC, daily</td>
<td>20mg</td>
<td>RRMS, CIS</td>
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<td>fingolimod</td>
<td>Gilenya</td>
<td>Oral, daily</td>
<td>0.5mg</td>
<td>only highly active or rapidly evolving severe RRMS</td>
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<td><strong>HOSPITAL-ADMINISTERED</strong></td>
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<tr>
<td>natalizumab</td>
<td>Tysabri</td>
<td>IV infusion, every 4 weeks</td>
<td>300mg</td>
<td>only highly active or rapidly evolving severe RRMS</td>
</tr>
<tr>
<td>mitoxantrone</td>
<td>Novantrone</td>
<td>IV infusion, every 3 months for 2 years</td>
<td>12mg/m²</td>
<td>only highly active MS</td>
</tr>
</tbody>
</table>

**Notes:**

RRMS: relapse remitting MS; SPMS: secondary progressive MS; CIS: Clinically isolated syndrome.

IM: Intramuscular; SC: Subcutaneous; IV: intravenous.

Beta interferon 1a and 1b are licensed to treat secondary progressive MS where relapses are still a major feature.

Fingolimod has been licensed for the treatment of rapidly evolving severe relapsing remitting MS (two or more relapses a year), and as a second line treatment for people whose MS remains active despite treatment with one of the beta interferon drugs or glatiramer acetate.

Mitoxantrone, has not been licensed for use in MS in the UK although it has in several European countries and the US. It is therefore used off-license in some specialist centres.

Natalizumab is licensed for people with highly active relapsing remitting MS who have failed to respond to beta interferon treatment and for people with rapidly evolving severe relapsing remitting MS (two or more relapses a year).

Infusion of mitoxantrone (20mg) in combination with methylprednisolone (1g) may also given every four weeks for six months.
Relapse and drug therapies

Beta interferons and glatiramer acetate

Beta interferons and glatiramer acetate

Glatiramer acetate and the beta interferons are different drugs with different modes of action. Large randomised trials have demonstrated these drugs reduce the number and severity of relapses by approximately 30% and the number of new lesions on magnetic resonance imaging (MRI)\(^{6-12}\). Results from clinical trials are reflected in clinical use\(^{14}\). Beta interferons appear to have beneficial effects on quality of life and may slow the accruing of disability for patients with relapsing remitting MS\(^{14}\) particularly when treatment is started early in the disease course. However, more evidence is required to support an influence on the long-term prognosis of MS\(^{15}\).

The Association of British Neurologists (ABN) has set out prescribing criteria for the beta interferons and glatiramer acetate for both relapsing remitting and, where appropriate, secondary progressive MS\(^{5}\). The criteria reflect clinical experience that treatment soon after the onset of MS is more effective in the long-term than treatment at a later stage of MS.

A number of studies have indicated that starting disease modifying treatment after a clinically isolated syndrome (CIS) - a person’s first episode of neurological symptoms (lasting at least 24 hours) - delays the onset of MS and can have long-term benefits, such as significant suppression of subsequent relapse and MRI lesion formation\(^{16-20}\). In spite of this evidence, the use of disease modifying drug treatment after a CIS remains controversial\(^{21}\). The current ABN guidelines only recommend that neurologists consider prescribing disease modifying drugs after a CIS if there is also MRI evidence suggesting a high likelihood of developing MS, and after discussing the risks and the benefits of treatment with the patient.

Interferons are cytokines, small proteins secreted by cells as a response to a variety of agents, in particular viruses. The body naturally produces several types of interferon: the main ones are alpha, beta and gamma. Alpha interferons are useful in cancer treatments, whereas gamma interferons have been found to increase relapses in MS. Two different forms of beta interferon, 1a and 1b, are available for treatment of MS, the difference resulting from the protein manufacturing process. Beta interferon modulates T-cell and B-cell activity and reduces the blood-brain barrier permeability to inflammatory cells\(^{22}\).

Glatiramer acetate is a synthetic combination of four amino acids, resembling the myelin protein surrounding nerve fibres. It is thought to lessen the immune reaction involved in demyelination by shifting the T helper (Th)1 lymphocytes in patients with MS towards a predominance of Th2 phenotype and by inducing the expression of anti-inflammatory cytokines\(^{23,24}\).

As both the beta interferons and glatiramer acetate are proteins and would be broken down in the digestive tract, they are given by either subcutaneous or intramuscular injection.

Dosage regimes vary and long-term compliance can be an issue. The disease modifying drugs are now available in easy-to-use formulations, including thinner needle size and auto-injector devices, which improve adherence, convenience, and help to manage self-injection anxiety in patients with MS\(^{25,26}\).

