MODULE 4:

Treating Multiple Sclerosis

English Version

professional msnurse

A Project of the European Multiple Sclerosis Platform

Module 4: Treating MS

1 Introduction

Intro

In this module, the pharmacologic management of multiple sclerosis (MS) will be reviewed. The disease modifying therapies (DMTs) will be explored, together with the nursing issues associated with them. In addition, symptom management strategies will be discussed with an emphasis on pharmacological management.

Although disease-modifying therapies (DMT) are increasingly used to reduce the frequency of relapses and delay the progression of disability, most people with MS will experience neurological symptoms [1]. Others will experience relapses during therapy which may give rise to new symptoms[1]. It has been suggested that DMTs represent a 'longer-term' treatment, or investment in the future, and therefore DMT should be combined with active symptom management[1-3].

As new research and emerging therapies change the treatment paradigm for MS, the nursing role and its associated demands are changing as well. Nurses specialising in the care of MS patients need to stay abreast of MS research and disease-modifying agents available, because patients are

eager to make use of these new treatments. Nurses also need to be aware of the complex and sometimes novel drug treatments, which can have complicated side effects, if they are to successfully and proactively support people with MS. The criteria for use of these treatments differ by country.

Following completion of this module you will be able to understand the options for DMT for people with MS, the efficacy and adverse events most commonly reported and how DMTs are typically utilised in different patient types. In addition, drug therapy for the more common symptoms experienced by people with MS is reviewed and summarised.

2 Treating an Acute Episode

2.1 Learning Objectives

In this section the management of the acute symptoms of MS will be reviewed. After review of this section, you will be better able to:

- Define what is a relapse
- Explain the impact of relapses on an individual patient
- Explain the management of a patient experiencing a relapse
- Describe the management of relapse symptoms
- Describe the benefits and side effects of steroid therapy.

2.2 Introduction

Most people with MS, apart from those with primary-progressive MS (PPMS), will, at some point during the course of their disease, experience an acute exacerbation (or relapse) of their symptoms. This may be a relapse from which they completely recover, although over time, some may experience increasing loss of function.

The natural disease course results in most people with RRMS progressing to secondary-progressive MS (SPMS) during which there is progressive disability with or without superimposed relapses. Similarly, people with PPMS may suffer periods of an acute worsening of symptoms that require treatment but will not experience relapses.

2.3 First, or inaugural Attack

MS can present in different ways and for many the initial symptoms are non-specific; for example sensory problems or optic neuritis which may resolve without intervention. A diagnosis of CIS or clinically definite MS may be made at this point (see Module 3: Diagnosis) and patients may require symptomatic management of their acute symptoms as described in section 4 (Treating symptoms of MS). Alternatively, for individuals presenting with symptoms of relapse, treatment may require high dose corticosteroid therapy, as described in section 2.4 (Relapse).

2.4 Relapse

2.4.1 Introduction / Background

According to the 2010 revisions to the McDonald Criteria of the International Panel on Diagnosis of MS, a relapse is defined as "a patient-reported or objectively observed event typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection."

A relapse typically develops over hours or days but will eventually plateau, which may last days or weeks, followed by complete or incomplete recovery at varying rates. The majority of relapses are monofocal (research states ~74%), but they can also be multifocal, and are mainly sensory (48%), pyramidal (34.4%) and visual (20%).[4]

Either way, a stable or improving period of 30 days should separate the onset of subsequent events for them to be distinguished as separate relapses.[5]

It is known that acute viral infections, such as influenza or a urinary tract infection (UTI), and possibly other stressors, including hormonal cycle in women, can affect neurological function and can be confused with a clinical relapse[6,7] .

It is important to distinguish between a true 'relapse' and a pseudorelapse, which is a relapse typically associated with an increase in heat whether this is from an infection, exercise or, occasionally, fatigue. Within the assessment of a relapse, nurses are likely to perform urinalysis and a recording of vital signs prior to any steroid prescription.[8] Some nurses will also take bloods for inflammatory markers. This assessment is likely to isolate any infection the individual is carrying that they may not know about. Some will check blood glucose to monitor for hyperglycaemia.

Comparing serial MRI scans may identify new plaques in the CNS but these additional lesions may be clinically silent; a causal relationship cannot necessarily be assumed. Distinguishing between an exacerbation and functional neurologic symptoms requires careful history taking and examination by an experienced neurologist.

2.4.2 Impact of a relapse on the patient

Relapses can have a significant impact, not only on the experience of physical symptoms, but also on the social, financial and psychological well-being of those affected. Whilst in relapse, many cannot drive; there can be loss of income and significant difficulties bringing up a young family, especially for single parents. There is a high level of anxiety and uncertainty associated with the unpredictable occurrence and possible long-term effects of relapses.[9] These impacts must also be taken into account when planning relapse management to contribute to a more optimal patient centred approach.[10]

2.4.3 Impact of DMTs on Relapses

The annual relapse rate (ARR) historically was approximately.1.5/year but it is dropping. It is a recognized feature that relapse frequency decreases with time from diagnosis and also with increasing age, and relapse-free periods are not uncommon.[11]

On average, a patient with RRMS may experience a clinically presented relapse every two years; DMT therapy can reduce the chances of a relapse in one year by approximately one-third (see section 3 Preventing relapse & disease progression: DMTs), and early initiation of DMT has been shown to delay progression from Clinically Isolated Syndrome (CIS) to clinically definite MS. Continuous DMT therapy has also been shown to delay progression to SPMS.

Early initiation of DMT (with either interferon beta or glatiramer acetate) has been shown to delay progression from Clinically Isolated Syndrome (CIS) to clinically definite MS.

2.4.4 Aims of Management of a Relapse

Even with DMT, relapse can occur, ranging from extremely mild to significantly disabling, at times requiring hospitalisation and supportive care[12]. Some relapses are clinically silent and may only be detected by MRI at time of inflammation so people with MS can accrue early loss of brain tissue without obvious signs of damage.

The aim of treatment, when initiated, is to reduce inflammation in the short term and to thereby hasten recovery. Many episodes will improve spontaneously regardless of therapy (usually steroid therapy – see section 2.4.5). It is important that the benefits of steroids are weighed up against the adverse effects of treatment; on average, physicians treat 25% of relapses[13].

2.4.5 Treatment of a Relapse

Steroid therapy: Principles and efficacy

High-dose, short-term steroids is the accepted treatment for MS relapses. Steroid therapy is effective in shortening the duration of an individual's relapse and accelerating recovery[14,15].

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Steroid preparations have been used to treat MS relapse events for over 50 years; the most commonly used are methylprednisolone and prednisone[14]. This is a long-acting, synthetic corticosteroid which is considered more effective than the natural substance cortisol. There is, however, no evidence that steroid therapy has any effect on the course of disease and it is important that the person with MS understands that long-term recovery from an acute relapse will be the same whether he/she receives steroids or not.

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There is considerable diversity amongst neurologists and in national guidelines regarding dose, duration and choice of steroid agent. Guidelines in the UK recommend oral treatment with 500mg methylprednisolone for 5 days; if patients are in hospital, or if oral steroids are not effective, intravenous treatment with 1g methylprednisolone for 3-5 days is recommended.[16] Oral treatment is now known to be as effective as the intravenous route.[14]

Commonly used regimens are:-

- Intravenous methylprednisolone, 500–1000 mg daily, for between 3 and 5 days, or
- High-dose oral methylprednisolone, 500–2000 mg daily, for between 3 and 5 days[15].

The decision to treat is best taken in conjunction with the patient in a process of shared decision-making (SDM) and is based on adequate information provision and an assessment of the impact of the relapse on the individual. In a randomized controlled trial, patients educated about the evidence

regarding steroid use during relapse decided to treat less relapses, opted for more oral than intravenous steroids, had higher levels of perceived autonomy and sought less contact with their clinicians.[17]

Steroids may sometimes not be administered if a patient has an optic neuritis; although the immunological characteristics of MS patients with optic neuritis is similar to those with other forms of relapse[18], effects of high dose methylprednisolone have been inconclusive; with some suggestion of improved symptoms on visual analogue scale, but not visual acuity[19]. The Optic Neuritis Treatment Trial was a 15 centre study undertaken in the US to compare prednisolone (1 mg/kg/day oral for 14 days), methylprednisolone (250 mg IV every 6 hours for 3 days) and placebo. The trial found that high-dose intravenous methylprednisolone followed by oral prednisone accelerated visual recovery but did not improve the 6-month or 1-year visual outcome compared with placebo, whereas treatment with oral prednisone alone did not improve the outcome and was associated with an increased rate of recurrences of optic neuritis. Most patients had complete, or near complete recovery 1 year after their attack[20,21].

The usual therapy for relapses is high-dose IV or oral steroids. The selection of steroid (usually methylprednisolone) and route varies between MS centres.

There is no substantial evidence regarding the optimum time to administer steroids when a patient is suffering a relapse. However, often they are given relatively early during a relapse episode. Sometimes the dose may be tapered (reduced) over a few days.

Some patients will find their relapse is so disabling it requires hospitalisation and supportive care[12]; others can be treated at home or as an out-patient.

There is some evidence to show that recovery from a relapse is improved by having rehabilitation as well as steroids.[22] Rehabilitation can combine many different approaches to managing MS including physiotherapy, occupational therapy, dietary advice, and employment services. Relapses may also prompt a change in therapy, for example a switch of DMT.

Side effects of steroid therapy
Not all patients experience side effects when they receive steroid therapy for a relapse. However, in one study of 55 patients who had received high dose steroids, 53% experienced adverse events[23].

Adverse events from steroid therapy include:

- Effects on the gastrointestinal tract and bloating
- Change in sleep patterns/insomnia
- Altered mood/; fear, mania and depression
- General malaise
- A metallic taste in the mouth (particularly during and after IV administration)
- Confusion
- Fluid retention

Other, less common events include:

- Hyperglycaemia (high blood sugar levels)
- Acne
- Transient reddening of the face
- Urogenital infections

- Increased blood pressure
- Oedema in the ankles and weight gain
- Infections

Long-term effects on bone density can occur, but this is less of a concern with short course therapy[24]. For some patients with MS (for example, those who have type 1 diabetes, a chronic infection such as TB, severe hypertension, history of psychosis/mania), high dose steroids are contraindicated. In these cases, alternative management of relapse is indicated.

Even though corticosteroid therapy is often used to treat relapse, relatively little data exist on how patients perceive the efficacy and overall value of this approach. Results of a new survey of 4,500 MS patients found that patients who receive treatment for relapses report better outcomes than those who are simply observed. However, 34% of patients feel that their symptoms following corticosteroid treatment are worse than pre-relapse symptoms and that treatment had no effect or worsened symptoms.[25]

Plasmapheresis
Other treatment options that are used less frequently include plasmapheresis. Plasmapheresis, also known as therapeutic plasma exchange, is a procedure that involves separating the blood, exchanging the plasma (typically with donor plasma or albumin solution), and returning the other components, primarily red blood cells, to the patient. It is typically reserved for those patients who experience an incomplete recovery with other treatments. Recently updated guidelines from the American Academy of Neurology suggest that plasmapheresis is probably effective as adjunctive therapy and possibly effective for exacerbations that fail to respond to high-dose corticosteroids.[26]

2.4.6 The Role of the MS Nurse
Only if relapses are accurately reported, recorded and assessed can patients be assured of receiving the correct treatment for their individual pattern of disease. MS Nurses are becoming increasingly active in relapse care and the UK has witnessed an evolvement of a MS nurse led relapse service; this has been accelerated since oral steroids (which can be prescribed by non medical prescribers such as MS Nurses) have been regarded as having similar efficacy as IV methylprednisolone and purport high compliance amongst patients.[27] However, primary research that supports or refutes the MS Nurse role in relapse management is lacking.

Part of the role of the MS Nurse involves the correct identification of relapse, the right assessment, and the application of the appropriate intervention.[28] To do this most effectively, there is a need for MS nurses to be clear regarding a definition of a relapse; this focuses not only on objectively observed events, but also that it is a 'patient reported event'. If the patient says the relapse is disabling and articulates how this is so, then the nurses will use this to form a management plan.

It is essential that MS Nurses can effectively communicate with the patient in order to build a reliable clinical history of their relapse experience;[29] this is particularly important when the patient is experiencing cognitive dysfunction or depression, as the MS Nurse will need to spend considerable time plotting the symptom history and keeping the patient focused on the assessment that is required. With lack of research to guide nursing practice, there has been a reliance on expert consensus groups to decide on key practical aspects of relapse management, such as the work by Perrin Ross *et al* (2012) who have designed the "Assessing Relapse in Multiple Sclerosis (ARMS) Questionnaire" which is growing in recognition.[10]

A key nursing role in relapse management is to educate patients about the possible adverse effects of steroid therapy. The MS Nurse should also be prepared to manage adverse events should they

occur. The MS Nurse plays an important role in educating why steroids might ***not*** be used, even if the patient thinks they are experiencing a relapse. They also need to inform the patient that whether they receive steroids or not, their outcome will be the same. They should also be mindful of the psychological impact of a "revolving door" of grieving, loss and anxiety, and the socio-economic burden of relapse.

An important nursing role in relapse management is to educate patients about the possible adverse effects of steroid therapy.

2.5 Summary

- Acute relapse management focuses on the initiation of therapy to resolve symptoms as required.
- This may include symptom management or for acute relapses/exacerbations, high dose steroid therapy (IV or oral).

Reflective learning point:
How would you ensure patients suffering a relapse receive appropriate support in addition to their steroid therapy, including those treated as out-patients?

Further relapses can be a revolving door of repeated bereavement, further loss and anxiety; how would you support a patient who may be experiencing such feelings?

3 Preventing Relapse & Disease Progression: DMTs

3.1 Learning Objectives

In this section the principles of disease modifying therapy (DMT) will be explored and the available therapies discussed in terms of safety/tolerability, efficacy and the role of the nurse before and during therapy.

After review of this section, you will be better able to:

- Summarise the DMTs commonly used for people with MS
- Distinguish between immunomodulators and immunosuppressants
- Explain the risks and benefits of therapy
- Explore the role of the MS Nurse in encouraging concordance/adherence
- Summarise the adverse events of therapy.

3.2 Types of DMT: Immunosuppressants and Immunomodulators

As described in Module 1: Understanding MS, MS is a complex disease. However, disease modifying therapy (DMT) is now the cornerstone of management for people with RRMS, with the vast majority of patients receiving a DMT. Subcutaneous interferon β-1a and glatiramer acetate are the most commonly prescribed DMTs. In order of importance, the characteristics most affecting selection of specific DMTs are reported by neurologists to be efficacy, safety, tolerability, patient preference, and convenience.[30]
The increasing availability of DMTs has had two major effects. Firstly, there is a renewed importance of relapse occurrence, both before and after starting first-line therapy because of the possibility of treatment escalation. Secondly, a zero-tolerance approach to relapses has become possible, leading to the concept of "No Evidence of Disease Activity" (NEDA) which is defined by no evidence of relapse occurrence, sustained disability progression, or new lesion appearance on MRI. Neurologists are divided on their opinion regarding NEDA, and therefore the degree of tolerance to ongoing inflammatory activity varies between countries.

Although most people with MS will require treatment of existing or emergent symptoms (see section Symptom Management), DMT therapy is used to reduce MS relapse rates and cumulative disability. In addition, DMT therapy can be helpful in some patients with SPMS and overlapping relapses (e.g IFNβ-1b) or rapidly deteriorating SPMS or PRMS (e.g. mitoxantrone).

DMT therapy is used to reduce MS relapse rates slow/delay and cumulative disability.

Evidence now available indicates that early intervention, for example with interferon beta or glatiramer in patients with CIS, can delay the onset of clinically definite MS[31,32].

The established therapies are administered parenterally which the patient may self-administer (e.g. interferon beta, glatiramer acetate), or may be given by a healthcare provider (e.g. natalizumab). However newer therapies, notably fingolimod, teriflunomide, and dimethyl fumarate are oral.

Early DMTs included conventional immunosuppressants which reduce the activity of the immune system, thereby reducing the autoimmune mediated effects underlying the pathogenesis of MS.

However, such therapy also reduces the ability of the immune system to react to foreign antigens. This can lead to an increased risk of infections and, potentially, some malignancies[33].

Immunosuppressants reduce the activity of the immune system, thereby reducing the autoimmune mediated effects underlying the pathogenesis of MS.

Although some conventional immunosuppressant therapy continues to be evaluated for MS, and mitoxantrone (section 3.9) has immune suppressive effects, there has been a focus on immunomodulators as DMTs. Immunomodulators act by suppressing specific stages of the auto-immune response, and ideally, allow the immune system to function against foreign antigens.

Immunomodulators act by suppressing specific stages of the auto-immune response, and allow the immune system to function against foreign antigens.

Currently approved disease modifying therapies include interferon beta, peginterferon beta-1a, glatiramer acetate, and natalizumab, as well as the newer therapies fingolimod, teriflunomide, dimethyl fumarate and alemtuzumab.

