Pharmacological treatments in MS
Multiple Sclerosis International Federation (MSIF)

MSIF’s mission is to lead the global MS movement to improve the quality of life of people affected by MS, and to support better understanding and treatment of MS by facilitating international cooperation between MS societies, the international research community and other stakeholders.

Our objectives are to:

- Support the development of effective national MS societies
- Communicate knowledge, experience and information about MS
- Advocate globally for the international MS community
- Stimulate and facilitate international cooperation and collaboration in research into the understanding, treatment and cure of MS

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Letter from the Editor

The Editorial Board and I believe this issue of MS in focus is particularly important for, and perhaps even anticipated for some time by, our readers. In a limited amount of space, the international expert authors have presented a clear picture of where we stand today in terms of pharmacological therapy for MS.

Before writing this letter, I looked at some old textbooks on MS as a reminder of how much there is to say compared to 20 years ago. In one book, under the heading of empirical treatments, I found the following statement: “…when a treatment is extremely useful, controlled trials may be either unnecessary or very brief”. In another book: “The earliest signs and symptoms of MS clear relatively quickly and completely regardless of how they are managed” The field of MS has made important strides since these statements were printed, not only in our knowledge of the disease, but also in our appreciation of the role rigorous scientific methods have in a more informed approach to assessing pharmacological possibilities.

This issue of MS in focus describes the tangible progress in which some people with MS now face the possibility – and the challenge – of evaluating various medications, based on side effects, dosing regimens, risks and benefits. Unfortunately for others, the treatment choices continue to be limited for various reasons, including cost and availability.

The fact that pharmacological options exist for some people with MS means they need to be increasingly more informed and updated about their disease, its daily management and about progress in research. This has resulted in an evolution in the relationship between the clinician, the MS nurse and the “patient”. Today, more than ever, a person with MS has the tools to be an active decision-maker when it comes to choosing a treatment.

Whether you are a healthcare professional, a person with MS or a family member, we hope that this issue of MS in focus answers your questions about MS pharmacological treatments.

We look forward to receiving your comments.

Michele Messmer Uccelli, Editor

Editorial statement

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Please note: This issue uses the formal chemical name of all drugs, not the “brand” or commercial name that may be more familiar. Such names vary in different parts of the world.

The next issue of MS in focus will be an update of fatigue (this topic was previously published in 2003). Please send questions and letters to michele@aism.it or marked for the attention of Michele Messmer Uccelli at the Italian MS Society, Via Operai 40, Genoa, Italy 16149.
Introduction to pharmacological treatments in MS

Christian Confavreux, MD, Professor of Neurology, Hôpital Neurologique Pierre Wertheimer, Bron, France

MS has long been considered an autoimmune disease, which means that the person’s immune system (its natural host defence system) is functionally distorted so that it self-attacks parts of the body, in this case the central nervous system. It is therefore not surprising that, as soon as immunosuppressants became available in the mid 1960s, they began to be advocated for preventing relapses and the progression of MS. Indeed, they are able to slow down, more or less vigorously, the immune system.

During the subsequent decades, people with MS in some countries were treated with such drugs, mainly azathioprine, methotrexate and cyclophosphamide. However, the clinical efficacy was far from dramatic in most cases, and safety and tolerance were a source of concern for many physicians. Furthermore, the efficacy of such treatments has never been definitively proved, as they have never been assessed in well-designed and well-conducted randomised, controlled trials.

Important turning points
The first turning point in MS treatment was in 1993 with the publication of the results of the multicentre randomised, double-blind, placebo-controlled trial of interferon beta-1b in relapsing-remitting MS (RRMS). This led to marketing approval of the first drug with demonstrated efficacy in RRMS. In subsequent years, intramuscular interferon beta-1a, glatiramer acetate and subcutaneous interferon beta-1a were also marketed for the treatment of MS. All of them interfere with the functioning of the immune system in a reversible way and are so-called immunomodulators. They are still in large use worldwide. They are commonly categorised as first-line, disease-modifying therapies for MS and are approved not only for active RRMS, but also, with the exception of subcutaneous interferon beta-1a, for the treatment of the first neurological episodes suggestive of MS, a so-called “clinically isolated syndrome” or CIS. They are also approved for the treatment of secondary progressive MS (SPMS) with superimposed relapses, with the exception of intramuscular interferon beta-1a and glatiramer acetate. None of them are approved for SPMS without superimposed relapses or for primary progressive MS (PPMS).

Initially, there was much controversy over which of the first-line, disease-modifying therapies is the most effective. Currently, after the completion of several comparative trials, the general consensus is

Neutralising antibodies
(From www.mstrust.org.uk, the website of the UK MS Trust)
Antibodies are created by the immune system as part of the response to foreign objects, such as bacteria and viruses. Antibodies are proteins that lock onto the surface of the invading particle, helping the body to kill it off.

It is known that some people with MS develop antibodies to the beta interferon drugs and natalizumab. These are known as neutralising antibodies as they can reduce the effectiveness of these drugs. Over the long-term, this may mean that people taking the beta interferons or natalizumab receive less benefit from them, and may experience as many relapses as they did before taking the drugs.
that their efficacy is similar. Intramuscular interferon beta-1a is a possible exception, being suspected by some experts of lower efficacy, but with the specific advantages of less frequent administration (weekly rather than daily) and limited induction of neutralising antibodies (see below, left) in the individual taking the drug.

Overall, first-line, disease-modifying therapies decrease the relapse rate by 30 percent and the MRI activity, as shown by the appearance of new or enlarging brain lesions, by 60 percent. Their effect on non-reversible disability accumulation and progressive brain atrophy, over the long-term, is questionable. Moreover, their tolerance and acceptability are far from ideal for a number of reasons, as outlined in the box above.

The second turning point in the development of disease-modifying therapies for MS was in 2006, with the publication of the results of two pivotal trials using a monoclonal antibody called natalizumab. The third turning point came in 2010 when the first oral medication for MS became available. Details of both these therapies are provided in the article on immunomodulators on pages 8-11.

Over the years, a number of drugs have been tested in the context of clinical research to assess their help alleviating the symptoms of MS, such as fatigue, pain and cognitive problems. Overall, evidence is not overly impressive but some progress has been made in recent years. For more detail about the treatment of MS symptoms, please refer to pages 16-19.

Guiding principles – how to use the therapies available?
In the absence of any definite cure and with new therapies being approved, the decision to treat or not, and how to treat, is becoming increasingly complex. The treatment decision should involve several considerations:

- MS is not usually life-threatening. It typically first affects people in their 20s and 30s. Any therapeutic interventions must therefore protect the person with MS from mid- and long-term complications, so that physicians treat but do not do harm.
MS has both an overall course and prognosis that are highly variable among individuals, with a full spectrum from very benign, even asymptomatic, to fulminant cases. There is currently no reliable and precise prognostic indicator for the individual, particularly at the onset of the disease.

Currently approved drugs have a demonstrated efficacy for preventing relapses from occurring. By contrast, their efficacy for preventing the long-term accumulation of disability is not evident. This dissociated efficacy is in line with the observations made on the natural history of the disease: relapses have only a marginal effect on the long-term accumulation of disability. Therefore, relapses, rather than progression, are indications for treatment with the currently available drugs for MS.

A clear relationship does exist between benefit and risk with these drugs: the stronger the efficacy, the higher the toxicity. According to the current consensus among MS experts, the first line is comprised of treatments with limited efficacy on the activity of the disease, virtually absent efficacy on progression, but excellent long-term safety.

This is the case for interferons and glatiramer acetate. Azathioprine and methotrexate are added to this list by many physicians, although they are not officially approved in MS for the above-mentioned reasons. They are still in use based on clinical experience.

The second line is comprised of treatments with clear efficacy on the activity of the disease, possible but not yet demonstrated efficacy on progression, good infusion-related tolerance, but a worrying safety profile. Natalizumab is one of these, with its risk of induced progressive multifocal leucoencephalopathy (PML – see page 11 for more).