There have been a number of comparative studies between different types of beta interferon, and between beta interferon and glatiramer acetate. Most comparisons have shown no major difference in efficacy although the higher, more frequently dosed beta interferons (Rebif, Betaferon and Extavia) may have a greater efficacy than the once a week regime (Avonex)\(^{27-34}\) in short-term studies of less than two years. In a minority of people the immune system reacts to beta interferon and produces neutralising antibodies that reduce its efficacy; although neutralising antibodies can disappear they may persist. Neutralising antibodies are easily detected by a simple laboratory test.
Natalizumab (Tysabri)

Natalizumab is administered as a single intravenous infusion (300mg) via a drip once every four weeks in a clinical setting under the supervision of a suitably qualified health professional.

Natalizumab is a recombinant monoclonal antibody against alpha-4 integrins. This is the first in a new class of drugs known as selective adhesion molecule (SAM) inhibitors. They act in MS by preventing the migration of immune cells across the blood-brain barrier, which would result in inflammation and myelin destruction.

Natalizumab has been licensed for use with people with highly active relapsing remitting MS (two or more disabling relapses in one year), and one or more gadolinium-enhancing lesions on MRI or a significant increase in T2 lesion load compared with a previous MRI. Results of large randomised clinical trials in patients with relapsing remitting MS showed that over a two year period natalizumab reduces the occurrence of relapse by around two thirds, has a 92% reduction in gadolinium enhancing lesions in MRI, and produces significant benefits on the risk of progression of disability and on quality of life.

Natalizumab has not been studied in CIS populations.

Health professionals, patients and their carers need to be aware that natalizumab can be associated with infections, including the brain infection progressive multifocal leukoencephalopathy (PML). PML is a rare, progressive, and potentially fatal demyelinating disease of the CNS that is caused by a mutant form of JC virus, which usually remains latent. The factors leading to activation of the infection are not fully understood.

The European Medicines Agency (EMA) recently reviewed natalizumab and the associated risk of PML. The report concluded that the risk of PML increases after two years of treatment, although this risk remains relatively low (less than three per 1,000) and the benefits of the drug continue to outweigh the risks for patients with highly active relapsing remitting MS. Three independent risk factors are associated with an increased risk of PML:

- treatment duration, especially beyond 2 years
- immunosuppressant use prior to receiving natalizumab
- presence of anti-JCV antibodies.

Anti-JCV antibody status identifies different levels of risk for PML in natalizumab-treated patients. Patients who are anti-JCV antibody positive are at an increased risk of developing PML compared to patients who are anti-JCV antibody negative. Patients who have all three risk factors for PML carry the highest risk. The JC virus is present in approximately 50% of the adult population. As the JC virus can be acquired at any time, annual testing is recommended in those who initially test negative.

Neutralising antibodies (NAbs)

Treatment with the beta interferon drugs (Avonex, Betaferon, Extavia and Rebif) and natalizumab (Tysabri) can lead to the development of neutralising antibodies (NAbs) in some patients with MS, which can reduce the effectiveness of these drugs. Patients can switch to an alternative treatment to help restore the effectiveness of disease modifying therapy, and in some people, the neutralising antibodies will disappear over time.
Fingolimod works by binding to receptors on the surface of lymphocytes, called sphingosine-1-phosphate receptors (S1P-R). This results in a large proportion of the lymphocytes becoming retained in the thymus or secondary lymph organs. By suppressing the migration of lymphocytes from circulating in the blood and entering the central nervous system, fingolimod reduces the autoimmune attack on nerve cells in the brain and spinal cord\textsuperscript{19,20}.

In addition, there is evidence that fingolimod may have a direct effect on nerve cell damage and stimulate remyelination by modulating the same sphingosine receptors in the central nervous system\textsuperscript{21}.

Fingolimod is the first disease modifying therapy for MS which can be taken in an oral formulation, as a capsule.

The EMA only approved fingolimod (0.5mg, daily) as a second line disease modifying treatment for patients with MS who continue to have relapses or find the relapse rate has increased despite a year’s treatment with one of the first line drugs (Avonex, Betaferon, Copaxone, Extavia, Rebif). It is also approved for use in patients with rapidly evolving severe relapsing remitting MS (two or more relapses a year).

Based on five years of safety data, fingolimod treatment can cause temporary changes in heart rate, blood pressure, shortness of breath and macular oedema (a swelling in the eye affecting vision)\textsuperscript{22}. The first dose of fingolimod should be taken in hospital so that these factors can be monitored.