Another important concept is that of reversibility of the DMT effect. Many immunomodulators only have activity while the drug is present in the body; this means that once the DMT is stopped, and levels fall below that which has any activity, the effects on the immune system are lost. In contrast, therapy which has an irreversible effect (for example, immunosuppressive therapy which inhibits synthesis of lymphocytes) requires not only drug concentrations to fall below therapeutic levels, but also for the immune system to be restored (in the example, through production of new lymphocytes) (Figure 1).

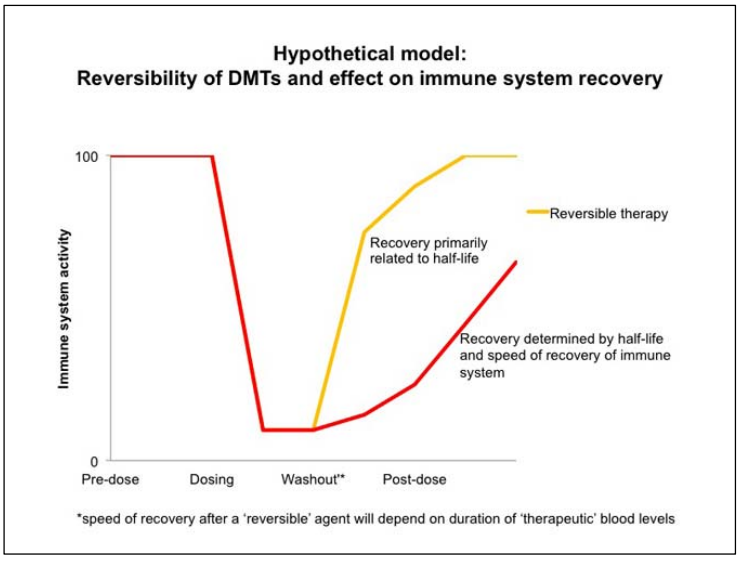


Figure 1: Hypothetical model of immune system recovery: The importance of reversibility

For those DMTs which are irreversible it is not only necessary to wait for drug levels to be 'sub-therapeutic', but also for natural reconstitution of the immune system (e.g. production of new immune cells). For reversible DMTs, effects are lost once the drug is 'washed out' (Figure 1). Table 1 summarises the recommendations when switching to, or from, currently approved DMTs (based on EMEA labelling); additional information and advice may be available from the relevant pharmaceutical companies. Furthermore, individual centres may have their own treatment protocols. This can have implications for the recommendations made when patients switch DMTs.

Product	Switching 'to'	Switching 'from'	Reference
Interferon beta	No specific recommendation	There is no specific protocol, and a 'drug holiday' when switching to another agent is not usually considered necessary unless there are related adverse events which could be worsened by starting a new therapy (e.g. neutropenia)	SmPC for Gilenya and Tysabri[34,35] Personal communication – Biogen Idec UK
Glatiramer acetate	No specific recommendation	There is no specific protocol, and when switching to another agent is not usually considered necessary unless there are related adverse events which could be worsened by starting a new therapy (e.g. neutropenia)	
Fingolimod	Patients can switch directly from IFN□ or GA provided there are no signs of relevant treatment-related abnormalities (e.g. neutropenia). Due to the long half-life of natalizumab and risk of concomitant immune effects for up to 2-3 months following discontinuation of natalizumab, caution is required when switching patients from natalizumab. Caution when switching from immunosuppressive medications to avoid additive immune suppressive effects.	On discontinuation of fingolimod, a 2 month interval without therapy is needed before starting other therapies. Lymphocyte counts progressively return to normal range within 1-2 months of stopping therapy	SmPC[34]
Natalizumab	Patients can switch from IFN□□or GA, providing there are no signs of treatment-related abnormalities (e.g. neutropenia) Confirm no immunosuppression in patients who have received immunosuppressants with a	The duration of effect (e.g. increased lymphocyte counts in the blood) persist for 12 weeks following the last dose. Although combined use of natalizumab with IFNb and	SmPC[35]

	prolonged effect (e.g. mitoxantrone, azathioprine).	GA did not raise any safety concerns, use of an immunosuppressant during this 'washout' should be carefully considered due to risk of additive effects.	

Table 1: Suggested protocols for switching to and from currently approved DMTs (based on EMEA labels unless otherwise stated; specific centres may make their own recommendations)

Patients with active MS who switch to fingolimod or natalizumab from other DMTs are likely to experience similar reductions in their use of healthcare resources. Of patients who switched to fingolimod, 68% were free of relapses. That was compared with 69% of patients who switched to natalizumab. The cohorts also recorded similar rates of hospitalizations and corticosteroid use, down significantly from the year before the switch ($p < 0.01$).[36]

3.3 Mechanism of Action of DMT therapy

By understanding the mechanism of action of DMTs, it is possible to also understand their possible effects. Approved MS therapies have differing modes of action (summarised in Table 2).

Therapy	Immunomodulator or immunosuppressant	Proposed mechanism of action
Interferon beta (1a and 1b) (figure 2)	Immunomodulator	Type I interferon with anti-viral and anti-inflammatory characteristics. Inhibits T-cell activation and reduces the permeability of the blood–brain barrier to inflammatory cells[37].
Glatiramer acetate	Immunomodulator	Moves the T helper lymphocytes in from Th1 towards a predominance of Th2 phenotype. Alters signals through the T cell receptor[38]
Fingolimod (figure 3)	Selective Immunosuppressant	Inhibits immune cell migration by interacting with sphingosine1-phosphate (S1P) receptors. S1P binds to S1P receptors on lymphocytes, signalling for them to exit lymph nodes and enter the circulation[39]. S1P also regulates diverse cellular functions such as survival and proliferation[40]. Fingolimod acts as a S1P receptor antagonist, preventing the binding of S1P, preventing lymphocytes migrating from lymph nodes. These lymphocytes may still react to systemic infection[41-44]
Natalizumab	Selective Immunosuppressant	A monoclonal antibody to $\alpha_4\beta_1$ integrin, a protein found on the surface of lymphocytes. $\alpha_4\beta_1$integrins interact with the vascular-cell adhesion molecule 1 (VCAM-1) enabling adhesion of lymphocytes to the vascular endothelium. Natalizumab prevents the migration of inflammatory

		lymphocytes across the blood brain barrier into the CNS[45]
Mitoxantrone	Immunosuppressant	Inhibits cell division of T cells and macrophages, blocking replication of these cells. Reduces Th1 proinflammatory cytokines and impairs antigen presentation[46]
Teriflunomide	Immunomodulator	Inhibits mitochondrial enzyme dihyrdro-orotate Cytostatic effect on proliferating T and B cells Reduces cytokine production Interferes with interaction between T cells and antigen-presenting cells (APC)[47]
Alemtuzumab	Immunosuppressant	Humanized mAb directed against the CD52 antigen expressed on the cell surface of both T and B lymphocytes, monocytes, macrophages, and eosinophils, but not stem cells. It depletes target antigen carrying cells, leading to rapid removal of T cells from blood, bone marrow, and organs. Thus, CD52-binding depletes target cells and leads to longer lasting immunosuppression[48]
Dimethyl Fumarate (BG 12)		The exact MOA is still unclear. In vitro experiments indicate: . Switching T-helper response from Th1 to Th2 phenotype[49] . Oxidative stress modulator[50-52] .Inhibits the accumulation of blood leukocytes[53] These data suggest that BG-12 could have dual neuroprotective and anti-inflammatory effect

Table 2: Mechanism of action of approved DMTs

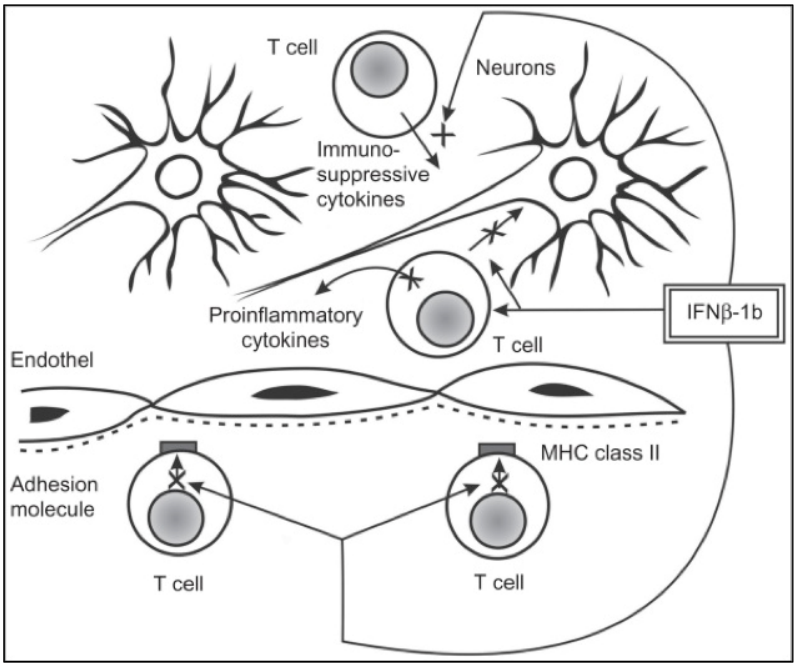


Figure 2 - Mechanism of action of interferon beta-1b

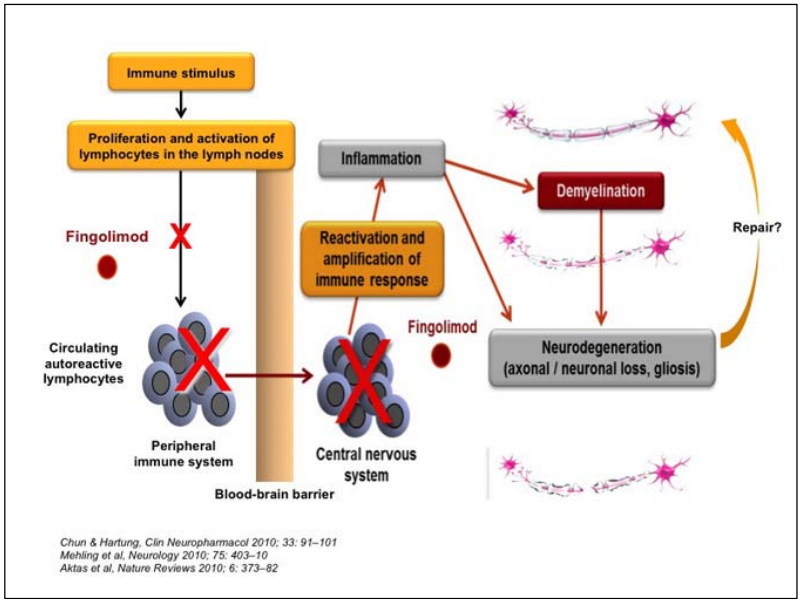


Figure 3 – Interaction of fingolimod with key immunological events in MS pathology

How, and when, would you explain the risk and benefit of DMTs to someone who is going to make a decision about treatment?

I try to explain the benefits and risks of DMTs at a time when the person with MS is able to attend and absorb information, is not fatigued, and has someone with them.

To support the given information, I often describe the Mechanism of Action, for example using a tool provided by the company that manufactures the specific drug. Most companies have these tools available and the nurse can use the tool that is most appealing to him/her.

I also try and provide the person with MS with written materials and information to support any conversations we have had about their DMT, which they can take away with them. This material should also contain information on drug handling, route and frequency of administration, possible treatment adverse effects and how to monitor for them. Booklets are often provided by the company and can be given to the patient.

In what way would you check their understanding and capacity to make a good shared decision about treatment?

The MS Nurse needs to ensure that the person with MS understands the information provided and is fully aware of possible adverse effects and what to do if they occur. It is always beneficial to have someone else in the consultation / information sessions. The pacing and timing of the information giving process is very important – try not to overwhelm the person with too much information as this will have an impact on how much they are able to process and understand. The nurse can ascertain the person understands by asking the patient to repeat the information given. The MS Nurse can also confirm understanding at a follow up appointment. This way the person with MS can read the booklets, digest this information and make an informed decision about treatment.

A number of **investigational therapies** with novel mechanisms of action are also under investigation.

Investigational therapies

Therapy	Proposed mechanism of action
Daclizumab	Blocks IL-2 binding domain of the alpha-chain (CD25) of the IL 2 receptor IL-2 receptor is involved in T-cell activation
Laquinimod	Possibly modulates the T-helper (Th) 1 and 2 balance and induction of transforming growth factor b May cause a downregulation of major histocompatibility complex II, T-cellchemokines in peripheral blood mononuclear cells and a reduction of TH17 responses Reduction in peripheral monocytes54
Rituximab	Monoclonal antibody that targets and selectively depletes CD20, an antigen present on pre-B cells and mature B cells, but not on antibody-producing plasma cells or stem cells in the bone marrow Reduces circulating B cells48
Siponimod	Oral, selective modulator of the sphingosine 1-phosphate (S1P) receptor subtypes 1 and 5 (S1P1, 5R modulator) with a short half-life leading to relatively rapid washout (6 days). The short half-life allows for a rapid recovery of blood lymphocyte counts following treatment discontinuation
Ocrelizumab	Humanized, recombinant monoclonal antibody targeted against CD20-expressing B cells. It has been shown to enhance antibody dependent cell mediated cytotoxicity and leads to a reduction in complement dependent cytotoxicity similar to rituximab
Ofatumumab	Type I, humanized monoclonal (IgG1) antibody against a novel epitope of CD20 on B lymphocytes. It is believed to mediate B cell lysis by complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. It targets a CD20 epitope which is distinct from that targeted by rituximab, by binding both small and large extracellular loops of the CD20 surface antigen.

Table 2s: Investigational DMTs for MS

3.4 The Role of the MS Nurse in Supporting Patients Taking DMTs: General Concepts

3.4.1 Role of the MS Nurse in Promoting Adherence

Patients who do not take disease-modifying therapies (DMT) as prescribed may compromise their future health and raise the risk of more relapses, potentially leading to disability and additional long-term care needs. A recent study found that approximately half of patients with MS discontinued their DMT within 2 years of drug initiation[55]. In addition, a 2010 prospective study using objective methods of adherence measurement found that approximately one-fifth of patients with MS miss over 20% of their scheduled doses[56]. The reasons associated with this include an unpredictable disease course, physical disability, feelings of hopelessness and cognitive impairment, as well as the fact that DMTs do not produce immediate results.

Recently there has been a shift from a paternalistic prescriber requiring compliance from the patient to adhere to a prescription plan, to that of a partnership with the patient who requires information to make an informed decision whether to embark on a course of medication (concordance). Concordance is a mutual understanding between healthcare provider and patient with regard to a treatment plan, and implies that the patient actively and willingly collaborates with the clinician, and takes responsibility for his/her own healthcare. The informed patient can understand any benefits or risks that may or may not be in conflict with his or her beliefs and attitudes.

Patient concordance/adherence to DMTs is an issue that should be addressed from the time of diagnosis throughout the disease course. In addition, it is vital that those patients taking oral therapy do not as a result, under-estimate their illness and therapy. The person with MS should be made aware of the importance of concordance/adherence and the need to take their diagnosis and their DMT 'seriously'.

The person with MS should be able to understand and acknowledge the importance of adhering to prescribed treatments and value the benefits of such treatments

It is therefore important that the MS Nurse is prepared to explain DMT for the patient; this may include explaining the mechanism of action or adverse events (see later sections).

The first stage of promoting adherence is the provision of information. One study shows that less than 50% of patients were satisfied with the information provided to them on the side effects and management of their drugs[57]. Before a patient begins DMT, the healthcare providers must educate the patient and family about the disease course. Education should emphasise the goals of slowing down the progression of disability and reducing the frequency of relapses and disease shown on magnetic resonance imaging. With insightful understanding of the disease process, the patient is better able to make treatment decisions and have more realistic expectations for therapy.

The decision to start DMT should include a discussion of approved treatment options, routes and schedules of administration, and potential side effects. Comprehensive education of both the patient and his or her family members is essential at this stage to set realistic expectations and discuss effective management strategies[58].

Educating patients with MS is a strategy of the MS Nurse to facilitate adherence through provision of understandable information, on how the drugs are administered, and benefits and potential side effects of the treatments. Many patients with chronic illness have some doubt about medication and

this behaviour can be even more marked when the benefits are not clear or are distant and are not of immediate effect[59]. DMTs are prescribed to patients with MS when they are often in remission, asymptomatic and ambivalent. It is important that the mode of action of reducing relapses is made clear, that there is no immediate benefit as this will only be demonstrated by a reduction in relapse rates. If patients do not understand this they may have unrealistic expectations about the treatment and find coping with side effects difficult, and consequently stop treatment.

Munschauer and Weinstock-Guttman[60] suggest that using a trans-theoretical model of change encourages the continued use of DMTs. The model is based on the idea that an individual's attitudes and beliefs are dynamic, and concordance with treatment can change at any stage (figure 4). The MS Nurse can intervene at any of the following stages by providing individual information tailored to the attitude of the patient:

- ***Pre-contemplative stage:*** The MS Nurse provides information to enable the patient to gain an understanding of the illness, encouraging him or her to verbalise any educational or personal barriers to treatment
- ***Contemplative stage:*** During this stage the nurse provides information that enables the patient to describe the process of DMT, as well as the potential benefits and side-effect profile
- ***Preparation stage:*** The nurse can evaluate the individual's learning needs and plan individual teaching sessions with the use of teaching aids
- ***Action stage:*** The nurse will need to supervise the patient at regular monthly intervals (or more frequently if required) for the first 3–6 months to assess how the patient is coping, to monitor any side effects and to assess the individual's injection technique
- ***Maintenance stage:*** The patient is considered concordant with treatment during regular 3–6 monthly follow-up appointments. Here, the nurse can assess any problems the individual may be experiencing which, if unchecked, may lead to the patient stopping therapy.