The third line is comprised of treatments with a possibly similar profile of efficacy as natalizumab, but less satisfactory tolerance and a larger spectrum of risks. This is the case for mitoxantrone and cyclophosphamide.

A general recommendation in MS is not to use medications in combination, since strong evidence on safe and effective combinations is not currently available: monotherapy (one drug at a time) is therefore advocated. This attitude is in contradiction with what prevails in other chronic autoimmune disorders, transplantation, infections and malignancies.

The less active the disease, the more circumstantial considerations will influence the decision-making process. Among these are age, desire for pregnancy, acceptability of a continuous treatment, frequent injections, ill-tolerated side effects and the preferences of the physician and the person with MS.

**Decision-making criteria**

With all of these considerations in mind, several objective criteria will guide the physician in his or her decision. Most of them are taken into account in the official recommendations put forward by various health authorities:

**Disease activity:** the therapeutic intervention is customised to the individual’s disease. When one or more relapses have occurred in the past year, or two or more relapses in the past two years, first-line therapies are usually contemplated. For cases with higher disease activity, natalizumab is usually preferred. For more aggressive cases of MS, mitoxantrone may be proposed, although the tendency is to use natalizumab first and to reserve mitoxantrone for people who do not tolerate natalizumab.

**Disease course:** all currently acknowledged therapies for MS are recommended for the relapsing-remitting phase of the disease, most for clinically isolated syndromes, some for the secondary progressive phase with superimposed relapses, but none for the primary progressive phase.

**Disease duration:** the typical candidate for treatment is the person with active RRMS.
However, thanks to the results obtained in pivotal studies, there is a tendency in some countries to treat people with MS as early as their very first clinical episode. This attitude is even stronger when the person is at high risk of further relapses, as anticipated from a highly suggestive MRI. Indeed, it makes sense to treat early for a process that, by nature, is chronic and progressing.

Conversely, there are a substantial proportion of cases for which treatment, or a sequence of treatments, have been prescribed, the disease has become less active or, conversely, has converted to secondary progression, and at the same time, the person with MS no longer finds the treatment acceptable. These are the cases for which treatments are abandoned, at least transitorily.

Treatment history: the choice of medication for people who have not been treated before is essentially based upon the above-mentioned guidelines. However, the situation is more complex when previous treatments have already been administered. Schematically, when the treatment is effective in controlling the disease activity but ill-tolerated, a switch to a treatment within the same “line” of efficacy is logically proposed. When the treatment is ineffective, a strategy of escalation is proposed, for example from an interferon beta to natalizumab, keeping in mind that escalating therapy may mean escalating risks. Conversely, in cases with a very active disease, a reverse strategy of induction followed by maintenance therapy may be contemplated. This is mandatory when using drugs such as mitoxantrone and, to some extent, cyclophosphamide, as a maximum cumulative dosage cannot be exceeded. But this strategy could also be contemplated following a prolonged clear response to a drug such as natalizumab.

Looking ahead

As one can see, there is a wealth of evidence-based data which can inform choice among currently available medications. Recent years will stand as a landmark in the history of MS therapy with strikingly increased efficacy in the control of clinical relapses.

However, this has been obtained at the expense of increased toxicity, and progress is still to be made for a better balance between efficacy and safety. Furthermore, the treatment of clinical progression is still the main unmet need in MS. This is the “new frontier” in MS therapy.

Besides these challenges, we are also facing increasing diversity in MS treatment with the arrival on the market of many new promising drugs, each with its own specificities regarding efficacy, safety, tolerance, convenience and route of administration. This is already the case with fingolimod, an oral immunosuppressive agent licenced for use in some countries in 2010 (see page 11).

In any case, newly available or soon-to-be available medications for MS are not intended to replace those currently available. Indeed, people who are stable with their current therapy would not be encouraged to change to a new drug. A change in therapy depends on many aspects that need to be considered, including the benefits, risks and lifestyle issues, for example.

The availability of even more treatment options for MS will result in increased decision-making complexity. The treatment of MS is undoubtedly a rapidly evolving, but also a rapidly improving, area.
The immune system and MS
Since 1993, the MS community has seen the advent of a succession of new treatments, called immunomodulating therapies, or IMT (also known as disease-modifying treatments, or DMT), aimed at preventing disability caused by this disease. MS is considered an autoimmune disease, which means that it is a disorder of the normal immunological mechanisms involving B and T white cells and antibodies, resulting in an attack on some component of the myelin or the myelin producing cell, the oligodendrocyte. IMT affect pathways in the inflammatory disease process of MS, with the hope of limiting injury to the brain and spinal cord.

Although the exact causes of MS are unknown, the increasing success of IMT in modifying the severity of the disease has reinforced the concept that a disorder of the immune system is the basis of MS. Inflammatory injury to the myelin or oligodendrocytes results in focal areas of demyelination called plaques, or lesions. Attacks of demyelination may produce symptoms and signs of damage called relapses if the plaque is in a strategic area of the central nervous system (CNS). Such clinical relapses, which may show as symptoms including double vision, sensory loss, unsteadiness or weakness, usually recover spontaneously within weeks to months. Repeated relapses characterise the most common form of MS, relapsing-remitting MS (RRMS). Although initial recovery of the neurological deficits is usually good, repeated attacks damage nerve fibres causing persisting disability. Eventually increasing loss of nerve fibres results in the secondary progressive form of MS (SPMS). In about 15 percent of people with MS, the disease presents with a slowly progressive course without significant relapses, called primary progressive MS (PPMS).

Attacks of inflammation can also occur in “silent areas” of the brain. It is estimated that for every attack resulting in a plaque that causes symptoms, there are 8-10 silent areas of damage to the brain, which can only be visualised by MRI scanning.

The aim of treatment with IMT
The basic aim of IMT is to limit the disorder of the immune system, and thus to suppress inflammatory attacks causing injury to the CNS myelin. By preventing attacks – both symptomatic relapses and silent plaques – the aim is to prevent, or at the very least to delay, the accumulation of disability and the onset of SPMS. At present we have no useful treatment for SPMS, which is why it is important to reduce the initial inflammatory phase of RRMS.

<table>
<thead>
<tr>
<th>Immunomodulating drugs for MS</th>
<th>Generic name</th>
<th>Dose</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>interferon–beta-1b</td>
<td>8 million international units</td>
<td>subcutaneous injection, every other day</td>
</tr>
<tr>
<td></td>
<td>interferon–beta-1a</td>
<td>30 micrograms</td>
<td>intramuscular injection, weekly</td>
</tr>
<tr>
<td></td>
<td>interferon–beta-1a</td>
<td>22 micrograms or 44 micrograms</td>
<td>subcutaneous injection, three times/week</td>
</tr>
<tr>
<td></td>
<td>glatiramer acetate</td>
<td>20 milligrams</td>
<td>subcutaneous injection, daily</td>
</tr>
<tr>
<td></td>
<td>natalizumab</td>
<td>300 milligrams</td>
<td>intravenous infusion, every four weeks</td>
</tr>
<tr>
<td></td>
<td>fingolimod</td>
<td>0.5 milligrams</td>
<td>tablet, orally, daily</td>
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What are the IMT?
The most commonly prescribed IMT (see table below, left) are the interferons and glatiramer acetate, followed by natalizumab. In the last five years, a number of trials have shown that new oral therapies, such as fingolimod, are effective in RRMS. Drugs presently under study, and which may become available in the next five years, include fumerates, alemtuzumab, daclizumab, laquinimod, rituximab and ocrelizumab. There is a very active worldwide programme of drug development for RRMS, which reflects both our increased understanding of MS and the need to address the considerable burden of this disease.