Fingolimod was licensed based on data\textsuperscript{23-44} from two major phase III studies in participants with relapsing remitting MS. Fingolimod showed a 30% reduction in progression of disability and a reduction in annualised relapse rate by about 50%.

There is no data on the use of fingolimod in patients with CIS, progressive MS or as add-on therapy to self-injectable DMTs. However, in the INFORMS study, fingolimod is being evaluated for primary progressive MS based on the evidence that the drug may have a direct effect on nerve repair\textsuperscript{25,45}. 

Fingolimod (Gilenya)
Mitoxantrone (Novantrone)

Mitoxantrone is licensed in the UK as a chemotherapy agent and acts by inhibition of DNA repair. Based on its associated safety profile (especially cardiomyopathy and treatment-related leukaemia), it is suggested that mitoxantrone should be used over a short time (limited to two years) to treat aggressive forms of relapsing remitting MS or in the early stages of secondary progressive MS ‘where relapses are still a significant feature’ and disease progression is not controlled by other immunomodulatory drugs.

Recent studies have suggested that the use of short-term mitoxantrone (for three to six months) as an induction therapy followed by a maintenance therapy, such as glatiramer acetate or beta interferon, may be a beneficial treatment option in patients with active, aggressive, relapsing remitting MS. There is no robust evidence to support the use of mitoxantrone in primary progressive MS, or in the later stages of secondary progressive MS (EDSS > 6.0).
Disease modifying therapies currently in clinical trials for MS

There is the potential for a more advanced therapeutic choice in the future if new drugs become available for MS with more specific targets, such as the monoclonal antibodies and oral treatments currently in development. These have the potential of increasing the therapeutic efficacy and offer some neuroprotection from MS, albeit they may raise new safety and tolerability problems. Listed below are some of the disease modifying therapies that are most advanced in clinical trials at the current time.

Teriflunomide is an oral agent which reduces the numbers of both B cells and T cells. In addition, it appears to have other immunomodulatory and anti-inflammatory actions. Teriflunomide reduced relapse rate by 31% at high dose (14mg daily) and the risk of disability progression (sustained for 12 weeks) by 30% 54. Various phase III studies are evaluating the effectiveness of teriflunomide compared to interferon beta 1a, as add-on therapy with beta interferon, and in delaying conversion from a first CIS to clinically definite MS.

BG-12 (dimethyl fumarate) is an oral agent, which produces both anti-inflammatory and neuroprotective effects by the activation of the NF-E2-related factor 2 (Nrf2) pathway 55,56. Phase III results showed that following two years of treatment BG-12 reduced the proportion of patients who relapsed by 49%, the number of lesions measured by MRI scans and the rate of disability progression by 53% compared with placebo (38%).

Alemtuzumab (Campath) is a monoclonal antibody that targets the T-cells involved in destroying myelin. Alemtuzumab is administered as an annual infusion. Phase III studies include the CARE-MS I study comparing alemtuzumab and interferon beta 1a and CARE-MS II. Initial results from the CARE-MS I showed that alemtuzumab reduced relapses by 55% compared to interferon beta 1a over two years 54. The effect on disease progression was comparable, with 8% of the alemtuzumab group and 11% of interferon beta group showing a worsening in their disability score. Four year follow-up data from phase II studies show 91% of people have no worsening of their disability with alemtuzumab compared to 68% taking interferon beta 1a, and by five years 65% were free of clinically active MS compared to 27% on interferon beta 1a 57-59.

Laquinimod is an oral therapy which shows immunomodulatory activity by affecting the levels of certain cytokines and trafficking immune cells into the CNS. Phase III data on laquinimod showed a 23% reduction in annual relapse rate, a 36% decrease in disability progression and a 33% reduction in brain atrophy after two years of daily treatment. Laquinimod appeared to have a favourable safety and tolerability profile. Slightly lower levels of efficacy were shown in the phase III, BRAVO, study comparing laquinimod 0.6mg with interferon beta 1a over a two year period.

Daclizumab is a monoclonal anti-CD25 antibody which inhibits activation of T-cells. The therapy, given as an injection under the skin or intravenous infusions, reduced the number of new or enlarged lesions in patients by 72% (25% at a lower dose) 58. Daclizumab was generally well tolerated. Treatment with daclizumab in combination with beta interferon is significantly more effective than beta interferon alone for active relapsing MS 51. The current DECIDE trial is a phase III comparator study with interferon beta 1a.