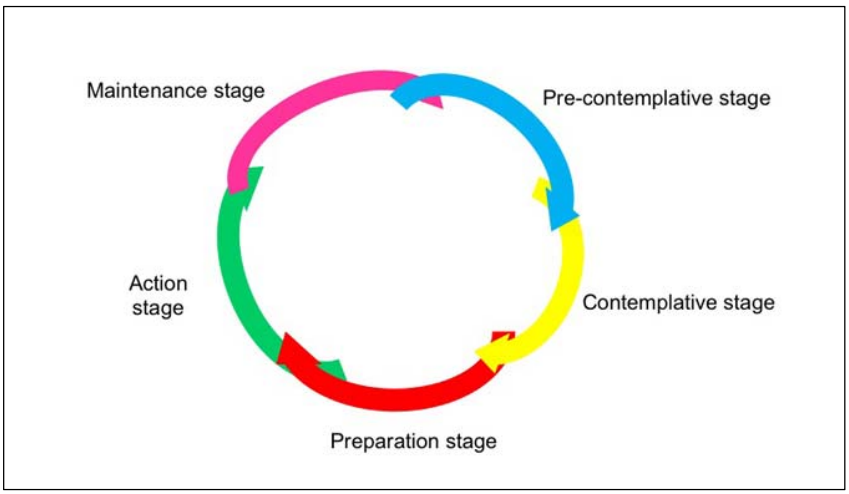


Figure 4 – A trans-theoretical model of change which may help achieve patient concordance[60]

There are times when a patient may become discouraged with DMT treatment for a number of reasons, including skin site reactions or recurrent flu-like symptoms. It is important that the MS Nurse offers support at these times and encourages people to remain on treatment. Patients with low self-efficacy will benefit from this focused support; they can be encouraged to keep a daily diary that can be discussed at each meeting. Highlighting any unpleasant side effects or problems can provide a feeling of commitment and control. Feeling in control of their medication will further empower patients with MS and achieve concordance.

The MS Nurse plays an important role in assisting people with MS to take their DMT as prescribed. This can include self-injection training and pro-active advice and support if any adverse events occur. The MS Nurse is able to spend time with the patient to demonstrate and teach the self-administration of the subcutaneous or intramuscular injection; one study suggests the MS Nurse may spend up to five hours training the individual in the self-injection techniques and management of side effects, either at home or in a clinical setting[61]. This gives the patient the opportunity to become familiar with the procedure in a relaxed environment and to practice the technique. It also allows the nurse to observe if the patient demonstrates any dexterity or cognitive problems that may have an impact on adherence and self-management. MS Nurses also play an important role in helping patients remain adherent with their prescribed medication, whether this is taken orally or by injection, through established follow-up strategies.

A recent UK and Ireland audit of patient adherence to subcutaneous interferon beta-1a injections using the RebiSmart(®) injection device found that mean adherence over the course of 24 months was 95%. This high adherence may be partly attributed to the expert support patients received, supplemented by routine and regular contact from the MySupport patient-support programme[62] (an industry-sponsored programme that provides support to patients with MS who have been prescribed sc IFN β-1a), as well as the self-motivation of patients who persisted with treatment for 2 or more years.[63] A personalised support programme, utilising one-to-one nursing support and additional support materials, can increase the probability of patients with MS remaining on treatment.

What might be some good ways of promoting treatment adherence?

A simple starting point to promote adherence is educating people with MS about the necessity for therapy, while setting realistic expectations. Proper counselling before therapy is initiated can prevent problems with adherence further down the road.

People with MS should be informed that available agents reduce the incidence of relapses and although they do not cure MS, they can help maintain function and quality of life through relapse reduction and delay in progression.

Moreover, people with MS who are in remission must understand that although they may not be experiencing relapses or signs of progression, the disease may be active at a subclinical level and thus, continuation of therapy is necessary to help reduce disease burden.

Education about injection techniques and about what can reasonably be expected from therapy, and from MS itself, is a key strategy to successfully maintaining treatment adherence and should be an on-going process.

In addition, the value of the regimen and the importance of adherence need to be reinforced repeatedly. Involving the family and friends so they are able to support the person with MS is also an important strategy.

When promoting treatment adherence the nurse should be aware of the following:

The two main reasons why people with MS stop therapy are adverse events and lack of efficacy. Adverse events cause people to stop sooner than the lack of efficacy. No reliable and specific marker has been found to determine whether DMT therapy is working optimally for an individual with MS.

Some people assume that their treatment is not working when current symptoms do not abate with regular DMT injections or they experience new symptoms. This perceived lack of efficacy can be the result of unrealistic treatment expectations.

3.4.2 Role of the MS Nurse in Helping to Manage Treatment Side Effects

Side effects of MS medications can influence adherence with prescribed treatment regimens when patients are not aware of the possible side effects and do not know how to manage them. Nurses are in a key position to educate patients about possible side effects and to prevent or minimise them. Often patients are reluctant to begin DMT because of fear of possible side effects that may disrupt their daily lives. Reassuring patients about the many ways to manage side effects is often the first step to getting treatment started.

The MS Nurse needs to ensure that the person with MS is fully aware of all possible side effects from the drugs and to know what to do about them should they occur. The most common side effects associated with IFNβ therapy include injection-site reactions and flu-like symptoms. Less common side effects include blood disorders, depression, hypertension, nausea and vomiting, raised liver enzymes, skin reactions and spasticity. Other side-effects occur more rarely, and due to variations between different DMTs, it is always advisable to check the prescribing information for each medication.

The most common side effects associated with glatiramer acetate are injection-site pain and reactions, and what is commonly referred to as ‘post-injection syndrome’ which consists of chest pain, palpitations and anxiety. Other effects include flushing, constriction of the throat and urticaria. These symptoms are usually transient and do not require specific treatment[64,65]. It is important for the nurse to educate patients and their support partners about this possible reaction. They should attempt to relax, take deep breaths, and wait until it passes, usually about 15 minutes.

The most common adverse reactions reported with fingolimod include headache, influenza, diarrhea, back pain, liver transaminase elevation, and cough; teriflunomide adverse reactions include ALT elevation, alopecia, diarrhea, influenza, nausea, and paresthesia; and dimethyl fumarate adverse reactions include flushing, abdominal pain, diarrhea, and nausea.

3.4.2.1 Injection-site Reactions

Injection-site reactions include redness, swelling, bruising, stinging, and pain. A common cause of these reactions is not using a dry needle for injection. Even a small amount of medication dripping out of the tip of the needle can be very irritating to the skin as the rest of the needle passes through. The introduction of autoinjector technologies has made subcutaneous injection easier and has improved patient satisfaction[66]. However, patients should still be instructed on proper injection techniques as well as on strategies to minimise injection-site reactions. Routinely rotating injection sites, allowing medications to come to room temperature, and cooling or warming the injection site before the injection are all techniques used successfully to reduce or prevent injection-site reactions[64,65]. Local anaesthetics may also be used to prevent injection-site pain[67].

3.4.2.2 Managing Pain and Cutaneous Reactions

Pain, in the form of tenderness to the touch, can occur immediately upon injection and/or appear 24–48 hours post-injection. Muscle aches have been reported following injection with IFNβ-1a and 1b.

Glatiramer acetate and IFNß sometimes cause a transient stinging sensation that rarely leads to treatment cessation. Glatiramer can cause localised redness, itching or inflammation. Some people have reported hard spots under the skin together with pain, but these are usually mild and diminish with time. A number of interventions are possible for the MS Nurse to manage these side effects. The MS Nurse should advise the person with MS to:

1. Ensure proper injection technique is being used
2. Ensure that injection sites are rotated and not used again for at least seven days (figure 5)
3. Apply ice before and after injection – but not to inject ice-cold solution, which should be allowed to come to room temperature first
4. Gently massage the injection site to disperse the solution – but not to rub
5. Inject only into healthy tissue, and after a couple of hours to check for redness, tenderness or swelling
6. Use vial adapters where available
7. Avoid exposing the injection site to excessive sunlight or UV light
8. Use paracetamol or ibuprofen if their doctor permits

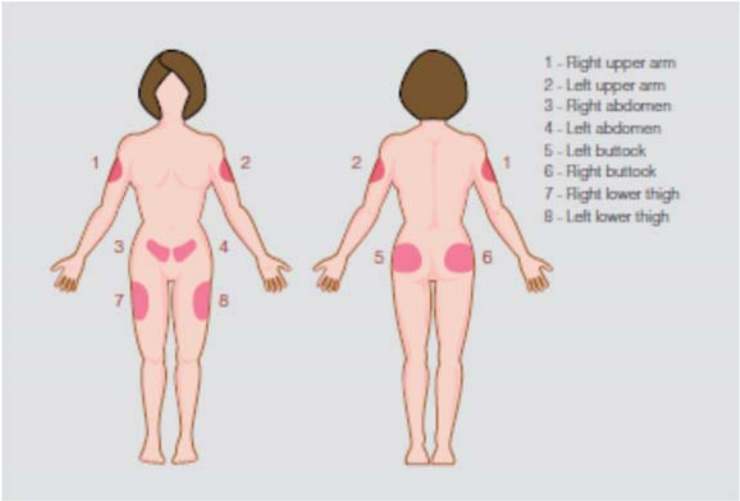


Figure 5 – Injection sites

Injection site necrosis (break-down of skin tissue) is a rare cutaneous reaction, but if ignored it can lead to complications such as infection and tissue loss. Appropriate topical treatments should be initiated based on white blood cell count, stage of the wound and presence or absence of infection, and antibiotics may be needed if infection is present. If these interventions fail and injection site necrosis continues to be a problem it may be necessary to suspend or switch treatment.

What might be the educational needs of a person with MS who is learning to self-inject – administration techniques to adopt, tips to minimise infection, site rotation etc?

Adherence to any MS therapy is an issue that needs to be addressed from the time of diagnosis throughout the disease course. When people with MS are asked to self-inject, common reactions include fear, avoidance, anxiety, autonomic reactions, and disgust. Some people with MS avoid self-injection by relying on family members to administer the injection. Depending on another person to

inject can be a barrier to adherence because it affects the person's independence and increases the likelihood of missed injections if the designated family member is not available.

I always try and provide written information and/or a DVD containing education about the injection technique, rotation of injection sites, and skin problems which might occur and how to manage them. It is also important to take into consideration that the ability to learn has to do with cognition and information processing.

- How might the nurse implement this education?

  Teaching the person with MS to self-inject is based on individual and unstructured approaches. It is important to try and choose the right learning style for that individual and to have a caring relationship with the person with MS. If the person with MS is motivated, interested and has familiarized him or herself with the material in advance, then this is a good starting point.

  If possible, go to the person's home - this is a safe environment for the person with MS. Also there are no distractions from other tasks you might have to perform. Also there is no lack of time and restlessness. Try and have the person's partner present, as two people hear and see more than just one.

  Try and be present for at least the first two administrations of the injection. Then ask whether the person with MS feels comfortable administering the injections alone. Schedule a telephone consultation for that same week and then 2, 4 and 6 weeks after.

3.4.2.3 Managing Flu-like Symptoms

Flu-like symptoms occur in many people, 2–6 hours after injection. Symptoms include myalgia, headache, nausea, chills, fatigue and fever. Symptoms usually resolve within 24 hours, but can sometimes persist for up to three or even six months. It may help to establish a titration schedule when initiating treatment if these symptoms are occurring. Many patients find that if they begin at a low dose and titrate the dose up slowly, they can adjust the side effects, and the flulike symptoms often will go away[51]. The use of analgesics is a possibility that can be discussed with the doctor, and if used, the time at which they are taken can be adjusted so that their full effects are felt at the time of injection. In addition, the time of injection can be adjusted so that side effects occur while asleep. Other measures that can be explored include drug formulation, solution temperature (close to body temperature at the time of administration), adequate hydration and a nutritious diet.[68] Helping the patient to include these measures into their daily routine can help with adherence. If these measures do not seem to be working it may be necessary for the doctor to reduce the dose of DMT for 3–4 weeks before gradually increasing it again as tolerated.

3.4.3 Barriers to Concordance and Strategies to Overcome them

A wide range of factors influence a patient's ability to adhere to therapy. Access to, and communication with, healthcare providers are key elements in the promotion of concordance. It is important that the MS Nurse is able to not only assess a patient with MS for 'clinical' signs and symptoms, but he or she can also engage with the patient's psychological needs and issues. It is only by properly understanding a patient's individual concerns and barriers that effective strategies can be put in place to ensure concordance with therapy (Table 3).[69]

Barrier	Strategy
Unrealistic expectations	• Acknowledge that relapses may still occur • Emphasize the relapses may be more frequent or severe without treatment • Emphasize that treatment can help maintain function and quality of life
Injection/needle phobia	• Educate about proper injection preparation and technique • Allay fears about safety of injection • Consider cognitive reframing or relaxation techniques
Adverse events	**Flu-like symptoms** • Inform patient of specific symptoms to expect • Gradually titrate dose to prescribed dose • Recommend prophylactic administration of acetaminophen or non steroid anti-inflammatory agents • Time or schedule injections on days when symptoms will be least disruptive **Injection site reactions/pain** • Routinely rotate injection sites • Thoroughly was hands before injecting • Clean injection site with alcohol or soap and water allow to dry • Allow medications to warm to room temperature • Cool or warm injection site for 30 or 60 seconds before injecting • Ensure complete needle penetration to prevent intradermal injections through use of autoinjectors • Use local anaesthetics to minimise pain
Complacency	Remind patients that although they are in remission, disease may be active at subclinical level
Treatment fatigue	• Reinforce the importance of therapy for maintaining health and quality of life • Readjust injection schedule to better fit lifestyle
Cognitive deficits/deteriorating fine motor skills	• Recommend reminder systems (eg alarms, notes) • Recommend therapies that are premixed in prefilled injectors • Have family member prepare and administer injection
Changed family circumstances	Discuss changes and arrange for home care nurse, if necessary
Changed financial circumstances	Refer patient to patient assistance programs offered by pharmaceutical companies

Table 3: Barriers to concordance and strategies to overcome them

Patients with MS who are receiving DMT may be planning pregnancy. The information available regarding pregnancy with different DMTs varies and the MS Nurse should be aware of up to date recommendations regarding contraception, pregnancy and risks. This information can vary over time as more information becomes available, so it may be necessary to seek additional expert advice, and perhaps check with pharmaceutical companies on a regular (e.g. annual) basis.

Establishing an open and honest healthcare provider-patient relationship, setting realistic expectations about therapy, and providing ongoing education about MS, injection technique, and adverse event management are responsibilities that both the healthcare provider and patient must embrace. Optimising motivation and therefore concordance in patients with long-standing MS will allow these patients to realise the maximal benefits of DMT.

How do you monitor concordance and assess treatment responsiveness: are there any follow-up processes that you use?

Clues to non-adherence include missed appointments and evasiveness on the part of the patient. People with MS should be asked about how they are coping with their treatment regimen in a specific, direct, and non-confrontational manner. Simply asking if he is taking his DMT is not sufficient; rather people with MS should be asked specific questions such as “How many injections have you missed in the previous month?” Or “Have you had to miss many injections in the last month, and what would be the main problems for you when you have?”

If a patient expresses difficulties with adherence, healthcare providers should make every effort to work with them to determine an acceptable solution. In some cases, the solution may involve seeking assistance from family members and/or friends. In other cases, reminder systems, such as drug diaries or alarms may be needed, especially for people with MS experiencing cognitive impairments. Regardless, several steps should be considered when determining the best way to maintain treatment adherence for an individual patient: set realistic expectations, address injection anxiety, and manage and cope with adverse events.

Optimising motivation and therefore concordance in patients with long-standing MS will allow these patients to realise the maximal benefits of DMT.

The MS Nurse plays an important role in assisting people with MS to take their DMT as prescribed; whether their DMT is taken orally or by injection. This can include self-injection training, pro-active advice and support if any adverse events occur and ensuring appropriate follow-up is in place.