First-line IMT
These include interferon beta-1b, interferon beta-1a and glatiramer acetate. These drugs, available for about 15 years, have all been shown in randomised, controlled trials (RCTs) to reduce relapse rates by approximately 30 percent and, in most, to reduce disability progression in the short-term. Their effects are modest, but this is offset by evidence of long-term safety. There have been a number of “head-to-head” studies suggesting that beta-interferons with higher frequency of administration may be more effective in relapse reduction than those with less frequent administration. Other studies comparing glatiramer with beta-interferons have shown similar efficacy.

How to decide which IMT to start on?
If a neurologist suggests the use of a first-line IMT to a person with MS, usually there will be a full, informed discussion between the doctor and the person and, in some countries, with an MS nurse. It is important that the person with MS realises that the treatment is preventative, that there are side effects, and that the treatment will not make them feel better or reduce symptoms or disability from previous relapses.

Ideally, the person with MS is given an information pack, helpful website details and contact information for their national MS society, if there is one in their country and, after the initial discussion, returns in a week or two. The preferences of the person with MS, injection frequency and side effects should then be discussed. The neurologist may, on the basis of their assessment of the disease severity, advocate using one particular type of IMT, but the decision should be an agreed one with the preference of the person with MS as paramount.

People who go through this ‘ideal’ process are more likely to adhere to therapy, which is an extremely important aspect of treatment. Adherence can be difficult when a treatment requires regular injections, has side effects, or when a person with MS is not experiencing any improvement in their MS symptoms, for example fatigue. In these cases, support from the neurologist, MS nurse and other resources, such as a pharmaceutical company-sponsored support programme, can be helpful in encouraging adherence.

Side effects
Flu-like symptoms. A common problem with all the beta-interferons is persistent flu-like symptoms for 12-24 hours after injection. Many find that these symptoms abate after 4-6 weeks of injections, but for some they continue and cannot be controlled with paracetamol. This group of people may opt to either go on glatiramer acetate or, if they have frequent injections, they may decide to reduce this to a weekly injection (interferon beta-1a). Dose escalation may also be tried.

Mood change. Depression is common in MS and there is evidence that this may be worsened by beta-interferons. If this occurs, treatment with an antidepressant may help. Alternatively a change to
glatiramer acetate may be suggested. **Injection site reactions.** These are a common problem. Injection technique should be discussed with an MS nurse if possible. Switching to another therapy may reduce side effects, but this needs to be discussed with the nurse and neurologist.

**Alterations in blood tests.** Regular testing of liver function and white cell count may show minor abnormalities in most people on beta-interferons and is of no consequence. More severe changes in liver enzymes or marked reduction in the white cell count may require stopping the medication for a month and restarting on a lower dose. Occasionally, because of persistent blood test abnormalities, the therapy needs to be changed.

**When relapses continue on first-line therapy**
First-line IMT do not stop all relapses and an occasional relapse, without any other evidence of worsening disease, may not be an indication to change therapy. However, relapses may indicate a need to use a more effective therapy. This decision may be taken if there has also been evidence of increased disability since the last assessment and MRI evidence of increased lesions since the last scan. One explanation may be neutralising antibodies (see page 4) counteracting the effect of therapy – these can be assessed using a blood test.

With the availability of more powerful therapies in the last decade, it is increasingly recognised that neurologists must be more active in assessing the response of the person with MS to first-line IMT, in order to treat the 20-30 percent of people with MS who have a more active disease. Failure to treat people with highly active MS using more powerful therapies will result in continued injury to the CNS and accumulating disability.

**Second-line therapies**
**Natalizumab** is the therapy of first choice for people who have inadequate disease suppression with first-line IMT. Natalizumab, in the pivotal, randomised, controlled trial, and in post-marketing observational studies, reduced relapse rates by 66-75 percent and reduced disability progression by 42 percent over two years. It is given every four weeks by intravenous infusion, typically in an out-patient hospital infusion unit.

**Mode of action:** Natalizumab has a unique form of action and was the first therapy specifically designed to block a part of the inflammatory pathway in MS. White cells gain access to the CNS by sticking to the lining of capillaries, using an interaction between an adhesion molecule, a4b1 integrin, on the surface of white cells and a vascular cell adhesion molecule on the vessel wall. Natalizumab blocks the a4b1 integrin molecule and thus prevents the cells entering into brain tissue.

**Guidelines:** Natalizumab is suitable for people with MS who have failed to respond to a full and adequate course of interferon beta, or people with rapidly evolving severe relapsing-remitting MS.

**Side effects:** Natalizumab is generally well tolerated. About one in 25 people taking it develop an allergy to the drug and it must then be discontinued indefinitely.

**Adverse effects:** By far the greatest concern with natalizumab is the occurrence of progressive multifocal leukoencephalopathy (PML). PML is an
opportunistic infection of the brain caused by the JC virus, which attacks the CNS in immunosuppressed people, resulting in widespread demyelination. It is a severely disabling and life-threatening illness. The overall rate of PML in people treated with natalizumab is 1/1000, but in the third year of treatment the rate rises to 1/500 and appears to fall thereafter. The risk factors for PML with natalizumab include duration of therapy, previous immunosuppressive therapy and pre-existing exposure to JC virus. There are plans to test all those who are considering natalizumab (and those already on it) for antibodies to JC virus using a very sensitive blood test. It is likely that people treated with natalizumab who have not had previous exposure to immunosuppressive medications, and who are JC virus negative, have a low risk for PML.

Clinical vigilance: In order to detect PML as early as possible, people taking the drug are monitored before every infusion in relation to new symptoms. If there is any cause for concern the person is not given the infusion and is seen by the neurologist. If necessary, a brain MRI is performed and, if required, a cerebrospinal fluid examination for JC virus DNA. People on natalizumab have yearly MRI scans to act as baselines for future comparison.

Fingolimod is the first approved oral therapy for RRMS. It is a selective immunosuppressant that blocks the capacity of lymphocytes to leave lymph nodes, causing a redistribution of lymphocytes. It is considered that this reduces the infiltration of pathogenic lymphocyte cells into the CNS. In trials, fingolimod reduced relapse rates by 54 percent and disability progression by 30 percent over 24 months, and showed superior efficacy to interferon beta-1a by a relapse reduction of 50 percent over 12 months.

Guidelines: The European Medicines Agency guidelines for fingolimod are similar to those of natalizumab and therefore in Europe fingolimod is a second-line therapy. Fingolimod has been approved in the USA by the Food and Drugs Administration with no stipulation that it is a second-line therapy, and thus it may be used as the first-line therapy for RRMS. The experience of the use of fingolimod outside clinical trials is limited. Only by observing significant numbers of people over years will it be possible to assess the safety of this drug.

Side effects: The most common side effects are influenza viral infections, headache, diarrhoea and elevated liver enzymes. Other side effects are herpes virus infection (shingles or herpes zoster), macular oedema, leucopenia, slow heartbeat, irregular heart rhythm, bronchitis and gastroenteritis.

Some of the therapies that may become available in coming years:

Alemtuzumab is a monoclonal antibody, a specific protein which sticks to receptors on the cell surface of lymphocytes and monocytes called CD52 receptors, and causes the death of these cells. Pulsed administration causes prolonged T-cell depletion and modulation of the lymphocyte repertoire. It is presently undergoing a phase 3 randomised, controlled trial (RCT) but has been used on a named patient basis in people with highly active RRMS. “Named patient basis” refers to a procedure in which a neurologist, whose hospital has been given ethical approval, can request that a medication be made available to a single patient in exceptional circumstances, particularly related to rapid worsening.

Dimethyl fumarate is an oral therapy undergoing phase 3 RCTs. It has a novel mode of action and has an excellent safety record.

Daclizumab is a humanised monoclonal antibody; that is, a specific protein which affects a receptor called the α subunit (CD25) of the human high-affinity interleukin-2 receptor. This results in a change in the immune state, similar to that which occurs in normal pregnancy, which reduces inflammation in RRMS. Daclizumab is presently under study in a phase 3 RCT.