Ocrelizumab (RG 1594), a monoclonal antibody targeting CD20, has demonstrated a significant reduction in disease activity as measured by brain lesions (96% for high dose and 89% for low dose) and relapse rate (73% for high dose and 80% for low dose) over 24 weeks 62. This agent is also being studied in patients with primary progressive MS.

Other research approaches to modifying the course of MS

It is now recognised that immunomodulatory drugs are of maximum benefit before axonal damage has occurred and clinical progression has been established. The aim of therapies therefore must be not only to reduce frequency of relapses 63 but also to repair neuronal damage and prevent transition to a secondary progressive course. The last decade has seen development of therapies that moderately affect the course of the disease where inflammation predominates over degeneration.

The challenge to repair and prevent damage caused by MS remains.

Remyelination using stem cell therapy

Under specific conditions, stem cells have the ability to divide and potentially differentiate into cells with special functions such as nerve or muscle cells. Theoretically, stem cells may have the potential to restore the damage caused by MS and...
may modulate the immune system to prevent further damage.

Neuronal repair could be achieved by encouraging stem cells already present in the body to develop into, for example, oligodendrocytes\(^4\). Alternatively, cells could be transplanted that would go on to differentiate into a therapeutic cell type.

Research with stem cells is still at a very early stage and has involved some small clinical trials of autologous stem cell transplantation (ASCT, also known as HSTC). ASCT has been shown to induce remission in people with rapidly evolving relapsing remitting and secondary progressive MS. Patients may have either surgical collection from the bone marrow or drug-induced mobilisation of haematopoietic stem cells from the bloodstream. Participants are treated with high dose immunosuppressants to suppress their immune system. Bone marrow cells are harvested, expanded in the clinic, and then returned to the patient’s blood stream by infusion.

In 2006, the European Group for Blood and Marrow Transplantation (EBMT) reported on a retrospective survey of 178 patients with MS who had received stem cell transplants for MS\(^6\). The analysis showed that the transplantation of haematopoietic stem cells produced a slowing down of disease progression in a sub-set of patients affected by severe, progressive MS. In 2011, the same group reported mixed results on the long-term effects of stem cell therapy, after participants were followed for between two and 15 years\(^6\). The stem cell treatment appeared to be most beneficial for young patients (35 years or less), those with recent diagnoses, and those with highly inflammatory MS. Patients with progressive MS responded less favourably. Overall, 16 of the 35 patients showed a small improvement in EDSS disability scale, lasting for an average of two years. Two of these remained improved over seven and eight years, respectively. Seven worsened during follow-up, but remained better than their disability level at the start of treatment, while seven others worsened. Two deaths were attributed to the treatment.

In another small trial in patients failing on interferon therapy\(^6\), all patients showed no worsening of disability, and 17 out of 21 improved EDSS score by at least one point. Also 16 people experienced no further relapses. This therapy is being further validated in a larger trial in North and South America.

Stabilisation of MS was also reported from a pilot study\(^6\) in six people with stem cells derived from their own bone marrow. In contrast to previous studies, stem cells were not pre-treated to increase certain subsets of cells and patients did not receive immunosuppressive preconditioning before their bone marrow stem cells were infused intravenously. This research will continue in a trial with 80 people with MS.

Research into stem cells is still in a very early stage, and it is likely to be many years, possibly as much as twenty years, before stem cell treatments may become routinely available for the treatment of MS. More research must be undertaken to ensure that large numbers of stem cells can be routinely generated before transplantation into a patient and that stem cells develop into the specific cell type that is required. It will also be important to show that cells can survive, integrate, function and not cause harm to the recipient.

In the meantime, patients with MS may need to be cautious of private stem cell treatments that are not part of clinical trials. The International Society for Stem Cell Research (ISSCR) has published a patient handbook\(^6\) to help people evaluate stem cell therapies they may be considering.

Neuroprotection using cannabis derivatives

Clinical trials into cannabis have shown some symptomatic relief of MS. Sativex (delta-9 tetrahydrocannabinol and cannabidiol) was the first cannabis-based medicine to be licensed in the UK for use as a second-line option for MS-related spasticity. Studies have also shown evidence of anti-inflammation, promotion of remyelination and neuroprotection\(^7\).\(^-\(^9\).\(^)

CUPID is a long-term research trial looking at whether tetrahydrocannabinol (THC), one of the active ingredients in cannabis, can slow the increase of disability in people with progressive multiple sclerosis. The trial will also try to assess the long-term safety of cannabis-based medicines.

References

Relapse and drug therapies

Disease modifying therapies currently in clinical trials for MS


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We hope you find the information in this book helpful. If you would like to speak with someone about any aspect of MS, contact the MS Trust information team and they will help find answers to your questions.

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