3.5 Interferon Beta

3.5.1 Introduction

Interferon beta (IFNβ) is one of the longest established DMTs for MS. Both IFNβ-1a and IFNβ-1b are available and there are different formulations which are administered by different routes (subcutaneously - SC or intramuscular - IM). The specific recommendations for dosing vary with product as summarised in Table 4. Pegylated interferon beta-1a is a molecule in which polyethylene glycol is attached to interferon beta-1a. This drug is administered subcutaneously. The pegylation increases stability, half-life, and peak concentration compared with standard interferon beta-1a. It has recently been approved for treatment of RRMS, with less frequent dosing and similar efficacy compared with currently available first-line injectable treatments. The pegylated interferon is administered once every 2 weeks with a pen-type autoinjector.[70]

Generic name	Trade name(s)	Dosing route	Dose	Dosing frequency
IFNβ-1a	Avonex	IM	30µg	Weekly
	Rebif	SC	22µg or 44µg	TIW (three times weekly)
IFNβ-1b	Betaferon Extavia	SC	250µg	EOD (every other day)
Pegylated IFNβ -1a	Plegridy	SC	125µg	Bi-weekly (every other week)

Table 4: Interferon beta formulations for MS

3.5.2 Efficacy

In clinical trials, as patients with different disease characteristics and baseline severity were enrolled, the pivotal trials of all IFNβ products showed similar efficacy over placebo (Table 5)[71]. In general these studies reported a reduction in annual relapse rate of approximately one-third, with a median time to the first relapse of nearly 1 year and around one-third of patients remaining relapse-free during the study.

Although these data cannot determine an effect on an individual patient, it is possible to say that overall, a patient is about one-third less likely to suffer a relapse over 1 year[71].

In general interferon beta therapy reduces annual relapse rate by approximately one-third with one-third remaining relapse free after 2 years therapy.

Agent	Dosage	Reduction in annual relapse rate (%)*	Relapse-free patients over 2 years (%)	Median time to first relapse (d)	Reduction in disease progression* (%)
IFNβ-1a	30 µg IM weekly	32	38	331	37
IFNβ-1a	22 µg SC TIW	29	27	228	23
	44 µg SC TIW	32	32	288	31
IFNβ-1b	250µg SC EOD	34	31	295	29
Pegylated IFNβ -1a	125µg SC bi-weekly	36	37		38

*Table 5: Key clinical results from pivotal trials of IFNβ in RRMS *vs placebo[71]*

Clinical trials have directly compared IFNβ formulations/doses[72,73] and IFNβ against glatiramer[74,75]. There is some evidence that higher doses of IFNβ may be more efficacious than lower doses[72] but this is conflicting[74]. Therefore, selection of IFNβ product may be driven by physician and/or patient choice. For those who prefer an autoinjector the available device and their preference (e.g. for a more 'technical' vs. 'medical' device) may also be important[76,77].

Long-term use of IFN in patients with RRMS has been shown to delay progression to SPMS, for example in the 'LTF Study', SPMS onset was delayed by over 6 years in those receiving continuous IFNβ-1b (Figure 6)[78,79].

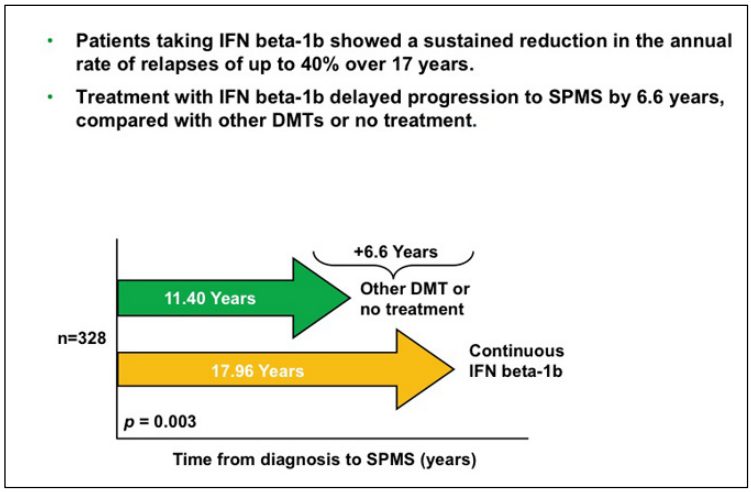


Figure 6: Impact of long term IFNβ in RRMS[789,790]

Early intervention with IFNβ in patients with CIS has also been shown to delay the onset of clinically definite MS; in one large study by 50% over 2 years[31] (Figure 7). Moreover, with additional follow-up early intervention was found to have reduced deterioration in cognition, quality of life and disability progression[80].

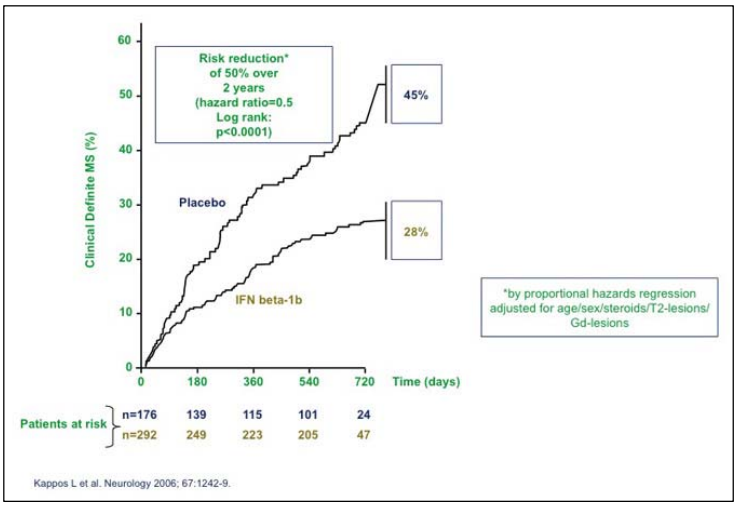


Figure 7: Impact of IFNβ-1b in delaying CDMS in patients with CIS[31]

Early intervention with IFNβ or glatiramer in patients with CIS has been shown to delay the onset of clinically definite MS. Long term IFNβ therapy in those people with RRMS has delayed progression to SPMS.

Patients with SPMS who continue to suffer highly active disease, defined as continued relapse episodes, may receive IFNβ-1b EOD[81,82] or IFNβ-1a TIW. However, low dose (weekly) IFNβ-1a was not found to be effective[83,84].

3.5.3 Adverse Events

In addition to teaching patients to self-inject, patients receiving IFNβ should be educated about potential adverse events.

Common events include flu-like symptoms, which are most frequent during the start of therapy, and injection site reactions (Table 6). Gradual titration of the dose of IFNβ and use of paracetamol (acetaminophen) can reduce flu-like symptoms. Patients should also be reassured that these symptoms are to be expected and, looking to the 'positive', related to how interferon works. Rotation of the injection site reduces the severity and risk of injection site reactions while use of an autoinjector can also help[77].

Event	IFNβ-1b 250 µg EOD (%)	Placebo (%)
Injection site reaction (during 2-year study)	48	9
During first year*	46	8
During second year†	30‡	7§
Flu-like symptoms (during 2-year study)	44	18
During first year*	42	15
During second year†	13§	10§
Headache	27	17
Asthenia	22	17
Leukopenia ¶	18	6
Upper respiratory tract infection	18	19
Paresthesia	16	17
Fever	13	5
Rash	11	3
Depression	10	11
Laboratory abnormality		
ALT ≥ 5 times baseline	18	5
AST ≥ 5 times baseline	6	1

Table 6: IFN-related adverse events; Experience from the BENEFIT study in early MS[31]

The incidence displayed is the number of patients reporting the respective AE (or having the respective laboratory change) at least once.
** Start date at or before day 360. † Ongoing AEs and AEs with start date after day 360.*
‡ N=250 IFN beta-1b patients reached the second year. § N=107 placebo patients reached the second year.
¶ If reported as an AE by the investigator

Depression is a concern with IFN-treated patients as this can be severe in some patients but there are conflicting results whether IFN-beta treatment may really induce depression. However, if it occurs, it can be difficult to distinguish between reactive depression (for example due to a patient's diagnosis, or to a relapse episode or life event) and that related to IFNβ. Prompt assessment, either by a patient's MS team or primary care provider, should be arranged for patients with significant symptoms of depression.

3.5.4 Laboratory Tests

Interferon beta can affect the blood count (leukocytes and neutrophils) and liver function tests (PIs). It is important that baseline bloods are taken before commencing treatment and then at regular intervals whilst on treatment.

Although relatively uncommon, patients with thyroid abnormalities at baseline, or who develop signs and symptoms suggestive of hyper- or hypo-thyroidism, should have thyroid function tests undertaken regularly[81,82].

3.5.5 Neutralising Antibodies

Patients receiving protein-based therapies, such as interferon beta and natalizumab may raise antibodies to these proteins. In general these are divided into 'binding' and 'neutralising' antibodies (BAb and NAb respectively). BAbs can affect the pharmacokinetics of the protein, however NAbs interfere with target receptor binding and thus can reduce the efficacy of therapy[85,86].

In general the risk of raising NAbs to a therapeutic protein is influenced by a number of patient and product factors. These include the route, dose and frequency of administration, the amino acid composition of the protein (i.e. how 'foreign' it is), and the specific formulation, including the presence of stabilising proteins such as human serum albumin or contaminant proteins[86]. In addition, factors such as storage may also play a role since this can promote the formation of aggregates which increase the immunogenicity of a compound. Furthermore the impact of NAbs and BAbs is dependent on their relative 'titers' and persistence[86].

In general it is not possible to predict which patients may develop NAbs, or the clinical implications of developing an antibody response. However, NAbs may be suspected in patients who lose response to therapy after an initial good response. In clinical practice, it is unusual to test for NAbs since management is not affected by the results; for patients losing response, but who are remaining compliant, it is appropriate to 'step up' therapy to a second line agent. A recent study investigated whether access to antibody (Ab) test results would alter usual care of IFNβ-treated patients and whether BAb could predict NAb.[87] Therapy changes differed between the Ab testing and usual care arms (19.6% and 14.0%, respectively; p = 0·004). Access to Ab test results impacted therapy management. BAb titres can predict NAb positivity in patients on high-dose IFNβ.

3.6 Glatiramer Acetate

3.6.1 Introduction

Glatiramer acetate (glatiramer), like interferon is administered as a daily (20 mg) SC injection (Table 7). It is often used as first-line therapy for RRMS.

Generic name	Trade name(s)	Dosing route	Dose	Dosing frequency
Glatiramer acetate	Copaxone	SC	20mg	Daily

Table 7: Glatiramer formulations for MS

3.6.2 Efficacy

Pivotal studies of glatiramer vs. placebo reported similar efficacy to IFNβ[71] (Table 8), confirmed by comparative trials which found similar efficacy of glatiramer and IFNβ-1a TIW over 96 weeks[75] and IFNβ-1b EOD over 3.5 years[74].

Agent	Dosage	Reduction in annual relapse rate* (%)	Relapse-free patients over 2 years (%)	Median time to first relapse (d)	Reduction in disease progression* (%)
Glatiramer	20 mg SC daily	29	34	287	12

*vs placebo

Table 8: Efficacy of glatiramer in RRMS[71]

Glatiramer has similar efficacy to IFNβ TIW or EOD, demonstrated in comparative trials.

Glatiramer has, like IFNβ, been tested in patients with CIS. In the PreCISe trial, glatiramer was found to reduce the risk of clinically definite MS by 45% over 3 years compared with placebo (Figure 8)[32].

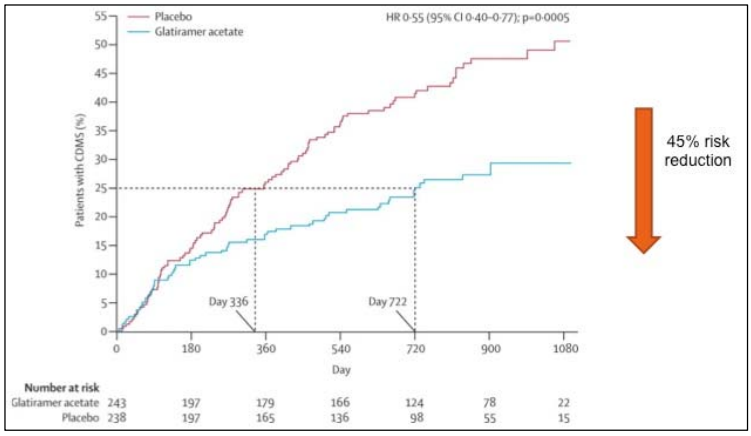


Figure 8: Impact of glatiramer in delaying CDMS in patients with CIS[33]

The CombiRx study was conducted to determine whether the combination of GA and IFN would be superior to either agent alone. Combining these two commonly prescribed therapies for MS did not produce a significant clinical benefit over three years. The results of this study confirm the safety of the combination therapy, but do not demonstrate sufficient clinical efficacy to warrant endorsement of this combination of drugs as yet.[88]

3.6.3 Adverse Events

In addition to injection site reactions such as erythema and pain, up to one-third of patients treated with glatiramer may experience post-injection reactions such as vasodilatation, chest pain, dyspnoea, palpitations or tachycardia within minutes of the injection[89]. Lipoatrophy is the loss of subcutaneous fat. It appears as large “dents” or depressions in the skin. Athough not common in the PreCise trial (table 8), this has been reported in as many as 45% of patients receiving glatiramer, and affects females more than males[90]. Other reported events include anxiety and depression, nausea and GI disturbances[89]. However in general, glatiramer is well tolerated, as indicated by the experience of patients in the PreCISe trial (Table 9)[32].

Event	Glatiramer acetate (%)	Placebo (%)
Lymphadenopathy	5.3	0.4
Urticaria	2.5	0.4
Influenza-like illness	4.1	0.8
Constipation	2.5	0.8
Pruritus	3.7	1.3
Erythema	3.7	1.3
Vomiting	5.8	2.1
Rash	3.3	1.3
Vision blurred	2.1	0

Table 9: Adverse events during glatiramer therapy in the PreCISe trial[32]

How do you explain the potential adverse events and their management so that the person with MS can effectively self-manage and also know when they should communicate with the medical team?

The MS nurse needs to explain possible adverse effects of treatment as often as is needed. People with MS don't always realise what you mean; for example they may not understand 'flu-like' symptoms until they experience them. Telephone support will often be needed to discuss possible adverse events as patients experience them.

The side effects of beta interferon which need to be communicated to the person with MS are:

- Flu-like symptoms
- Headaches
- Redness, swelling, or tenderness at the injection site.
- Depression
- Anxiety, confusion, and eating and sleeping disturbances

The side effects of immunosuppressants are more severe than those of immunomodulators and patients need particular careful counselling.

3.7 Fingolimod

3.7.1 Introduction

Fingolimod is an oral DMT (Table 10) which in some countries is approved for first-line use (i.e. as an alternative to IFNβ or glatiramer), while in others it is approved for **rapidly evolving RRMS**, and those who continue to suffer highly active disease while receiving IFNβ. These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion.

Generic name	Trade name(s)	Dosing route	Dose	Dosing frequency
Fingolimod	Gilenya	Oral	0.5 mg	Daily

Table 10: Fingolimod formulations for MS

As the first oral DMT available in most countries, fingolimod offered a new option for patients who, until then, were required to self-administer their IFN or glatiramer, or to attend out-patients for infusions (e.g. natalizumab). Although substantially more convenient, an oral therapy requires the same amount of 'commitment' from the patient – concordance with their prescribed treatment is equally important and therefore patients must continue to take their DMT 'seriously'. The MS Nurse should be prepared to emphasise the importance of taking fingolimod every day, and provide help and advice that will encourage the person with MS to take their treatment as prescribed. In a recent US survey, fingolimod was the DMT with the highest neurologist-reported percentage of patients who were "Very/Extremely Satisfied" with treatment (31.0%); adherence was also rated at 94%.[30]

The MS Nurse should be prepared to emphasise the importance of taking fingolimod every day, and provide help and advice that will encourage the person with MS to take their treatment as prescribed.

Rapidly evolving RRMS
Rapidly evolving RRMS is defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on MRI or a significant increase in T2 lesion load as compared to a previous recent MRI. –link to module 1

Fingolimod works by reversibly blocking a large proportion of lymphocytes (which are involved in the auto immune attack) from leaving the lymph nodes and subsequently entering the central nervous system[91-93]. On discontinuation of therapy, lymphocyte counts return to normal but benefits of therapy will be lost[34].

3.7.2 Efficacy

Two large clinical trials have evaluated fingolimod (FREEDOMS and TRANSFORMS).

One trial compared fingolimod with placebo over 2 years (FREEDOMS – Table 11) in patients with RRMS who were largely treatment experienced[94]. This reported a 54% reduction in annual relapse rate compared with placebo, and a 48% reduction in confirmed relapses over the 2 year study; after 2 years 70% of patients receiving fingolimod 0.5 mg were relapse free compared with 46% of placebo-treated patients (Figure 9)[94]. There was also a reduction in MRI activity as measured by the number of new and enlarged T2 lesions (mean 2.5 vs 9.8) and the number of T1 Gd-enhancing lesions (mean 0.2 vs 1.1); there was also significantly less loss of brain volume with fingolimod.