Conclusion

There has been a remarkable expansion in both the variety and efficacy of drugs for the inflammatory phase of RRMS. What is lacking is any drug to increase remyelination, or any neuroprotective agent to slow the degeneration of axons in the progressive forms of MS. This latter defect in the therapeutic armoury needs to be addressed urgently.
Immunosuppressant drugs in MS

Mauricio F Farez, MD, MPH, and Jorge Correale, MD, Department of Neurology, Dr Raúl Carrea Institute for Neurological Research (FLENI), Buenos Aires, Argentina

Introduction
Immunosuppressants, or immunosuppressive drugs, are a group of drugs characterised by their ability to broadly inhibit cell division, shutting down key components of the DNA replication or repair machinery, making cells unable to divide at a normal rate. The immune system is one of the most targeted by immunosuppressants, especially if its cells are activated. The fact that immunosuppressants do not discriminate between cells from different body systems explains not only their therapeutic effects, but also the broad range of adverse effects they have.

Therapeutic regimen options
Since current immunotherapies are not completely effective in all people, and MS is a very heterogeneous disease, the challenge is to identify the most effective treatment for each individual. In this framework, immunosuppressants can be administered using two very different treatment regimens: induction or escalation.

The most aggressive approach is induction therapy, in which powerful immunosuppressive drugs are given from disease onset, with the goal of harnessing inflammation processes early to prevent further structural damage and potentially delay progression. Usually, immunosuppressants are administered for a short period of time until disease activity is under control, and then replaced by immunomodulatory agents, thus limiting drug exposure, and consequently potentially serious side effects. This strategy is reserved for people with very active and aggressive disease at onset, therefore justifying potential risks. Studies using mitoxantrone, followed by maintenance therapy with interferon beta or glatiramer acetate, have been promising, and have provided superior disease control compared to immunomodulatory drug monotherapy.

In escalation therapy, an initial treatment is selected among drugs with the most favourable risk/benefit ratio, changing to or adding later drugs with greater expected benefit but more toxicity, as needed. The key problem with escalation therapy lies in establishing clear criteria for treatment failure, and consequently timing the correct moment to switch to an alternative treatment.

Escalation therapy is a well-established concept in other autoimmune disorders, such as rheumatoid arthritis and inflammatory bowel disease. For MS, a rational escalating approach would be to start with interferon beta or glatiramer acetate as first-line therapy, continue with second-line immunosuppressive drugs and natalizumab, then use third-line combination therapy, and finally, intensive immunosuppressive alternatives (autologous bone marrow transplantation and high dose cyclophosphamide).

The potential advantage of this approach is to target different immune dysfunctions, particularly in combination therapies. Furthermore, combined regimens should allow the use of lower immunosuppressant doses, reducing the risk of side effects.
However, it is important to note that combination therapies have yet to be rigorously tested in clinical trial settings in order to identify which is the most appropriate. Published combination trials should be interpreted with caution.

Regardless of the therapeutic regimen selected, all people with MS should be rigorously monitored for serious adverse effects, pregnancy should be avoided, and cryopreservation of sperm and ovules should be offered to people of childbearing age due to the risk of infertility if treated with chemotherapy-based medications.

Each of the most important immunosuppressive medications for MS is addressed below:

**Azathioprine (AZA)** is a pro-drug, meaning a drug administered in an inactive or significantly less active form that is activated by metabolism in the body. Through metabolism, it is broken down into two immunosuppressant compounds that alter DNA synthesis, primarily affecting lymphocytes, the cells that play a central role in cell-mediated immunity.

It has been widely used in organ transplant recipients, as well as in other autoimmune diseases. In the case of MS, AZA has shown a modest effect in reducing both disease progression and relapse rate.

Moreover, the drug has been tested in small combination therapy studies together with different interferons, showing modest clinical and radiological results. AZA is administered at a dose of 2–3 mg per kg per day, as maintenance for people with MS who have high relapse rates, and would otherwise require prolonged treatment with steroids.

Gastrointestinal problems, hepatic toxicity and leucopenia, or a decrease in the number of white blood cells, are the most common adverse effects reported and can be prevented with monitoring and dose adjustment.

AZA poses a potential concern related to increased risk of Hodgkin’s Lymphoma and skin cancer with prolonged use (more than 10 years or a cumulative dose of over 600g).

**Cyclophosphamide** is extensively used in cancer treatment, as well as in other autoimmune diseases such as systemic lupus erythematosus. It generates breaks in DNA that mainly affect rapidly expanding cells, such as lymphocytes, and has also been shown to be capable of modulating or triggering changes in the immune system.

Cyclophosphamide was first tested in 1966, and has since been used in different treatment regimens with conflicting results. Nevertheless, today it remains an option in selected people with MS. One of the regimens most applied consists of monthly intravenous infusions at a dose ranging between 500–1,500 mg per m² body surface. Levels can be modified by 100–200 mg until white blood cell counts stabilise between 2,000 and 2,500 cells per mm³ or to acceptably decreased numbers. Optimal treatment duration has not been determined, but most regimens last two to three years.

Side effects can include minor gastrointestinal disturbances including nausea and vomiting, as well as more severe effects such as leucopenia, hemorrhagic cystitis, myocarditis, infertility and hair loss. In people being treated with cyclophosphamide for other cancers, an increased risk of secondary leukaemia has been reported. Increased risk of malignancy appears to depend on total dose, and care must be taken when the cumulative dose exceeds 80–100g. People with MS receiving cyclophosphamide should be monitored for lymphopenia, or abnormally low levels of lymphocytes in the blood, and any sign of infection. Bladder toxicity can be avoided with extensive hydration.

Overall, a significant effect on MS progression has not been proven, and the drug is reserved for people with disease progression occurring
over a relatively brief period of time and with frequent clinical and radiological relapses, who do not respond well or tolerate other less toxic immunosuppressant medications.

*Methotrexate* (MTX) is a drug that interferes with DNA synthesis by inhibiting an enzyme called dihydrofolate reductase. It acts mainly by depleting lymphocytes, but has also shown some immunomodulatory effects such as the inhibition of chemokine and cytokine secretion.

MTX is widely used in other autoimmune diseases such as rheumatoid arthritis and psoriasis. MTX was tested in a trial involving people with primary and secondary progressive MS using weekly oral doses of 7.5 mg, demonstrating only a reduction in the rate of progression of upper-extremity functional impairment, without significant impact on other clinical measures. MTX has also been tested in combination with other drugs such as interferon beta and methylprednisolone, with promising results, but findings await confirmation in more extensive studies.

When administered orally at a weekly dose of 7.5 mg, mild adverse reactions can include gastrointestinal discomfort, nausea, headache, flushes, fatigue and hair loss. Liver toxicity is a potential major adverse effect, although blood disorders are uncommon with this dose of MTX, and potential cancer risk has not been shown in large series using similar doses for other diseases. Folic acid supplements can reduce potential side effects.

*Mitoxantrone* is a drug that has been widely used to treat breast and prostate cancer as well as lymphomas and leukaemias. It blocks an enzyme called topoisomerase-II, thus disrupting DNA synthesis and repair. It also decreases antibody secretion by B cells, inhibits monocyte and lymphocyte migration and decreases proinflammatory cytokine secretion.

It is the only drug in this group approved by the Food and Drug Administration (FDA) in the USA to treat people with relapsing-remitting MS (RRMS) who suffer frequent relapses or incomplete remissions, or for people with rapidly progressing secondary progressive MS (SPMS).

Mitoxantrone has been studied in two trials using different treatment regimens: one FDA approved protocol uses a 12 mg per m² body surface infusion every three months, and another administers mitoxantrone at a dose of 20 mg, together with methylprednisolone monthly for six months. Data from these trials indicate that mitoxantrone may represent a treatment option for people who experience suboptimal response to interferon beta or glatiramer acetate, as well as in people with SPMS with increasing disability.

Unlike cyclophosphamide, dosage is not usually adjusted and white blood cell counts should be monitored carefully for development of leucopenia starting habitually 7-10 days after infusion. Other common adverse effects include transitory amenorrhoea (absence of the menstrual period), nausea, vomiting and hair loss. The most serious adverse effects are cardiotoxicity and risk of leukaemia. Congestive cardiomiopathy has been observed above cumulative doses of 140 mg/m² usually after 1-2 years of treatment. People on this treatment should undergo ultrasound monitoring at baseline and before each infusion. Treatment should be discontinued if left ventricular ejection fraction (LVEF – the fraction of blood pumped out of the left ventricle with each heart beat) drops by 10 percent, or if LVEF is under 50 percent on repeat examinations.

Risk of therapy-related acute leukaemia has been estimated at 0.7 to 6.7 per 1,000. Since there are no tests to identify susceptible people before treatment, all people with MS receiving this drug should be monitored using blood tests during follow-up, and for up to five years after therapy discontinuation. Further, people treated with mitoxantrone have an increased risk of PML (see page 11) if subsequently treated with natalizumab.
Conclusions

Immunosuppressants are useful in some cases and using specific therapeutic approaches, especially when disease control is insufficient with immunomodulatory drugs, or as induction therapy, given that early inflammatory events appear to correlate with later disability.

Approval of mitoxantrone to treat rapidly progressing SPMS, or RRMS with high relapse rate, or cases showing insufficient response are proof of the potential this group of drugs has. However, immunosuppressants also retain major drawbacks limiting their clinical use, namely their serious adverse effect profile and lack of clinical evidence from prolonged, large-cohort trials. Risk of developing cancer, especially leukaemias and lymphomas, as well as potentially life threatening infections, have been reported but not thoroughly addressed. In the case of mitoxantrone, cardiotoxicity represents another critical limitation, which could be potentially avoided by limiting the total drug dose allowed in an individual, and being selective when deciding which individuals are most appropriate for receiving this drug.

In terms of clinical studies, a great challenge related to this group is that many of these drugs have lost patent protection, meaning that the pharmaceutical company no longer has exclusive rights to the drug. This may result in a lack of interest on the part of the pharmaceutical company in conducting large clinical trials to study therapeutic effectiveness or in identifying patient subgroups benefiting from their use. Carefully designed studies with long-term follow up addressing these questions are lacking.

Whether to add an immunosuppressant drug, use it to replace current treatment in people that do not achieve disease control or in induction therapy regimens, are decisions that should be made carefully by the neurologist together with the person with MS, while we await more evidence or the development of safer, second generation immunosuppressant drugs.

The clinical use of many immunosuppressant drugs will benefit from further large-scale clinical trials.
Pharmacological treatments for MS symptoms

Jaume Sastre-Garriga and Mar Tintoré, Unitat de Neuroimmunologia Clínica, MS Centre of Catalonia (CEM-Cat), Barcelona, Spain

MS symptoms are the result of neurological impairment related to disease progression and/or relapses. They may be transient or fixed, and may be the result of damage at many levels of the central nervous system. As a consequence, it is very difficult to provide a complete list of symptoms experienced by people with MS, but a non-exhaustive account should include: fatigue, cognitive impairment (including language disorders), depression, pain, dysarthria (speech difficulties), dysphagia (swallowing impairment), spasticity, tremor, vertigo, walking difficulties related to weakness, visual symptoms (including double vision and impaired visual acuity) and bladder, bowel and sexual dysfunction.

A number of drugs have been tested in the context of clinical research. Evidence is not overly impressive but some progress has been made in recent years. MS clinical trials have obtained positive results for the symptoms of spasticity and gait problems, but for other symptoms, such as fatigue and cognitive impairment, evidence has been conflicting and, thus, recommendations are neither definitive nor clear.

Evidence coming from clinical trials performed in subjects with other conditions but similar symptoms, provide some basis for treating urinary and sexual dysfunction, vertigo, seizures, mood disturbances and pain. Unfortunately, a number of symptoms in MS are not easily treated with medications because of the lack of any evidence (positive or negative), or because of non-significant results from clinical trials. Among these are ataxia and tremor, double vision, visual loss, impaired sensation, dysphagia and dysarthria.

An important challenge in symptom management is balancing treatment benefit with the risk of side effects. It is very possible that when treating a given symptom with good results, another symptom may be worsened. An example of this is the successful control of spasticity that produces a reduction in pain as well, but a marked worsening in mobility. For this reason a comprehensive approach is needed. Any intervention with the aim of alleviating existing MS symptoms should take into account the person with MS and their carer’s perspectives, so as to make sure that the goals are realistic and achievable. Although pharmacological therapy may be an important part of symptom management in people with MS, other approaches should also be considered, including rehabilitation strategies.

An excellent summary of these key points can be found in the introduction for the section “Managing specific impairments” from the UK’s National Institute for Health and Clinical Excellence guidelines on the management of MS (2003):
"The range of potential symptoms is vast... In most people there will be several if not many symptoms... in practice the overall situation of the individual must always be borne in mind before acting. Thus for each impairment there is an unwritten first recommendation – do not start or modify treatment until all aspects of the individual's clinical situation have been established and understood, and the wishes and expectations of the person with MS have been established."

Pharmacological treatments for specific symptoms

**Fatigue.** Fatigue in people with MS can be due to different causes. Primary fatigue is experienced as a direct result of damage to the central nervous system. Secondary fatigue can be related to sleep disturbances, infection, exertion, medication, depression and environment (for example, temperature or poor lighting). A number of drugs have been tested with the aim of reducing primary fatigue in people with MS, including modafinil, amantadine, pemoline, methylphenidate, aspirine, Prokarin® (a combination of histamine and caffeine), L-carnitine and aminopyridines.

Although there are some positive results, final recommendations from systematic reviews of the available literature always conclude that little or no base of evidence is available to guide their use in helping people with MS manage their fatigue. In spite of this, recent studies show that, in some contexts, more than one third of people with MS with moderate or high levels of fatigue had received drug treatment for fatigue (primarily amantadine, but also methylphenidate, pemoline or modafinil). It is also worth mentioning that some disease-modifying therapies have shown a decrease in fatigue levels in their pivotal trials; however, this was not the main goal of these studies and thus, caution should be used when interpreting such findings.

Finally, fatigue has also been approached through other non-pharmacological strategies such as energy conservation courses, cooling therapy or yoga. In any case, a comprehensive approach is needed, including the consideration of other triggering factors such as ineffective night time rest periods due to pain or spasticity, and the impact of depression.

*It is estimated that up to 90% of people with MS experience fatigue.*
Cognitive impairment. The pharmacological approach to cognitive deterioration has mostly been restricted to cholinesterase inhibitors (the same group of drugs used in Alzheimer’s disease). Unfortunately, negative evidence has resulted from controlled trials for rivastigmine and donepezil, and even worse outcomes when compared to placebo have been observed for memantine (from another family of drugs). A recent systematic review highlighted good levels of evidence in favour of some strategies of cognitive rehabilitation targeting specific domains, such as memory and learning. Further, cognitive outcomes have been included in a number of studies with disease-modifying drugs and non-conclusive evidence is available that treatment for the underlying disease may halt or diminish the pace of cognitive deterioration.

Depression. This may occur as a reaction to receiving a diagnosis of MS or as a result of the MS disease process itself. Psychotherapy and antidepressant medication are often used in combination for treating depression. The most common medications are selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and sertraline. Tricyclic antidepressants, such as amitriptyline and imipramine, are also used, although less frequently due to side effects which can worsen other MS symptoms, including drowsiness, constipation and urinary retention. In order to encourage adherence, people with MS should be informed that the benefit of antidepressants can be seen after six to eight weeks.

Spasticity. A Cochrane review on anti-spasticity agents for MS concludes that: “The absolute and comparative efficacy and tolerability of anti-spasticity agents in MS is poorly documented and no recommendations can be made to guide prescribing” (2009). However, a number of medications are available that have shown efficacy in limited clinical trials or clinical practice settings including baclofen, tizanidine, clonazepam, diazepam, gabapentin, dantrolene, cannabinoids and botulinum toxin. Baclofen can also be administered intrathecally, as can phenol, in cases of severe spasticity, which are unresponsive to other types of therapy and mostly affecting the lower limbs.