Agent	Dosage	Reduction in annual relapse rate* (%)	Relapse-free patients over 2 years (%)	Median time to first relapse (d)	Reduction in disease progression* (%)
	0.5 mg orally once daily	54	70	N/R	30

*vs placebo

Table 11: Efficacy of fingolimod in RRMS[94]

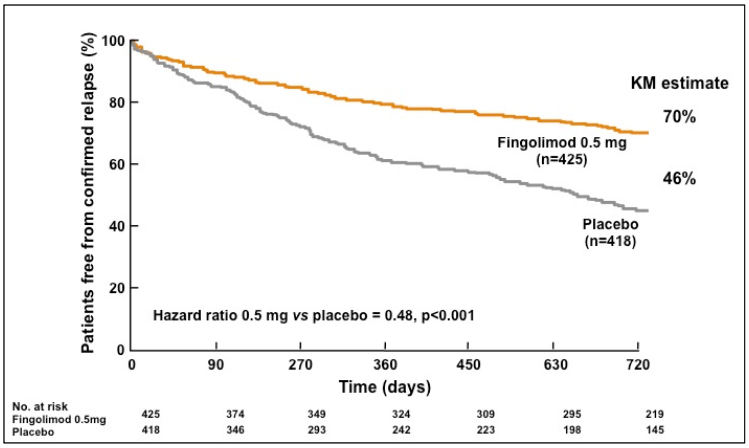


Figure 9: Time to first relapse; fingolimod 0.5 mg vs placebo[94]

In addition, in a 1-year trial (TRANSFORMS), fingolimod was found to be superior to IFNβ-1a IM weekly in terms of annual relapse rate and MRI-related outcomes[95]. The results of this trial are summarised in Table 12.

Agent	Dosage	Annual relapse rate (%)	New and enlarged T2 lesions (0–12 months)	Gd-enhancing T1 lesions (at 12 months)	Brain volume change (at 12 months)
Fingolimod	0.5 mg orally once daily	0.21	1.7	0.23	-0.3
IFNβ-1a	30 μg IM weekly	0.42	2.6	0.51	-0.5
Relative reduction (%)		52%	35%	55%	40%
P-value		<0.001	0.004	<0.001	0.001

Table 12: Efficacy of fingolimod vs IFNβ-1a IM[95]

Patients who completed this study were given the option to continue in an extension study to receive fingolimod 0.5 mg; those taking IFNβ-1a were reassigned to fingolimod, those assigned fingolimod continued on therapy. One year into this extension study, relapse rates and inflammatory activity on

MRI scans were significantly lower for those taking fingolimod for the entire two year period, compared to those switching to fingolimod[96].

In the two large clinical studies another dose of fingolimod (1.25 mg) was tested, however this dose was found to be no more efficacious than the dose 0.5 mg dose, but was associated with an increased risk of adverse events[34].

3.7.3 Adverse Events

More common events occurring during fingolimod therapy include influenza virus infection, headaches, cough, diarrhoea, liver function changes (increased ALT) and back pain[34] (Figures 10 and 11). Other events which were more frequent with fingolimod than placebo include dyspnoea, hypertension, bronchitis, blurred vision, migraine, lymphopenia and leukopenia[94].

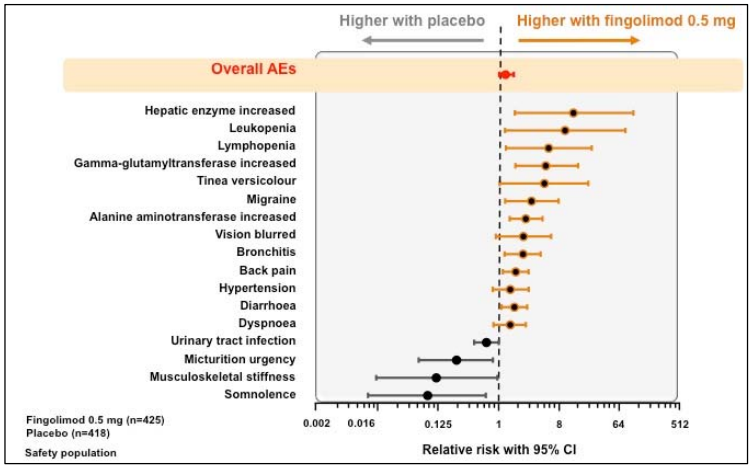


Figure 10: Adverse events; fingolimod versus placebo

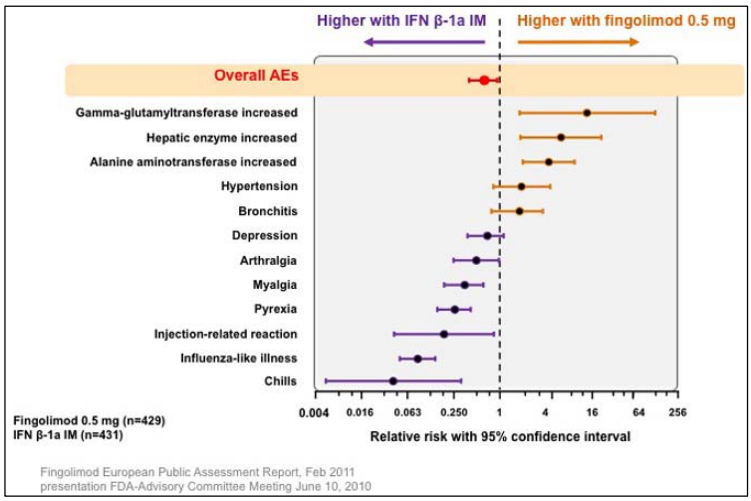


Figure 11: Adverse events; fingolimod versus IFN

Because transient decreases in heart rate were reported in some patients, it is recommended that patients are observed for 6 hours after taking their first dose for signs of bradycardia and admitted if symptoms occur until these resolve[34]. Although the current European SmPC for fingolimod recommends observation for signs and symptoms of bradycardia[34], in other countries, ECG

monitoring is recommended. Recently a 'Dear Healthcare Professional' letter issued by Novartis to European healthcare providers made some recommendations for the 6-hour observation period:-

- Baseline and discharge 12-lead ECG should be available
- Continuous ECG monitoring for the 6 hour first-dose observation
- At least hourly blood pressure and heart-rate assessments.

Specific recommendations to continue extended assessment are also made in patients with signs and symptoms suggestive of bradycardia or changes on ECG. Some centres may have adapted these recommendations to develop internal protocols.

Patients receiving fingolimod should also be warned to report any signs of symptoms of bradycardia (e.g. dizziness, shortness of breath) immediately to their MS Nurse or doctor.

Macular oedema has also been reported in a small number of patients (0.4% with 0.5 mg in the clinical development programme). As a result patients require an eye examination 3 – 4 months after commencing therapy, or if any visual disturbances occur during therapy[34]. Patients with diabetes or a history of uveitis also require a pre-treatment eye examination. If macular oedema is suspected, treatment should be discontinued. Macular oedema will generally resolve once fingolimod is stopped. It is however, important to arrange prompt referral if there is uncertainty whether an individual patient's symptoms are suggestive of macular oedema or MS-related optic neuritis.

Macular oedema
Macular oedema is a painless condition characterised by swelling or thickening in the central retina. It is usually, although not always, associated with blurred or distorted vision.

Other tests which may be required before or during fingolimod therapy include a negative pregnancy test pre-screen, liver function tests, varicella zoster status (VZV), blood cell counts and blood pressure. In addition, patients may be at increased risk of respiratory infections and patients should be warned to report any symptoms of infection to their doctor or MS centre[34]. Due to a lethal VZV infection during the pivotal trials, it is recommended to perform a VZV vaccination before treatment onset in case of a negative VZV-antibody test. The tests required with fingolimod therapy are summarised in Figure 12.

Vaccinations may be less effective during and up to 2 months after treatment with fingolimod. The use of live attenuated vaccines should be avoided during this time. MS Nurses need to discuss this with patients and help them plan their lifestyle to avoid the need for vaccines during this 2 month period.

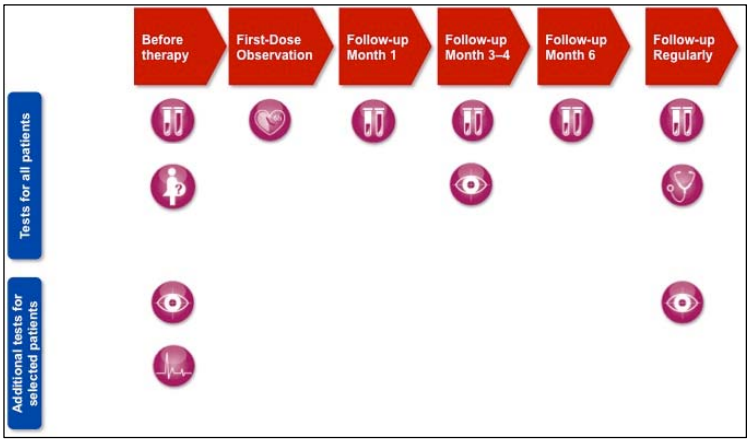


Figure 12: Tests to perform before and during fingolimod therapy

3.7.4 Nursing Considerations

As summarised, there are a number of assessments required before fingolimod is taken, when the first dose is taken, and during routine follow up.

In addition, patients will perceive that taking an oral medication is easier and more straightforward, and of course does not require them to inject. However, although fingolimod is an oral therapy, like other DMTs it can be associated with adverse events, and requires follow-up and monitoring, and a level of commitment from the patient to be concordant/adherent. The MS Nurse plays an important role in communicating both the benefits of an oral therapy (in terms of convenience), but also in explaining to the patient possible adverse events to be aware of and signs and symptoms which should be reported immediately to their MS Nurse, doctor, or both. The MS Nurse is likely to be involved in monitoring treatment initiation, providing support in the case of adverse events and promoting patient adherence to the prescribed treatment regimen.

Fingolimod is an oral DMT tested in people with RRMS. It is superior to placebo over 2 years and, in a 1-year trial, was found to be superior to IFNβ-1a IM weekly. There are specific requirements for pre- and on-treatment assessments including a 6-hour first dose observation.

3.8 Natalizumab

3.8.1 Introduction

Natalizumab is a monoclonal **antibody** which inhibits migration of lymphocytes across the blood-brain barrier into the CNS. Like fingolimod it does not cause lymphocyte depletion and on discontinuation of therapy lymphocyte levels will be restored, and therefore, disease activity will return[97,98].

Antibody
Antibodies are naturally occurring proteins produced by the immune system in response to foreign substances. Once produced by the body, they recognize and bind to specific proteins (antigens) on bacteria, viruses, and toxins, to help the body fight disease. Monoclonal antibodies, such as natalizumab, are produced in cell culture systems. They can be designed to bind to receptors on the body's normal cells. By recognizing and attaching to these receptors, monoclonal antibodies can interfere with (or alter) normal or abnormal cellular responses. In this way, monoclonal antibodies may be useful in the treatment of certain diseases.

The use of natalizumab varies in different countries; however in general it is used for those patients with **rapidly evolving RRMS** or for those who continue to relapse despite being on DMTs.

Rapidly evolving RRMS
Rapidly evolving RRMS is defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on MRI or a significant increase in T2 lesion load as compared to a previous recent MRI

Natalizumab is given as an IV infusion once every 4 weeks (Table 13). This is followed by a 1-hour observation period for signs of hypersensitivity[35].

Generic name	Trade name(s)	Dosing route	Dose	Dosing frequency
Natalizumab	Tysabri	IV infusion (1 hour)	300 mg	Every 4 weeks

Table 13: Natalizumab for MS

3.8.2 Efficacy

The efficacy of natalizumab in a largely treatment-naive RRMS population, over 2 years is summarised in Table 14[98].

Agent	Dosage	Reduction in annual relapse rate* (%)	Relapse-free patients over 2 years (%)	Median time to first relapse (d)	Reduction in disease progression* (%)
Natalizumab	300 mg IVI q4w	68	67	N/R	42

*vs placebo

Table 14: Efficacy of natalizumab in RRMS[98]

It is important to remember that in many countries natalizumab is initiated only after 'first line' therapy has failed, or in rapidly evolving RRMS; it is not clear whether natalizumab will show the efficacy observed in the Phase III clinical trials in this more advanced patient population.

3.8.3 Adverse Events

In clinical trials natalizumab was well tolerated; the most common events reported were dizziness, nausea, urticaria and rigors associated with infusions. Up to 4% of patients suffered hypersensitivity reactions, but less than 1% suffered anaphylactic reactions. Symptoms reported included hypotension, hypertension, chest pain, chest discomfort, dyspnoea and angioedema[35].

Event	Natalizumab (%)	Placebo (%)
General		
Headache	38	33
Fatigue	27	21*
Arthralgia	19	14
Urinary urgency or frequency	9	7
Allergic reaction	9	4*
Chest discomfort	5	3

Local bleeding	3	2
Rigors	3	1
Syncope	3	3
Infections		
Urinary tract	20	17
Lower respiratory tract	17	16
Gastroenteritis	11	9
Vaginitis	10	6
Tonsillitis	7	5
Depression	19	16
Gastrointestinal condition		
Abdominal discomfort	11	10
Abnormal LFTs	5	4
Skin		
Rash	11	9
Dermatitis	7	4
Pruritis	4	2
Menstrual disorder		
Irregular menstruation/dysmenorrhea	7	4
Amenorrhea	2	1
Neurologic condition		
Vertigo	6	5
Tremor	3	3
Serious events		
Relapse	6	13*
Cholelithiasis	<1	<1
Need for rehabilitation therapy	<1	,2
Urinary tract infection	<1	0
Depression	<1	<1
Anaphalactic reaction	<1	0
Hypersensitivity	<1	0
Fall	<1	<1
Breast cancer	<1	0
Anaphalactoid reaction	<1	0
Convulsion	<1	<1
Gastritis	<1	0
Cervical dysplasia	<1	0
Alcohol poisoning	<1	<1
Head injury	<1	<1
Thermal burn	<1	0

Table 15: Adverse events during natalizumab therapy in RRMS[98]

Therapy with natalizumab has been associated with Progressive Multifocal Leukoencephalopathy (PML). PML is an opportunistic infection caused by JC virus (John Cunningham virus), which may be fatal or result in severe disability. Such infections are common but remain dormant in people with healthy immune systems. Prior to the introduction of natalizumab, PML was seen primarily in immunocompromised patients such as those with HIV or undergoing immunosuppressant therapy. Symptoms of PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory and orientation, leading to confusion and personality changes. The progression of deficits can lead to

death or severe disability over weeks or months. A recent study found that the combination of three risk factors – prior positivity for JC virus antibody, history of receiving immunosuppressant drugs, and duration of natalizumab therapy – resulted in the highest risk for developing PML in MS patients treated with natalizumab[99].

As of February 29, 2012, there were 212 confirmed cases of PML among 99,571 patients treated with natalizumab (2.1 cases per 1000 patients).Recent data reported in the *New England Journal of Medicine*[99] change these risk levels slightly for patients with positive JC virus antibody, as follows:

- No prior immunosuppressants and exposure 1 to 24 months: 0.56 per 1,000 (95% CI 0.36 to 0.83)
- No prior immunosuppressants and exposure 25 to 48 months: 4.6 per 1,000 (95% CI 3.7 to 5.6)
- Prior immunosuppressants and exposure 1 to 24 months: 1.6 per 1,000 (95% CI 0.91 to 2.6)
- Prior immunosuppressants and exposure 25 to 48 months: 11.1 per 1,000 (95% CI 8.3 to 14.5)

Immunosuppressants in this context include several agents that have been used off-label to treat severe MS flares, including mitoxantrone, methotrexate, azathioprine, cyclophosphamide, and mycophenolate mofetil.

It is therefore usually advised that people starting natalizumab have the **JCV antibody test**.

JCV antibody test
The JCV antibody test determines whether a person with MS has been exposed to the JC Virus by detecting antibodies; a person that has antibodies to JC virus is at an increased risk of PML whereas the risk is very low when the JCV antibody test is negative. A commercial test for JC virus antibodies was introduced in 2011, and natalizumab's label now suggests that patients be tested before starting on the drug and periodically during treatment to detect new infections. The test is now included as routine screening for people beginning therapy with natalizumab and can significantly reduce risk of PML. The test does not indicate if someone will or will not get PML. The test indicates an individual's relative level of risk, information that can be used to make decisions about ongoing treatment. A positive test will require that the person's health is carefully monitored during treatment with natalizumab.

Up to November 2013 there were 418 confirmed cases of PML.[100] Reflective of this data, the risks of PML are 1 in 10 000 if the patient is JCV negative. If the patient is JCV positive, their risks are 1 in 1429 in the first 2 years, 1 in 189 for months 25–48, and 1 in 164 for months 49–72. If the patient is JCV positive and also had previous immunosuppression, their chances of PML are 1 in 556 in the first 2 years and 1 in 89 for the following 25–48 months.

Planned interruption of natalizumab therapy might lessen PML risk, but no prospective controlled studies have previously examined the effects of natalizumab treatment interruption. RESTORE was a randomized, partially placebo-controlled exploratory study examining MS disease activity during a 24-week interruption of natalizumab therapy.[101] Despite use of other therapies, MRI and clinical activity of MS recurred during natalizumab interruption in some patients who had been relapse-free for 1 year. Therefore, stopping natalizumab appears to increase the risk of MS relapse or MRI disease activity as compared with continuing natalizumab.

3.8.4 Nursing Considerations
While natalizumab can be highly effective, there are a number of precautions and the MS Nurse should be prepared to counsel the patient appropriately, and if necessary, organise pre- or on-treatment assessments for JC Virus antibodies

The patient should also be advised of possible adverse events which may occur between infusions, and to report them as appropriate. In particular, patients taking natalizumab should, together with their caregivers, be instructed on early signs and symptoms of PML (e.g. progressive weakness on one side of the body or clumsiness of limbs, visual disturbance, changes in thinking, memory and orientation leading to confusion and personality changes, cognitive or psychiatric symptoms)[35].