Common side effects of these drugs are sedation and weakness so that dose titration should be closely monitored, actively involving the person with MS, so as to find the right dosage to achieve desired effects without hampering mobility or cognition. Rehabilitation approaches, namely physiotherapy and occupational therapy, are also applied in spasticity management, typically in combination with pharmacological therapies.

Problems with walking are among the most common mobility limitations in MS.

Impaired walking ability. Fampridine has been recently approved in Europe and USA to improve walking speed in people with MS. Fampridine prevents potassium particles from leaving neurons and enhances propagation of nerve impulses to stimulate the muscles. Seizures are a worrisome potential side effect of fampridine, although their frequency seems to be very low at presently recommended doses.

Bladder dysfunction. Based on evidence from studies performed in other conditions, antimuscarinic drugs, such as tolterodine or oxybutynin, may be recommended in the management of bladder overactivity leading to...
urgency and incontinence in people with MS. Increased urinary retention is an adverse effect of antimuscarinic drugs and may lead to increased risk of infections. Their use is not recommended in cognitively impaired individuals, as antimuscarinic drugs may further worsen cognitive performance and induce confusion.

An intranasally-administered drug, desmopressin, has been shown to be useful in decreasing urine production and is especially recommended to control nocturia. This drug cannot be used more than once a day, however, as it would lead to potentially severe liquid retention.

**Sexual dysfunction.** Sildenafil has been shown to be effective in enhancing erectile response in men; newer drugs from the same family, such as tadalafl and vardenafil, may also be effective in men with MS with sexual dysfunction, although supporting evidence is not currently available. No such evidence is available in women with MS. However, oestrogen creams or a vaginal suppository may relieve vaginal dryness, pain or burning. It should also be noted that some MS medications can have an affect on sexual functioning, for example reduced libido.

**Pain.** There are different forms of pain that can affect people with MS, arising from a number of sources which can, in turn, respond to specific medications. It is therefore very important to begin with a thorough evaluation in order to accurately classify the pain. In general, evidence is lacking in support of definitive strategies for pain treatment in MS, and often clinical decisions are based on studies performed in other conditions.

Carbamazepine, gabapentin, lamotrigine, misoprostol and topiramate can be used in treating trigeminal neuralgia; carbamazepine (or its newest formulation, oxcarbazepine) may be a first-line choice, but side effects such as impaired balance and double vision are frequent and careful titration of the drug is needed. Although there are no indications based on randomised clinical trials in MS as to the overall efficacy or the best dosing schedule, neuropathic types of pain, such as those affecting the limbs in a persistent fashion, can be treated with tricyclic antidepressants such as amitriptyline, or with pregabalin. Gabapentin and levetiracetam may also be used. Side effects of these drugs should be considered on an individual basis so as to achieve favourable risk-benefit ratios.

Cannabinoids have been studied in randomised clinical trials, but their effectiveness, as well as their long-term effects, need to be studied further.

**Conclusions**
Obviously, further research is needed in all areas of symptomatic therapy in MS. It is important that newly tested strategies include a combination of pharmacological and non-pharmacological approaches, as it is expected that not only additive but synergistic effects can be observed, as is the case, for instance, of physiotherapy and drug therapy for spasticity.

Where evidence of effectiveness is lacking, a person-centered, integrative approach is even more important in the management of MS-related symptoms. Since MS symptoms infrequently occur in isolation, the benefits must outweigh the risks associated with the use of many symptomatic drugs with adverse effect profiles.
Treating an exacerbation

Robert M Herndon, MD, University of Mississippi Medical Center and the Veterans Administration Medical Center MS Clinic, Jackson, Mississippi, USA

MS exacerbations or “attacks” appear with the onset of new symptoms or worsening of previous symptoms lasting more than 24 hours. It is a clinical event that results from active destruction of myelin in the brain or spinal cord. A typical attack might consist of visual loss, weakness, numbness or problems with balance or coordination. Subclinical attacks, that is, attacks without new, recognisable symptoms, also occur since there are many demyelinating episodes that can be seen by magnetic resonance imaging (MRI) in the absence of new symptoms.

Attacks are typically treated with intravenous methylprednisolone, 1gm daily for 3-5 days. The initial dose may be followed by a taper using a particular medication reduction regimen. High-dose steroids work by shutting down production of inflammatory cytokines and destroying activated lymphocytes. Low-dose steroids only shut down inflammation by shutting down cytokine production without destroying the inflammatory cells.

The high-dose regimen gained credence when it was shown in an important international study, called the Optic Neuritis Treatment Trial, that low-dose steroids doubled the rate of recurrent optic neuritis while the high dose regimen decreased new attacks for two years. Since steroids do carry a very slight risk of joint damage, psychosis or elevated blood sugars, minor attacks are often not treated.

It should be noted that disease progression is not influenced by steroids, they only decrease relapse time. Often the person with MS will need input from various members of a multidisciplinary healthcare team to help regain function after a relapse.

Pseudo-exacerbations are the recurrence of symptoms due to an illness with fever or overheating from other causes such as exercise. For example, exercise in someone who has recovered from optic neuritis may cause a deterioration of vision which returns to normal when the body temperature returns to normal (Uhthoff’s phenomenon). Pseudo-exacerbations occur because demyelinated fibers are temperature sensitive, and may quit transmitting signals with even a slight increase in temperature that returns to normal when temperature returns to normal.
Safety in clinical trials of new pharmacological therapies

New pharmacological therapies for MS are tested and approved because people with MS are willing to participate in clinical trial research. Before agreeing to participate, a person should be aware of how the trial will be monitored and exactly what their role will be. Healthcare professionals who work with people with MS can be an important source of information regarding safety in clinical trials. Below are some of the key safety issues to consider.

Regulating clinical trials
In order to obtain approval for a clinical trial of a drug, a company must submit a detailed study protocol to the national health authority. It is the responsibility of the health authority (and an ethics committee if the research takes place in a hospital) to ensure the dignity, rights, safety and well-being of the people who take part in medical research. They do this by evaluating the content of the research protocol. Research studies involving people must receive health authority and ethical approval in order to be carried out.

The World Medical Association has also developed the "Declaration of Helsinki", which sets the ethical standards for research involving humans. In addition to this, the US Food and Drug Administration, the European Agency for the Evaluation of Medicinal Products as well as multiple legislative texts at the European Union level, have very specific rules to protect people involved in clinical trials.

Informed consent
Participation in a clinical trial requires that the person signs a form saying that they have given informed consent. Signing the form confirms that the person has been given all the important facts about the trial, understands them and has agreed to take part of their own free will. An informed consent is not a contract and the person can change their mind and withdraw from the study at any time without repercussions.

Contents of an informed consent document
While informed consent documents can vary, they should be easy to comprehend and include:
- the purpose of the clinical trial;
- a description of procedures or tests, how frequently they will be applied, and where they will take place (at home, in the hospital or clinical centre, for instance.). If it is a trial in which subjects are randomised to different groups, the document should make clear what procedures each group will undergo and also indicate the chances of being placed in either group;
- the duration of the trial and whether it involves follow-up over time;
- information about any circumstances under which the investigator might remove the person from the trial (for example if MS worsens or new information indicates the person should not continue);
- potential risks of the trial, including foreseeable physical and non-physical risks, the likelihood of these occurring, how serious they may be, and whether they are more likely to be short-term or long-term;
- benefits of participating in the trial, both personally and for others with MS;
- alternatives to participation, such as other care options, including, for example, other therapies;
- information about confidentiality;
- costs, if any, and whether participants will be paid;
- participant’s rights;
- contact information about who to call in case of questions or problems;
- the signature of the participant and a witness.

Finally, clinical trials of pharmacological therapies can seem very complex. The potential participant should have ample opportunity to ask the investigator any questions about the study before making a decision about their participation.