Natalizumab IV every 4 weeks has shown significant activity against RRMS compared with placebo and is generally well tolerated. According to its EMA indication, it is used for rapidly evolving RRMS or those with active disease on first-line DMTs.

3.9 Mitoxantrone

3.9.1 Introduction

The immunosuppressant mitoxantrone has also been studied in people with MS and although not approved in many countries, in the United States and elsewhere it has been approved for use in worsening RRMS PRMS, and SPMS, and it may be used in other settings.

Mitoxantrone is generally given as an intravenous injection at a dose of 12 mg/m^2 every three months (Table 16)[102].

Generic name	Trade name(s)	Dosing route	Dose	Dosing frequency
Mitoxantrone	Novantrone, Generics	IV	12mg/m^2	Every 3 months

Table 16: Mitoxantrone for MS

3.9.2 Efficacy

In a study of patients with worsening RRMS or SPMS mitoxantrone reduced the progression of disability compared with placebo[102]. Although the primary endpoint analysis of this study was different to those used in other DMT trials, assessment of the annualised relapse rate indicated a 63% reduction in year 1 vs. placebo, and 68% for year 2 (66% reduction in years 1 and 2 combined). More than one-half of patients were relapse free (57%) compared with 37% on placebo at the end of year 2[102].

Additional smaller studies have confirmed a treatment effect in these populations[103].

3.9.3 Adverse Events

Up to 75% of patients receiving mitoxantrone suffer nausea and vomiting. In addition to bone marrow suppression (leukopaenia), mitoxantrone is also associated with functional cardiac changes (congestive heart failure, decreased left ventricular ejection fraction[104]. As a result, it is recommended it should not be used for people with MS who have a left ventricular ejection fraction below the lower limit of normal[105] and monitoring prior to, and during therapy, is undertaken. This should include evaluation of LVEF and an ECG[105]. A complete blood count is also required prior to each dose.

In addition, for people with MS a cumulative dose of more than 140 mg/m^2 should not be administered[105]; this is equivalent to just over 11 doses at the recommended schedule (12 mg/m^2), or 3 years' therapy.

In a follow-up of over 800 MS patients who had received mitoxantrone, there was one report of congestive heart failure and 5% of patients had asymptomatic reductions of left ventricular ejection fraction which was persistent in 11 patients. There were also two cases of treatment-related leukaemia[106]. These concerns, and in particular the approval of fingolimod and natalizumab, mean that mitoxantrone is no longer usually considered as a 'first line' therapy for RRMS.

3.9.4 Nursing Considerations

Mitoxantrone is an immunosuppressant and it is recommended that the preparation and administration follows those steps required for cytotoxic chemotherapy[103]. Doctors should have experience of the use of cytotoxics and it is usually recommended that mitoxantrone is administered as a slow IV infusion to reduce the risk of cardiotoxicity[103]. Patients with nausea and vomiting may benefit from prompt administration of antiemetic therapy, while in some centres these may be given as prophylaxis before the first dose. As described in section 3.9.3, patient also require ECG assessment and a complete blood count, prior to each dose of mitoxantrone[103]. During the infusion it is also important to be vigilant to signs of extravasation, since in severe cases this can lead to tissue necrosis[103].

Mitoxantrone is an immunosuppressant which can be used for RRMS, PRMS or in those with worsening RRMS. There is a risk of cumulative toxicity to heart function and also leukaemia and therefore the duration of therapy is limited to 3 years.

How would you support the person with MS to achieve reasonable, realistic expectations of proposed treatments?

The person with MS needs to understand DMTs reduce the relapse rate by about one third. This means that a person with MS can still experience relapses. No one therapy is effective for all people and it is hard to predict whether the medicine will help a particular individual.

Treatment with DMTs is a long term treatment, efficacy is not immediate. People with MS need to understand this, and be reminded of this at every follow up consultation. The nurse can use an analogy of longer term investment – there is no immediate payback but benefits come in time.

People with MS are often very vulnerable and visit dubious websites as they search for a "cure". It is therefore important to provide people with MS with evidence based, accurate information about treatment options and to supply "good" Internet website addresses.

3.10 Teriflunomide

3.10.1 Introduction

Teriflunomide, an oral DMT, was approved in August 2013 for the treatment of RRMS. It prevents the division of rapidly-dividing cells from progressing into the DNA replication phase of the cell cycle. As T lymphocytes are rapidly-dividing cells, they are affected by teriflunomide so there are fewer to invade the CNS and attack neurones.

Generic name	Trade name(s)	Dosing route	Dose	Dosing frequency
Teriflunomide	Aubagio	Oral	14 mg	Daily

Table 17: Teriflunomide for MS

3.10.2 Efficacy

Results of the TEMSO trial showed a significant reduction in annualized relapse rate and sustained accumulation of disability with both 7mg and 14 mg daily doses vs placebo.[107] Both doses of teriflunomide reduced annual relapse rate by about one third compared to placebo. The higher dose (14 mg daily) reduced the risk of disability progression (sustained for 12 weeks) by 30%.

A second trial, TOWER, showed a significant reduction in annualized relapse rates and sustained accumulation of disability with the 14-mg dose *vs* placebo.[108] The higher dose reduced relapse rates by 36% compared to placebo and reduced the risk of disability progression (sustained for 12 weeks) by 31.5%. Key results from these two trials are displayed in table 18.

Trial	Dosage	Reduction in annual relapse rate* (%)	Relapse-free patients over 2 years (%)	Reduction in disease progression* (%)
TEMSO	14 mg orally once daily	31.5	57	30
TOWER	14 mg orally once daily	36	52	31.5

*vs placebo

Table 18: Efficacy of teriflunomide in RRMS[107,1083]

A third phase 3 trial, TENERE, compared two doses of teriflunomide with interferon beta 1a in 324 people over two years.[109] Teriflunomide failed to show statistically significant superiority over interferon in reducing the risk of treatment failure (the study's primary composite endpoint). At the higher teriflunomide dose (14 mg), 37.8% of patients had confirmed relapse or permanent treatment discontinuation over a period of 2 years compared with 42.3% of the interferon-treated patients. Overall, patients reported greater satisfaction and less fatigue with teriflunomide than with IFNβ-1a.

Trial	Dosage	Time to failure at wk 48 (%)	Annual relapse rate (%)
Teriflunomide	14 mg orally once daily	37	0.26
IFNβ-1a	44 μg SC 3 x weekly	33	0.22
P-value		NS	NS

Table 19: Efficacy of teriflunomide vs IFNβ-1a IM

The most recently reported phase 3 trial "TOPIC" looked at the effect of teriflunomide versus placebo in patients with first clinical symptom of MS.[110] The study randomly assigned 618 patients with CIS to 7 mg or 14 mg of oral teriflunomide once daily or placebo. The average duration of teriflunomide exposure in TOPIC was approximately 16 months. The study reported that teriflunomide significantly reduced the risk for conversion to clinically definite MS in patients with CIS. Results showed a 37% reduction vs placebo in conversion to clinically definite MS (the primary endpoint) with the 7-mg dose and a 43% reduction with the 14-mg dose. There was also a significant 30% to 35% reduction in the key secondary endpoint of new clinical relapse or lesion on MRI with both doses.

Together with outcomes from TEMSO and TOWER, these findings support the beneficial effect of teriflunomide in patients with RRMS early and later in their disease course.

3.10.3 Adverse Events

The most common adverse events associated with treatment included increased alanine aminotransferase levels, alopecia, diarrhea, influenza, nausea, and paresthesia. Teriflunomide is contraindicated in patients with severe hepatic impairment, on the basis of postmarketing reports of severe liver injury, including fatal liver failure in patients with rheumatoid arthritis treated with leflunomide.

3.10.4 Nursing Considerations

Health-related warnings for teriflunomide include that of elevated liver enzymes and possible hepatoxicity and risk of teratogenicity. Therefore, there are a number of laboratory tests which need to be conducted prior to, and during, treatment.

Timeframe	Suggested parameters to monitor
Prior to initiation	CBC and LFTs (within 6 months prior to initiation) Measure blood pressure Screen for latent tuberculosis Pregnancy test
After initiation	Monthly LFTs for the first 6 months, then every 6 months thereafter CBC should be assessed if signs/symptoms of hematologic toxicity Monitor blood pressure periodically

CBC, complete blood count; LFT, liver function test.

Table 20: Safety monitoring guidelines for teriflunomide

Patients should be advised to notify their nurse immediately if they experience symptoms of liver problems (nausea, vomiting, stomach pain, loss of appetite, tiredness, skin or whites of eyes yellowing, dark urine), serious skin problems (redness or peeling), infection (fever, tiredness, body aches, chills, nausea, vomiting), or interstitial lung disease (cough, dyspnea, with or without fever) occur.

Patients should also be instructed to notify healthcare professional if symptoms of peripheral neuropathy (numbness and tingling in hands and feet different from symptoms of MS), kidney problems (flank pain), high potassium level (nausea or racing heartbeat), or high BP occur. It is also important that patients consult their healthcare professional before taking any new medications. Instruct patient to avoid vaccinations with live vaccines during and following therapy without consulting healthcare professional.

Contraception and pregnancy

Based on data in animal studies, there is an increased risk of having a baby with birth defects if teriflunomide is taken during pregnancy. The FDA categorizes teriflunomide into pregnancy risk category

X. Teriflunomide remains in the blood for a long time after stopping treatment, so this risk may continue for up to two years. Women of childbearing age must have a negative pregnancy test before drug therapy. They must also use an effective method of contraception during treatment and for two years after stopping teriflunomide.

Women who suspect that they are pregnant while taking teriflunomide, or in the two years after stopping treatment, should contact their healthcare provider immediately for a pregnancy test. If the test confirms pregnancy, the blood level of teriflunomide can be reduced rapidly to safe levels by taking certain medicines (cholestyramine or activated charcoal). Women who wish to become pregnant should stop taking teriflunomide. The removal of teriflunomide can be speeded up using the medicines described above. A blood test can confirm that levels of teriflunomide are low enough that it is safe to attempt to become pregnant.

Males are cautioned not to father a child while on therapy as teriflunomide may be transmitted in semen and the degree of transvaginal absorption is not well characterized. Therefore all individuals taking teriflunomide should practice strict contraception.

3.11 Dimethyl Fumarate

3.11.1 Introduction

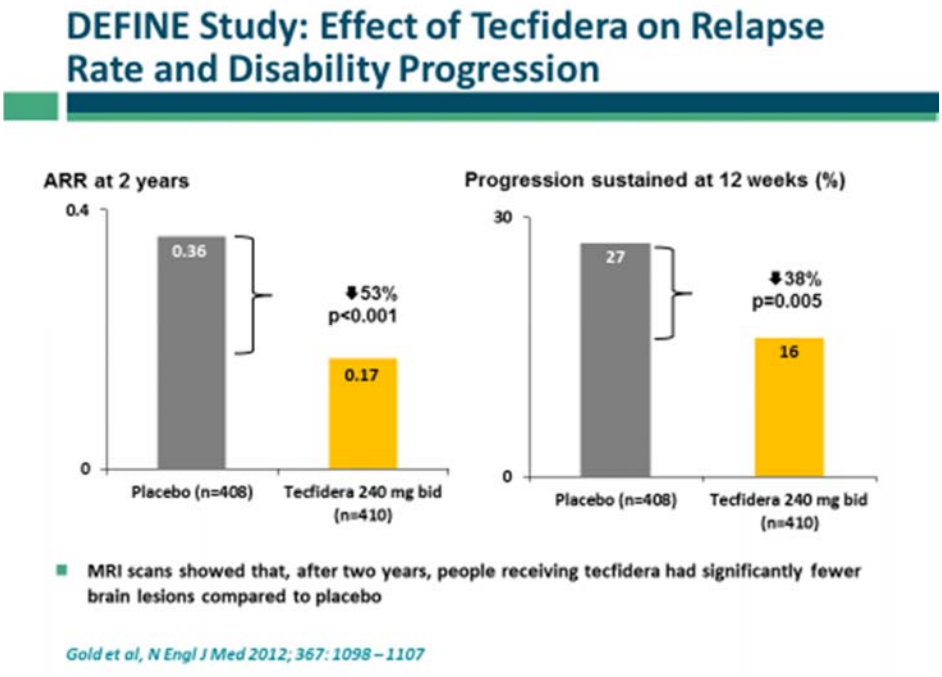
Dimethyl fumarate (DMF) is the most recently approved oral DMT for the treatment of relapsing forms of MS. The starting dose of DMF is 120 mg by mouth twice daily for 7 days, and then increased to 240 mg by mouth twice daily. DMF has demonstrated efficacy as a first-line therapy and should be considered as such in treatment selection for individuals with RRMS. DMF is thought to work in MS by several potential mechanisms. It has been found to induce T-cell apoptosis, potentially protect against oxidative stress, inhibit adhesion molecules, and potentially shift the immune response toward a Th-2 (helper T-cell) response.

Generic name	Trade name(s)	Dosing route	Dose	Dosing frequency
Dimethyl fumarate	Tecfidera	Oral	120 mg twice daily for 7 d, then 240 mg twice daily	Twice daily

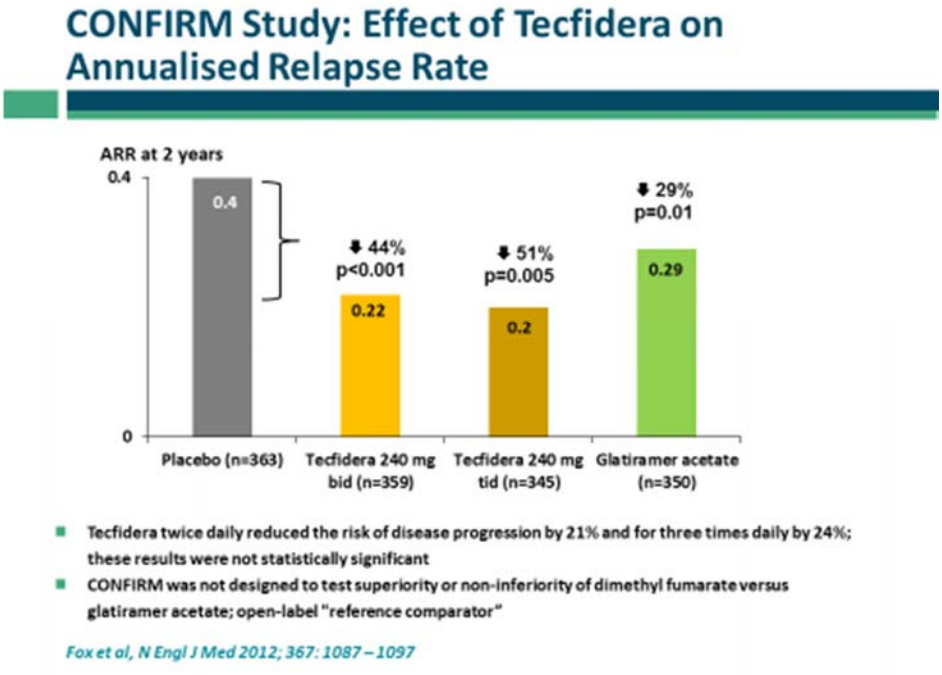
Table 21: Dimethyl fumarate for MS

3.11.2 Efficacy

The DEFINE (Determination of the Efficacy and Safety of Oral Fumarate in RRMS) study compared DMF 240 mg twice daily against placebo.[111] The primary endpoint of the study was met, with the proportion of patients who relapsed by the end of 2 years being 27% for DMF and 46% for placebo (P<0.001). Additionally, secondary endpoints of annualised relapse rate and time to disability progression were significant. The annualised relapse rate was 0.17 for DMF and 0.36 for placebo (P<0.001) consistent with a relative reduction of 53% for the DMF arm, and confirmed disability progression occurring throughout the 2-year study was 16% for DMF and 27% for placebo (P=0.005). Further, MRI measures of new or enlarging T2 lesions and the number of gadolinium-enhancing lesions were significantly reduced with DMF compared with placebo.



CONFIRM (Comparator and an Oral Fumarate in RRMS) compared DMF 240 mg twice daily against placebo and included an open-label reference comparator of glatiramer acetate 20 mg subcutaneously once daily.[112] The primary endpoint of annualised relapse rate, was significantly lower for DMF 0.22 twice daily with 0.29 for glatiramer acetate, and 0.4 for placebo, demonstrating a relative reduction of 44% for dimethyl fumarate ($p<0.001$), and 29% for glatiramer acetate ($p=0.01$). There were also significant reductions in new or enlarging T2 lesions in all treatment arms as compared with placebo ($p<0.001$ for each comparison). In contrast with the DEFINE study, there was no significant difference in disability progression when compared with placebo in CONFIRM



There have been no head-to-head clinical trials comparing DMF with other DMTs. Nevertheless, Hutchinson et al recently performed a meta-analysis using mixed treatment comparisons.[113] Mixed treatment comparisons are typically used in the absence of sufficient direct head-to-head comparisons allowing for analysis across clinical trials. The investigators analysed data from 27 randomized clinical trials of disease-modifying treatments using standard FDA-approved dosages and demonstrated that DMF 240 mg twice daily significantly reduces the annualized relapse rate as compared with placebo, IFN, glatiramer acetate, and teriflunomide. No significant difference was found when comparing DMF with fingolimod. Natalizumab was superior to DMF in reducing the annualized relapse rate in this meta-analysis.