Adapted from FAQ on Clinical Trials, EGAN-European Genetic Alliances Network. Download the complete publication free at http://www.fgcp.be
Access to treatment worldwide

Zoe Burr, Head of International Development, MSIF

People with MS live all over the world and experience many different challenges in terms of access to support, services and MS medication. The challenges facing people living with MS in emerging countries are often as diverse and complex as the symptoms of the disease itself. High levels of political and economic instability; a susceptibility to climatic extremes and the presence of other, more widespread diseases mean that already stretched resources are often focused on addressing other, more immediate, needs. These factors, coupled with a relatively low recorded incidence of MS – due, in part to a lack of available diagnostic tools – leaves the MS population and their families underserved by services and support.

Dao Mai (far right), Vietnam

I have had MS since 2000. My symptoms include foot drop, limb stiffness, imbalance, weakness, spasms, optic neuritis and mild bladder and bowel dysfunction. Recent additions include a burning sensation, numbness, slurring of words and pins and needles. For my MS course, I’m taking azathioprine and corticosteroids when there is an attack. For my symptoms I’m taking baclofen (spasticity), sifrol (restless legs syndrome), carbamazepine (anti-convulsion), and some supplements such as vitamin D3, potassium, magnesium and calcium.

Access to medication is a huge issue in Vietnam. MS is rare here, so experience and treatments are limited. The only option available is steroids plus some medications for symptoms that are available on the “black market” with its danger of counterfeits, or at pharmacies in the big cities only. Although drugs can be bought easily without a prescription, people in rural areas find it hard to access them. MS is not on the list of “health security”.

Receiving an MS diagnosis leads to many questions about the course the disease will take and the impact it will have on someone’s personal life and career. Receiving the diagnosis in a country where little is known about the disease, and there is limited or no support from the state and no, or only an embryonic, MS organisation, often leads to the diagnosis being hidden.

People may hide their diagnosis for fear of becoming a burden on their family, of being isolated from everyday life or of losing their job. These are fears which a well-established MS society can help to allay through information and advice, support groups, organising events and activities, and getting MS on the government agenda through campaigning for change.

We have to pay all medication costs ourselves. The average income in Vietnam is US$100/month so most people with MS cannot afford the US$1,000/month required for disease-modifying drugs. Patient assistance programmes are available in many countries, but not here.

MS Vietnam, www.ms-vietnam.org

Margarita Ruiz Peraza, Cuba

I have had MS since 1967. It began with epileptiform convulsions (once or twice a year) until 1985, when I started having walking difficulties and altered sensation. My MS was the relapsing-remitting form until 1990, and now I am more or less stable, but have a high degree of disability, near to 9, according to the Expanded Disability Status Scale. I cannot stand up because my legs are like gelatine and I can use only my left hand.

I am now taking symptomatic medications (gabapentine, amantadine, clonazepan) and doing rehabilitation. In my opinion, for the first stages of MS, remaining optimistic and continuing to work are very important. If it is not possible to stay in your own profession, look for new alternatives.
Access to medication is an issue for people with MS in Cuba. The symptomatic medicines are subsidised by the government and they are affordable, but often unavailable. The treatments for acute exacerbations (high-dose intravenous methylprednisolone) are free. However, out of an estimated 2,000-2,500 people with MS in Cuba, only 50 people with MS received disease-modifying drugs in the last year because of their very high cost. All these people are either children or young people who are newly diagnosed. The government always buys the expensive drugs in foreign countries and gives them to people with MS for free. It is very unusual that somebody here has enough money to buy this kind of treatment with his or her own resources. We are hopeful that at least 100 people will receive disease-modifying drugs next year.

Esclerosis Múltiple Cuba, emcuba@infomed.sld.cu

Kürsat Korkut, Turkey
I have had MS for nine years. My main symptoms are dizziness, difficulty speaking, and also the strength in my legs – I have been using a walking stick for two years now. I take interferon beta-1a. We are lucky here in Turkey – access to MS medication is relatively easy and free. We have a national health service, so when I see my doctor and I am given a prescription, I can go to my pharmacy to collect the medication. We have other issues in Turkey though, in particular access to transport and public buildings.

Türkiye Multipl Skleroz Dernegi, www.turkiyemsdernegi.org

Isabel Tilyard, New Zealand
I have had MS for 15 years, but was only diagnosed five years ago. I have general weakness in my muscles, the usual bladder dysnergia, fatigue and muscle twitches. In essence I have a broad range of symptoms (almost everything on the list with a few twists) – none serious enough to stop me yet, although my left leg was affected by a relapse and has not fully recovered. I cannot walk more than about 200m without the limp becoming apparent, although fatigue usually stops me just as much. Hand-eye-coordination, balance and shaking also affect me at times. I am on baclofen for muscle twitches and could not live without vitamin D3. I also take a herbal supplement.

I am not sick enough yet for any other medication. However, one of the reasons why I am soon moving to Australia is that there I believe I will be entitled to MS medications that are not just aimed at combating the symptoms. New Zealand has tough requirements for government subsidised medication for MS – a person has to have had two relapses in a 12-month period and have limited mobility. The medication is available here without government assistance, but it is prohibitively expensive for most. I find this incredibly frustrating – it would seem to me that keeping people with MS working and paying taxes would be preferable to waiting until they are unable to work and thus are then being supported by the government.

MS New Zealand, www.msnz.org.nz

Pille-Katrin Levin, Estonia
I had my first symptoms in 1993 with double vision, followed by a loss of sight. At that time diagnosing MS was difficult in Estonia – we didn't even have an MRI machine. Despite that, the eye doctor told me about MS and that I may have it. For many years, I thought it would only be a short time until I would need a wheelchair. I wasn't depressed or panicked, I just felt calm and rational about planning my life. Now, 18 years later, I discover that I may end up standing till the end!

I've been on glatiramer acetate since 2007, when it first came to Estonia. I had had my first child and was in a pretty bad condition. Eight months later I was able to do everything again. Since then, I've had just one relapse.

The main treatments (interferon beta 1a and 1b and glatiramer acetate) are available to people with MS in Estonia and are 100% subsidised by the Estonian Health Insurance Fund. However, as in many countries, treatment is prescribed only after two relapses during two years. But all in all, I think the situation in Estonia is quite good as the first choice treatments are available for those who need them. Negotiations with the Health Insurance Fund for getting the second choice drugs, natalizumab and fingolimod, accessible and subsidised in the future look promising.

Eesti Sclerosis Multiplex’i Ühing, www.smk.ee
Choosing medication: two views

The perspective of a person with MS:
Ali Hijjawi (right), President of the Palestinian Authority’s MS Patients and Friends Society, Nablus City, West Bank. www.mspf.org.ps

How long have you had MS and what are your main symptoms?
I have had MS since 1977, 35 years already! My main symptoms are occasional weakness in one leg (sometimes my left leg and sometimes my right leg) together with numbness on the same side. Sometimes an attack causes balance problems and a loss of feeling in different parts of my body. At the beginning and for the first three-to-four years the attacks were far apart, but they have become closer and are now nearly once every six months.

Do you take a disease-modifying medication?
After my diagnosis I took intramuscular interferon beta-1a because it was the most easily available interferon in our country at that time. But it changes, depending on which kind of interferon the Ministry of Health provides for people with MS.

How was the decision about which medication to take determined?
My neurologist discussed the limited choices available. I then started to search for information about MS medication from around the world. In the end, I came back to my neurologist and together we decided I should take intramuscular interferon beta-1a.

Is access to medication an issue for people with MS in your country?
It was. Since the establishment of our MS Society in Palestine we have lobbied the Ministry of Health to make MS medication more available. We succeeded in getting it registered on the essential drugs list in 2008. Now access to medication has become easier for all the officially diagnosed people with MS in Palestine, who are now able to get medicine by paying the monthly minimum registration fees.