3.11.3 Adverse Events

DMF may cause flushing (e.g. warmth, redness, itching, and/or burning sensation). 40% of patients taking DMF reported flushing which was mostly mild to moderate in severity. Taking DMF with food may reduce flushing. DMF may also cause gastrointestinal (GI) events (e.g., nausea, vomiting, diarrhea, abdominal pain, and dyspepsia). The most common GI events reported in clinical studies were: abdominal pain (18% vs 10%), diarrhea (14% vs 11%), nausea (12% vs 9%). The incidence of side effects decreased with time on therapy. DMF was not associated with an increased risk of malignancy, serious infections, or opportunistic infections.

A case of PML has been reported in a person who had been taking dimethyl fumarate.[114] The person, who subsequently died of complications from pneumonia, had been taking dimethyl fumarate for more than four years. It is not yet clear whether dimethyl fumarate was directly responsible or whether other factors caused this case of PML. Biogen is working with the regulatory authorities to ensure that prescribing information for dimethyl fumarate includes appropriate warnings.

Adverse Reactions Reported for Tecfidera 240 mg BID at ≥2% Higher Incidence Than Placebo[1]	Tecfidera (n=769)	Placebo (n=771)
Blood and Lymphatic System Disorders		
Lymphopenia	2%	<1%
GI Disorders		
Abdominal Pain	18%	10%
Diarrhea	14%	11%
Nausea	12%	9%
Vomiting	9%	5%
Dyspepsia	5%	3%
Vascular Disorders		
Flushing	40%	6%
Skin and Subcutaneous Tissue Disorders		
Pruritus	8%	4%
Rash	8%	3%
Erythema	5%	1%
Investigations		
Albumin Urine Present	6%	4%
Aspartate Aminotransferase Increased	4%	2%

Table 22: Adverse events during dimethyl fumarate therapy in RRMS

3.11.4 Nursing Considerations

A complete blood count is recommended prior to initiation of DMF, and should be repeated annually for safety monitoring. Additional CBC counts should be obtained if clinically indicated. Withholding dimethyl fumarate therapy should be considered if the patient develops a serious infection.[115]

Urinalysis should be performed before initiating treatment with DMF, after 6 months of treatment, then every 6 to 12 months, and as clinically indicated. Liver transaminases should also be checked (within 6 months) before initiating treatment. During treatment, evaluation of transaminases is recommended after 6 months of treatment, then every 6 to 12 months and as clinically indicated. [115]

Dimethyl fumarate can be taken with or without food; however, administration with food may reduce the incidence of flushing. Capsules should be swallowed whole and intact and not crushed or chewed; the contents of an open capsule should not be sprinkled on food. Pretreatment with aspirin can decrease the incidence and severity of flushing, but this method is not mentioned in the product labeling.

Dimethyl fumarate is classified in Pregnancy Category C; there are no adequate and well-controlled studies in pregnant women. Animal studies found problems with offspring survival, growth, sexual maturation, and neurobehavioral functions. All female patients beginning treatment with DMF should therefore be counselled regarding use of adequate contraception. If a pregnancy occurs during

treatment with dimethyl fumarate therapy, the patient should be encouraged to enroll in the *Tecfidera* Pregnancy Registry. [115]

3.12 Alemtuzumab

3.12.1 Introduction

Alemtuzumab is a humanized monoclonal antibody, approved in September 2013 for the treatment of adult patients who have RRMS with active disease defined by clinical or imaging features. Alemtuzumab has a novel dosing and administration schedule consisting of 2 annual treatment courses. The first course is given as an intravenous infusion over 5 consecutive days, and the second over 3 days 12 months later.

Generic name	Trade name(s)	Dosing route	Dose	Dosing frequency
Alemtuzumab	Lemtrada	IV	12 mg/day for 5 days during the first course and for 3 days during the second course a year later.	Annual

Table 23: Alemtuzumab for MS

3.12.2 Efficacy

Two pivotal randomized phase 3 studies compared treatment with alemtuzumab to high-dose subcutaneous interferon beta-1a in patients with RRMS who had active disease and were either new to treatment (CARE-MS I) or who had relapsed while on prior therapy (CARE-MS II). In CARE-MS I, alemtuzumab was significantly more effective than interferon beta-1a at reducing annualized relapse rates; the difference observed in slowing disability progression did not reach statistical significance.[116] In CARE-MS II, alemtuzumab was significantly more effective than interferon beta-1a at reducing annualized relapse rates, and accumulation of disability was significantly slowed in patients given alemtuzumab vs interferon beta-1a.[117]

Endpoint	Interferon Beta 1a	Alemtuzumab	Rate Ratio (95% CI)	P value
Relapse rate (%)	40	22	0.45 (0.32 – 0.63)	<0.0001
Relapse-free at 2 years (%)	59	78	-	<0.0001
Sustained accumulation of disability (%)	11	8	0.70 (0.40 – 1.23)	Ns

Table 24: Key efficacy results from CARE-MS I[116]

Endpoint	Interferon Beta 1a	Alemtuzumab	Rate Ratio (95% CI)	P value
Relapse rate (%)	51	35	0.51 (0.39 – 0.65)	<0.0001
Relapse-free at 2 years (%)	47	65	-	<0.0001
Sustained accumulation of disability (%)	20	13	0.58 (0.38 – 0.87)	0.0098

Table 25: Key efficacy results from CARE-MS II[117]

A recent study assessed a subgroup of patients in CARE-MS II who had the most active disease — 2 or more relapses in the year before randomisation, and 1 or more baseline gadolinium-enhancing lesions.[118] Results showed that 24% of 101 hard-to-treat patients who received alemtuzumab were disease activity–free at the end of 2 years (P =0.0002) compared with 0% of 42 similarly hard-to-treat patients taking interferon. Disease activity–free was defined as no relapse, no sustained accumulation of disability, as

measured by Expanded Disability Status Scale (EDSS), and no new gadolinium-enhancing lesions or new or enlarging T2-hyperintense lesions. Therefore, it would appear that alemtuzumab benefits the hardest to treat MS patients.

3.12.3 Adverse Events

The most common adverse effects of alemtuzumab are infusion-associated reactions, infections (upper respiratory tract and urinary tract), lymphopenia, and leukopenia. Serious autoimmune conditions can occur in patients receiving alemtuzumab including thyroid disorders and immune thrombocytopenia, both of which require careful monitoring and management. A comprehensive monitoring risk management program is now in place for all patients treated with alemtuzumab to ensure early detection and management of these autoimmune events. Careful patient selection and structured monitoring programs allow for effective patient management resulting in a favourable risk benefit profile.

3.12.4 Nursing Considerations

Nurses will need to be aware of all potential side effects of alemtuzumab. Infections and the development of other autoimmune diseases (thyroid abnormalities, ITP, and possibly nephropathies, including Good pasture disease) are the main concerns. Monitoring for early detection of these potential side effects is necessary and will be a key role for the MS Nurse. Such monitoring involves routine laboratory tests and patient education so that side effects can be identified early and managed before significant complications arise. The infrequent administration schedule of alemtuzumab could present a challenge for MS nurses in terms of encouraging patients to maintain communication and routinely follow up.[119]

3.13 Other Emerging Therapies

Therapy for MS is a rapidly evolving field with many agents in development, which could become available for clinical use in the future. These include oral therapies such as laquinimod and siponimod[120], and parenteral agents such as daclizumab, ocrelizumab and ofatumumab[121]. Most of these are being tested in RRMS; a significant unmet need remains therapy to affect the disease course in progressive MS[121].

3.14 Summary

- A number of DMTs are available for patients with RRMS suitable for use in those with CIS or mild disease activity, those with highly active disease, and also for those who fail first-line therapy.
- For most patients with RRMS initial therapy will be IFNβ or glatiramer. These require administration by SC or IM injection and the MS Nurse plays an important role in training patients how to self-administer their DMT, either using a syringe and needle, or an autoinjector.
- In some countries the oral agent fingolimod and natalizumab are alternatives to IFNβ or glatiramer for RRMS, while in others fingolimod and natalizumab are used for patients who progress on first-line therapy (e.g. IFNβ) or those with highly active RRMS.
- For patients with SPMS who continue to experience relapses, IFNβ-1b has been used, and some centres will continue a patient on their existing DMT while there is clinical benefit. Mitoxantrone may also be used in SPMS, or PRMS, although due to concerns about long-term toxicity, for a defined duration of time.

- It is important to inform patients of likely adverse events, how to manage the more common events and when they should report specific events to their MS Centre or primary care physician.
- In addition, each DMT has different requirements for routine follow-up assessments and tests and it is important patients are informed and followed-up appropriately to ensure these are undertaken as required.

Reflective learning points:

- Which DMTs are used for people with MS in your centre? How will you assist patients to take their DMT as prescribed and ensure they are fully informed regarding possible benefits from therapy, and possible adverse events?

- How might the introduction of oral therapy change the role you have with patients compared with those receiving parenteral DMTs

4 Treating Symptoms of MS

4.1 Learning Objectives

In this section the management of the symptoms of MS will be reviewed. After review of this section, you will be better able to:

- Summarise the symptoms that people with MS may experience
- Describe the management of these symptoms.

4.2 Introduction: The Importance of Symptom Management

Intro

People with MS experience a spectrum of symptoms which are the result of past disease progression (Figure 13)[1].

Importantly, these symptoms may not improve with DMT treatment alone and to achieve a more immediate benefit in terms of symptom management and quality of life, individualised therapy to manage symptoms is required[2]. Improving symptoms can maintain quality of life and patients' ability to undertake activities of daily living and ability to maintain employment[2,3].

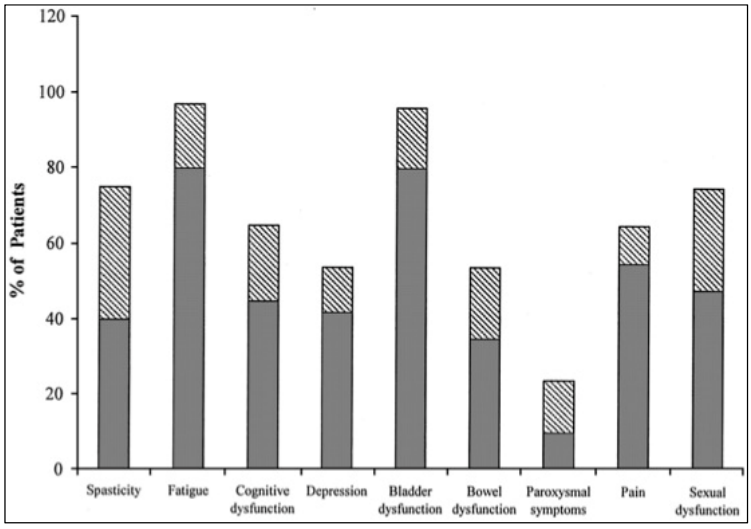


Figure 13: Symptoms of MS[1]

Symptom management is a critical part of care of those with MS; left untreated symptoms can significantly impair patients' quality of life and their ability to fully engage in daily life and continue in their work[1,3]. In addition, symptoms can also lead to the development of additional symptoms; for example, fatigue will likely lead to decreased exercise, which in turn can lead to spasticity and

constipation and also depression[1]. Bladder dysfunction, another common symptom in people with MS, can affect sleep patterns which in turn can affect cognition and aggravate depression.

Breaking the so called 'cycle of symptoms' requires an individualised approach which focuses on the needs of the patient and may include drug and/or non-pharmacological therapy and effective patient communication. Therefore, the MS Nurse is an important member of the multidisciplinary team (MDT) and can help ensure an individual patient's needs are effectively addressed[1].

The MS Nurse is an important member of the MDT and can help ensure an individual patient's needs are effectively addressed.

In order to provide optimal support and advice as appropriate to people with MS-related symptoms, the MS Nurse must be aware of the likely treatment options, and for pharmacologic therapy, an understanding of the likely benefits from therapy, knowledge of the common dose regimens and possible adverse events the patient may experience.

The following sections summarise some of the common therapies for the more frequently reported symptoms experienced by people with MS. Supportive care strategies are also important and this section should be reviewed within Module 5 (Care and Support).

4.3 Walking

4.3.1 Background

Impaired ability to walk is one of the major signs associated with MS[122]) and may affect more than three-quarters of people with MS[122,123]. Loss of walking ability leads to patients needing walking assistance or a wheelchair leading to problems with undertaking tasks of daily living and to loss of patient quality of life[123-125]. Moreover the effect on a patient's family/caregiver is significant[126].

Impaired ability to walk is one of the major signs associated with MS.

4.3.2 Management

The usual approach to management is physical rehabilitation and retraining, with management of any associated spasticity[123]. Treatment of spasticity can help walking by improving muscle tone but this has no impact on the underlying gait disorder[88]. In advanced stages of MS, wheelchairs or power scooters may be unavoidable[127].

4.3.3 Fampridine

A new treatment approved by the EMEA to **improve walking** in people with RRMS and SPMS is **fampridine**. In two clinical trials 35% and 43% of patients were 'responders'[128,129]. In these patients, walking speed increased by approximately 25% (approximately 15.5 cm/second) over 25 feet (7.62 meters). This sustained release tablet is taken twice daily, 12 hours apart[130].

Improve walking
The efficacy of fampridine was measured using the 'Timed 25-foot Walk' (T25FW) test. The walking speed of patients was timed over 25 feet and a 'responder' was defined as a patient with a faster walking speed for at least three of the four visits during treatment compared with the maximum off drug128,129,131. The results of two phase III studies were very similar; the proportion of responders was increased with fampridine (34.8% vs 8.3% and 42.9% vs 9.3%, p<0.001 in both studies). Responders increased their walking speed in both studies by approximately 25%, or an increase of approximately 0.51 ft/second (approximately 15.5 cm/second). The MS Walking Scale-12 (MSWS-12) was also used to assess patient response and this measure also improved in fampridine-treated patients which was also correlated with 'response' as defined using the T25FW primary endpoint.

Fampridine works by improving the ability of neurons to transmit a signal and therefore acts to improve the neurological deficits associated with demyelination[129,131,132].

Fampridine
The Fampridine is a 'potassium channel blocker'[131,132] which prolongs the duration of Na++ influx and hence the action potential of nerves, reducing the amount of current necessary to transmit a nerve signal. In addition, calcium influx at nerve ends is also increased which can improve the conduction of signals to other nerves or muscle[131].

Fampridine is excreted unchanged by the kidneys. Therefore, while there is no documented risk of interactions with drugs metabolised by the liver, there is a risk of increased levels in patients with renal impairment and fampridine should not be used in patients with creatinine clearances <80 ml/min. It is suggested that renal function should be assessed in elderly patients prior to starting therapy[130].

Although fampridine is usually well tolerated, the mechanism of action of fampridine means that is may cause convulsions (seizures). Indeed, there have been reports of convulsions during use of fampridine, particularly in early studies of higher doses (e.g. 20 mg) and the clinical trials could not confirm the magnitude of risk with the 10 mg twice daily dose of the approved sustained release preparation of fampridine[128-131]. Patients with a history of convulsions should not receive fampridine[130].

The most common adverse events with fampridine are mild and resolve without specific management. Common events reported include dizziness/balance disorders, tremors, insomnia, anxiety, fatigue, back pain and gastrointestinal disturbance (nausea, vomiting, diarrhoea, constipation)[128-131].

There are no reports of pregnancy during use of fampridine, however animal studies have reported adverse effects to the foetus and it is recommended that use of fampridine is avoided in pregnancy[130].

4.4 Spasticity

4.4.1 Background

Up to three-quarters of people with MS experience spasticity, the muscle affected depending on the location of MS lesions[1]. Spasticity is associated with a number of additional symptoms including pain, bowel and bladder function, and significantly compromises the ability of individuals to continue with activities of daily living[1,133]. Spasticity can compensate for muscle weakness in people with MS and therefore treatment can 'unmask' weakness[1].

4.4.2 Management

For individual patients affected by spasticity, physiotherapy and carefully planned exercise can be helpful. Exercise should be carefully planned in collaboration with rehabilitation services and include flexibility exercise, aerobic exercise and relaxation[1,,134].