The healthcare professional’s approach:
Dr Ari Green, Neurologist, UCSF Multiple Sclerosis Center, San Francisco, California, USA

Do you introduce the topic of medications such as disease-modifying therapies and symptomatic drugs at the same visit as the diagnosis is communicated, or at a later time?
This depends on whether we are confirming the diagnosis or introducing the diagnosis for the first time. If we are confirming the diagnosis then we will discuss therapeutic options. If we are introducing the diagnosis for the first time, we leave discussion of therapeutics up to the person with MS. Many people want to know what they can do to treat their condition, while others need time to process the information and think about their questions. We frequently schedule a return visit to further discuss therapeutic options after our initial discussion.

What is your approach with a person who needs or wants to start a disease-modifying treatment?
I generally recommend therapies based on particular needs and the features of the disease for an individual person with MS. Although I may recommend particular therapies, I present all the options to the person and discuss the benefits and disadvantages of each
individual therapy. Particularly with newer therapies, I advise individuals about the risks of therapy and the unknowns of long-term safety.

**What is your approach with a person who requests a medication that you wouldn't necessarily be in favour of?**

I strongly believe in the importance of patient participation in all treatment decisions. I would discuss the reasons for my recommendations and listen to the preferences and thoughts of the person with MS regarding their individual therapy. Generally, that person's preferences and wishes take precedence over my opinion. My role is to be an expert advisor to my patients, and I would only refuse if I thought a treatment plan was harmful, unnecessary or otherwise unethical.

**What is your approach with a person who is not eligible for a certain medication, for example an individual with progressive MS who asks to be prescribed interferon beta?**

It strongly depends on who is determining the criteria for "eligibility". I always inform the person with MS of the scientific data regarding medications and their use and limitations. If a person desires to use a medication outside of its indication and I feel it is not warranted I will advise them of this concern. I also advise people with MS who have medical insurance if I think that insurers will not pay for their medication because it is not indicated.

**How would you define shared decision-making and do you think this concept is important in decisions regarding treatment of MS?**

Shared decision making is person-centred decision-making. Physicians cannot make decisions for their patients that reflect the different individual’s differing needs unless they understand the wishes and preferences of that person. This comes about by listening and discussing options with each person and seeking to understand their hopes, fears and concerns. As physicians we cannot abdicate our responsibility to provide advice and guidance, but we must recognise the limitations of our own knowledge.

Many people want to know what they can do to treat their condition, while others need time to process the information and think about their questions.

We hope to provide people with MS with objective and unbiased assessments of the evidence, so that together we can make treatment decisions that achieve their goals and wishes. As people with MS are increasingly sophisticated and have access to a variety of information sources, our job is to ensure that they are given a balanced venue for discussing and interpreting that information.

**What are the key issues that a person with MS should understand about a medication before starting therapy?**

People with MS need to understand how a medication will influence their lives in the short-term and over time. This means we discuss the practicalities of taking an individual medicine, but also how they will feel on this drug and its short- and long-term risks. They need to understand the limits of our knowledge but they also need to know that we only recommend therapies when the benefits outweigh the risks. Some people wish to understand how the medicine works in their body and this can empower them to feel in control of their disease, which is important in many ways.

**What do you feel is the most important factor that influences correct adherence to a therapy regimen and how does the neurologist and/or nurse facilitate correct adherence?**

Person-centred decision-making improves adherence because it ensures that we are focused on an individual's needs and wishes.
Your questions answered

Charlene Fink, an MS Nurse at the Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland, Ohio, USA, answers your questions.

**Q:** I am a nurse relatively new to MS. What are the most common obstacles that interfere with good adherence to therapy that MS nurses should be aware of? Are there any solutions?

**A:** Drug adherence is important in effectively managing MS. When people are diagnosed with MS they are often overwhelmed. It is therefore important that the MS nurse establishes a good therapeutic relationship with the person with MS early in the disease course, and that the individual is involved in the choice of disease-modifying therapy (DMT) that will work best for managing their disease and that can fit into their daily routine, alongside work and family responsibilities.

A common reason people with MS discontinue medications is the side effects. MS nurses need to discuss the importance of reporting these, and to use simple strategies to help people tolerate their medication better and thereby maximise adherence.

Although injection site reactions are rarely serious they can result in negative attitudes about self-injecting. Teaching good injection technique, such as rotating sites and skin preparation are essential. Smaller and shorter needles can help decrease pain. Auto injectors can help people with needle phobia. Flu-like symptoms and headache commonly occur with interferon. These may be effectively managed with the use of acetaminophen or ibuprofen before and after injections.

Cognitive problems, mood disorders and fatigue are other aspects that can influence adherence and should be carefully evaluated and monitored. The person may need support from their family to ensure they remember to perform injections. Medications and regular exercise can help mood and fatigue management and also help the person develop a positive outlook towards their DMT. Injections can be performed earlier in the day if fatigue is worse in the evening. Also, doing injections at the same time every day will help set up a regular routine that incorporates the injection into daily living.

**Q:** What can I do to encourage people with MS to keep taking their medications when they get discouraged?

**A:** MS nurses play a vital role in helping to educate and assess people with MS on DMTs. It is important to:

- Inform the person that the goal of therapy is to prevent further worsening of their disease and that it will help decrease relapses and new lesions.
- Clarify expectations early when starting treatments so the person can be realistic about the goals of DMTs, for example, they do not relieve existing MS symptoms.
- Teach people with MS that taking their therapy consistently helps them to control and manage their illness, maintain current functional status and ultimately empowers them to prevent progression and disability. The person’s perceived benefit from DMT is a critical element in adherence.

MS nurses can remind people that medications to help control their disease were not available 20 years ago, and that new therapies are being developed all the time. Acknowledging this may help the person recognise the value of treatment.

It is important to stress that the medication can only work if it gets into their body. Having an open dialogue during the visit and asking whether or not they have missed an injection and the reason it was missed is also important. This can help target specific areas to help improve their adherence. One study reported that the most common reason for missing injections was that the person forgot to take it.

Having support from a family member or friend can help develop a positive atmosphere encouraging adherence, and provides a support system that is often needed in the long-term.
**Glossary**

**Adherence**
How closely a prescribed treatment is followed.

**Autoimmune disease**
A disease that results from an overactive immune response of the body against its own cells.

**Clinically isolated syndrome**
A first neurological episode, caused by inflammation or demyelination of nerve tissue. An episode may be monofocal, in which symptoms present at a single site in the central nervous system, or multifocal, in which multiple sites exhibit symptoms.

**Cryopreservation**
To preserve by freezing.

**Fulminant**
Occurring suddenly and with great intensity or severity.

**Immunomodulating treatments**
A treatment that is capable of modifying or regulating one or more immune functions.

**Immunosuppressant treatments**
A treatment capable of suppressing immune responses.

**Intramuscular injection**
An injection directly into the muscle.

**Intrathecal injection**
An injection into the spinal canal, the space surrounding the spinal cord.

**Lymphocyte**
A type of white blood cell in the immune system.

**Monoclonal antibody**
Antibodies are proteins produced by the immune system to fight foreign substances, such as infections. Each antibody is targeted at a single type of cell, although the body will make millions of copies of a specific antibody during the immune response. Monoclonal antibodies can be produced in large quantities in a laboratory. They can be designed to bind to proteins on the body’s normal cells, altering the immune response. In terms of drug production, this means that if antibodies can be identified that bind to cells which are involved in attacking nerve cells and causing disease activity in MS, treatments may be developed that will only affect those cells.

**Randomised controlled trial**
A type of scientific experiment most commonly used in testing the safety or effectiveness of a pharmacological or non-pharmacological intervention. Study subjects – after assessment of eligibility and recruitment, but before the intervention to be studied begins – are randomly allocated to receive one or other of the alternative treatments under study.

**Subcutaneous injection**
An injection administered into the fatty layer of tissue directly under the skin.
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**With many thanks**

MSIF would like to thank Merck Serono for their generous unrestricted grant, which makes the production of *MS in focus* possible.