First-line drug therapy is usually baclofen or tizanidine[1,2] **(Table 26).**

Agent	Dose	Adverse Events	Comments
Baclofen	Initial dose: 5mg orally 2 – 3 times daily. Titration: no more than every 3 days Usual effective dose:20 mg 3 x daily. Maximum dose:100 mg unless the patient under close medical supervision in hospital135. Up to 200 mg daily may be required1.	Most occur during the start of treatment: Sedation Drowsiness Nausea Less commonly: Dry mouth Dizziness Tiredness Confusion Rarely: Parasethesia Depression. There may also be a lowering of the threshold for convulsions, particularly in epileptic patients Exacerbation of psychiatric disorders possible; patients with pre-existing psychiatric conditions should be treated cautiously and kept under close surveillance135	Taking the tablets with milk or food helps alleviate nausea The effects of baclofen on blood pressure may be increased by the concurrent use of antihypertensive therapy; therefore , used with extreme care in patients receiving therapy for hypertension135
Tizanidine	or 4 times daily1 Initial dose: 1mg or 2mg at bedtime (due to risk of sedation); three or four times daily Titration: no more than half weekly according to response. Maximum dose: 12mg (single dose), and no more than 32 mg daily 1,136	Sedation Hypotension Dizziness Tiredness Nausea and GI disturbances (constipation). More rarely: hallucinations and weakness1,136	Patients should be counselled that alcohol can worsen the sedating effects of tizanidine. The effects of tizanidine on blood pressure may be increased in patients taking antihypertensive therapy and caution is recommended. Because of the (rare) risk of liver dysfunction, liver function tests required before and during therapy at doses greater than 12 mg daily136. Care is necessary when discontinuing tizanidine as rebound hypertension has been reported136.

Table 26: First line agents used for spasticity

Oral baclofen and tizanidine have similar effects on spasticity[1]. In a systematic review[137] the data for baclofen were described as limited, however improvements in spasticity were reported in at least some studies[137]. There was also evidence that baclofen improves range of motion and frequency of spasms and potentially, gait. However, there is no evidence that baclofen improves functional ability.

Although the evidence for tizanidine was described as more complete, the efficacy was described as similar, with improvements demonstrated in the pendulum test and spasticity score, as well as tone, in some studies. Again, like baclofen, no effect on functional ability was detected[137]. In an analysis of comparative studies no difference between tizanidine and baclofen could be observed[137].

For non-ambulatory patients not responding to baclofen or tizanidine, dantrolene may have effects on spasticity; however the data are limited[1,137]. The frequent adverse events (weakness and GI symptoms) limit the role of dantrolene[137], and the risk of liver function abnormalities means patients require frequent monitoring of liver function[1]. Diazepam may also be used for spasticity, which while as effective as baclofen and tizanidine is also more often associated with adverse events including sedation and weakness[137]. Patients who are prescribed diazepam should be warned of the sedative effects and advised to take their medication in the evening before bed[1].

Nabiximol is a cannabis extract which works on the cannabinoid receptors in the brain and spinal cord. It is licensed in MS as an add-on therapy for those people whose spasticity and spasm has not responded to the other available drugs[138,139]. It is available as an oral spray. Side effects can include dizziness, sleepiness and feelings of light headedness. Occasionally the spray can cause soreness in the mouth so it is important to change the spray site regularly. About half of people with MS will respond to nabiximol; whether someone is a responder can be identified after a four week trial of the drug. The dose can then be controlled by varying the number of sprays taken each day.

Combination therapy may be helpful to minimise the doses of each agent used, and therefore the potential severity of adverse events[1]. Patients may however require help to plan their medication as the drugs used are administered with different schedules.

Patients who lose response to oral medication, or who cannot tolerate therapy may gain relief from intrathecal baclofen. The baclofen pump is a surgically implanted programmable pump and catheter that delivers the baclofen directly into the intrathecal space where fluid flows around the spinal cord. Most people report that the programmable pump is not uncomfortable or restrictive, and does not interfere with their movement. After a test injection a pump can be used to provide ongoing administration[1]. Intrathecal baclofen has been shown to improve rigidity and spasms, particularly bilateral leg spasticity[1,134].

Abrupt discontinuation of intrathecal baclofen has resulted in withdrawal symptoms that include high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity, that in rare cases has advanced to rhabdomyolysis, multiple organ-system failure and death. Patients and caregivers should be advised of the importance of keeping scheduled refill visits and should be educated on the early symptoms of baclofen withdrawal. Special attention should be given to patients at apparent risk (e.g. spinal cord injuries at T-6 or above, communication difficulties, history of withdrawal symptoms from oral or intrathecal baclofen).

Botulinum toxin has been used off-label for the management of spasticity in people with MS for many years, based on the results of studies in patients after stroke which demonstrated efficacy[2]. In some countries certain formulations may be approved for spasticity, or even specifically MS-related spasticity[2]. Treatment with botulinum toxin is generally considered salvage therapy after first-line therapy has failed. Adverse events reported include difficulty in swallowing, speaking or breathing and fatigue and weakness – the latter being a particular concern in people with MS[2].

4.5 Fatigue

4.5.1 Background

Fatigue is reported by most people with MS[1], and significantly impairs quality of life, and also the ability to continue in employment[139,140]. Up to one-third of people with MS may identify fatigue as their most disabling symptom, and fatigue may lead to the onset, or worsening of other symptoms including depression, loss of cognitive function, and through an effect on exercise, muscle weakness.

Up to one-third of people with MS may identify fatigue as their most disabling symptom, and fatigue may lead to the onset, or worsening of other symptoms including depression, loss of cognitive function, and through an effect on exercise, muscle weakness.

4.5.2 Management

Non-pharmacologic therapy for fatigue can include a cooling vest, air conditioned environments and cool showers or cold drinks to reduce elevated body temperature. In addition, aerobic exercise and occupational therapy can both help patients with fatigue (Figure 14).

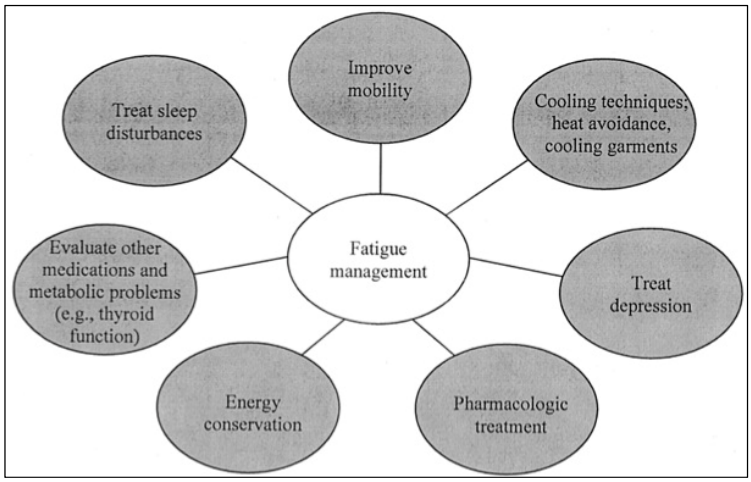


Figure 14 : Fatigue management[1]

Pharmacologic therapy to alleviate fatigue is with CNS stimulants such as methylphenidate, modafinil, amantadine, and although not available in many countries dextroamphetamine[1] **(Table 27).**

Agent	Dose	Adverse Events	Comments
Amantadine	100 mg twice daily. If tolerance develops a drug 'holiday' of 2 to 3 weeks can be used to prolong therapeutic benefits1.	In general well tolerated (<10% of patients discontinues therapy in clinical studies) Generally mild: Vivid dreams Nausea Hyperactivity Anxiety Insomnia Constipation Rash	Usual first-line therapy

		Much less commonly: Hallucinations141	
Modafinil	100-200 mg daily (usually, the second dose is taken before 2pm to avoid insomnia)	Generally well tolerated. Most commonly: Nausea Constipation Nervousness Restlessness Loss of appetite1. Insomnia is a possible event but was not reported in the MS trials141 Rare but serious events include skin reactions, psychiatric adverse effects and hypertension141	

Table 27: Pharmacologic therapy for fatigue

None of these agents are approved for the management of fatigue in people with MS[1,141], for example methylphenidate is indicated for the treatment of ADHD, modafinil for excessive somnolence in patients with narcolepsy, and amantadine is used for the prophylaxis and treatment of symptoms of influenza.

Amantadine is most commonly considered the first-line therapy for fatigue[141,142]. Four short term clinical trials of amantadine have reported the effects of amantadine and reported improvements in fatigue and patient preference for amantadine over placebo[141,142]. Overall between 20% and 40% of people with MS with mild-moderate fatigue show short-term reduction in fatigue with amantadine[1,2,143].

Modafinil has been shown to improve fatigue in three main trials[144-46]. However, two additional studies could find no benefit compared with placebo[147,148]. The European regulatory agency (EMEA) has stated that the risk-benefit of modafinil is positive only for narcolepsy[141].

4.6 Bladder Dysfunction

4.6.1 Background

Many people with MS have bladder dysfunction[1,149]. MS lesions lead to detrusor instability and sphincter problems which can produce symptoms of overactive bladder (urinary frequency, incontinence) or urinary retention[1,150]; overactive bladder/destrusor instability is the more common condition, reported in approximately 60% of people with MS[150].

4.6.2 Assessment: Role of the MS Nurse

Patients may be reluctant to report incontinence and other bladder issues as many people can feel a sense of shame and embarrassment. It is important, therefore, that the MS Nurse is prepared to raise this with their patients and that the nurse considers how he/she might handle these discussions with care and discretion. Simple questions may help patients discuss their symptoms in an open and trusting environment[151].

Patients may be reluctant to report incontinence and other bladder issues and it is

important that the MS Nurse is prepared to raise this with their patients.

4.6.3 Management

Managing bladder and bowel problems requires a comprehensive and holistic approach that sees a step wise escalation of interventions. Although behavioural therapy and bladder training (e.g. **Kegel exercises**) may be helpful in patients with OAB, most will require pharmacologic therapy – the mainstay of therapy being anticholinergic agents such as oxybutinin, tolterodine, solifenacin, trospium, or tricyclic antidepressants[1,152]. Although there is a lot of evidence for these drugs to treat OAB, there is less information on their use in people with MS[152]. A systematic review identified only five trials, of which only a study of oxybutinin reported significant effects on frequency[152].

Anticholinergic therapy is associated with typical side effects including dry mouth, blurred vision and constipation[1], with some evidence that the newer agents (e.g. tolterodine, fesoterodine, darifenacin, trospium and solifenacin) are less frequently associated with troublesome anticholinergic symptoms and some permit dose adjustment to achieve an acceptable compromise between efficacy and tolerability[151,153]. In addition, the older antimuscarinic agents have been associated with cognitive changes; this is less frequently reported with the newer agents; notably trospium.

Kegel exercises
Kegel exercises can help both men and women who have problems with urine leakage or bowel control. The aim of Kegel exercises is to improve muscle tone by strengthening the pubococcygeus muscles of the pelvic floor. Kegel exercises can be done at any time and any place. Most people prefer to do the exercises while lying down or sitting in a chair. After 4 – 6 weeks, most people notice some improvement but it may take as long as 3 months to see clinical benefit. Instructions for Kegel exercises[151]:

- Pull in or squeeze your pelvic muscle as if you were trying to stop urine flow
- Hold for several seconds
- Relax and repeat
- Perform at least 3 sets of 10 contractions every day

For those not responding to first line therapy, or developing recurrent UTIs referral to a urologist may be necessary[1]. Treatment strategies that may be considered in patients not responding to anticholinergic therapy may include **'transcutaneous posterior tibial nerve stimulation' (PTNS/TPTNS)**, which may be used to provide long term control of OAB without the adverse events of anticholinergic therapy by some urologists[154]. In one study of PTNS in 70 people with MS, daily TPTNS sessions over 3 months produced clinical improvement in over 80% of patients[155]. However, it is not possible to definitively define the appropriate role of this therapy owing largely to study design flaws that inhibited rigorous intention to treat analyses for the majority of these studies.

'transcutaneous posterior tibial nerve stimulation' (PTNS/TPTNS)
Percutaneous posterior tibial nerve stimulation (PTNS) for overactive bladder involves inserting a fine needle into a nerve just above the ankle. A mild electric current is passed through the needle and carried to the nerves that control bladder function

For patients with refractory OAB, **botulinum toxin** is being increasingly used to provide relief[156], including those with MS[157-159]. In a study with people with MS, three-quarters reported clinical improvement, including one-half of patients who reported 'complete success' (total continence). Non-response was more likely in those with advanced MS[159]. In this study no complications from therapy were reported, but potential complications include pain, urinary tract infections, and haematuria[157,159].

botulinum toxin
For the treatment of OAB, botulinum toxin is diluted in saline and during cytoscopy injected in small quantities into the detrusor muscle, avoiding the triogene. Analgesia, e.g. through inhaled anaesthetic such as nitrous oxide is provided and patients must be taught self catheterisation as an increase in post-void volume can occur.

Nocturnal incontinence and night-time urinary frequency are two of the worst problems associated with urinary impairment. For most people with MS, symptoms are helped significantly by taking an oral antimuscarinic before going to bed. Sometimes difficulties persist and desmopressin at night may be effective as it reduces the volume of urine produced overnight by the kidneys (when they are at their most productive). Its action lasts for 3-6 hours and it is safe when taken precisely as instructed. Desmopressin is usually taken as a spray. It can be used during the daytime but it is essential that the user realises the possible dangers of retaining too much water if it is used more than once in 24 hours. It should not be prescribed to people over 65.

Patients suffering from retention may need to learn self-catheterisation and there is some evidence that α-adrenergic antagonists may provide some benefit[1,149].

4.7 Bowel Dysfunction

4.7.1 Background

Bowel symptoms in MS include constipation, bowel urgency, and bowel incontinence. Loose stool that isn't caused by some type of infection or medication is usually the result of impaction or stool blockage, whereby looser stool from higher in the digestive tract leaks out around the impaction. Constipation is the most common bowel symptom, and is defined as infrequent, incomplete, or difficult bowel movements.

4.7.2 Assessment: Role of the MS Nurse

Managing dysfunction begins with assessment by an experienced health professional followed by ongoing collaboration with the individual to develop an approach which meets their particular needs. Factors that could contribute to constipation include poor mobility, voluntary fluid restriction to minimise urinary incontinency, anticholinergic drugs taken for concomitant bladder symptoms and poor dietary habits. Faecal incontinency may arise as a result of diminished perineal and rectal sensation, weak sphincter squeeze pressures, faecaloma leading to rectal overloading and overflow, or any combination of these factors.

4.7.3 Management

Although general recommendations for management of bowel dysfunction in MS include maintaining a high-fibre diet, high fluid intake, regular bowel routine and the use of enemas or laxatives, the evidence to support the efficacy of these recommendations is scant[160]. Long-term pharmacological treatment to prevent bowel dysfunction is not recommended and can lead to habituation. However, pharmacological treatment cannot always be avoided[161].

Sacral nerve stimulation has been used for the treatment of faecal incontinence[162]. This procedure has not been systematically studied in MS, but may lead to substantial benefit in some patients.

4.8 Sexual Dysfunction

4.8.1 Background

Normal sexual function involves a complex series of physical and psychological factors that are easily disturbed in a chronic disease such as MS. Sexual problems are not only distressing but can have a large impact on QoL for both patients and their partners[163]. The most prevalent sexual

complaint in men with MS is erectile dysfunction (ED), which has been estimated to affect up to 70% of patients[164,165].

4.8.2 Assessment: Role of the MS Nurse

The MS Nurse can approach sexual health and well-being in a number of ways. A first step may be to normalise the topic with an open question; *for example* "Many people with MS find they have some problems with sexual function and it is a very common problem – have you experienced any issues". This can bring an opportunity to begin immediate discussion about the issues of sexual and personal relationships, or allow for the person to come back to you when they feel able. Information about locally available counselling and support services can also be made available. The individual and any partner(s) should be offered an opportunity to see a specialist in sexual problems for advice on lubricants and the use of sexual aids, and for general information regarding sexual relations[166].

4.8.3 Management

Treatments for sexual dysfunction in patients with MS of both genders are, in the main, the same as for the general population and largely depend on the aetiology of the problem. Oral phosphodiesterase 5 (PDE5) inhibitors can be prescribed for patients with ED and there is evidence to suggest that sildenafil can be effective in both sexes at doses up to 100 mg, although the data in men are more robust[167]. Tadalafil has the advantage of being effective for up to 36 hours which may mean less planning and pressure to have sexual intercourse to a schedule. In an Italian study, 78% of men with MS responded to 10-20mg doses of tadalafil, with statistically significant improvements in erectile function and in sexual satisfaction scores[168].

A variety of topical lubricants, gels and creams are available to overcome vaginal dryness, and androgen therapy with such compounds as methyltestosterone or dehydroepiandrosterone can help to increase libido, particularly in women with low androgen concentrations[169]. However, long-term use of these latter compounds is not advised due to their side effect profile.

Pelvic floor muscle training, alone or in combination with intravaginal neuromuscular electrostimulation or transcutaneous tibial nerve stimulation, has also been shown to contribute to the improvement of sexual dysfunction in women with MS.[170]

The most important intervention is to have an open discussion with the patient and their partner, and refer on to appropriate specialist if desired and necessary.

4.9 Depression

4.9.1 Background

Depression will be experienced by over one-half of people with MS at some point in their lifetime[1]. Depression may be related to underlying disease processes, the challenge of living with MS, DMT therapy, or a combination of these[1]. There are higher levels of anxiety syndromes and suicide risk in people with MS.

4.9.2 Assessment: Role of the MS Nurse

People with MS should be assessed for depression during routine clinic visits, and urged to report symptoms to their MS Nurse and/or their general practitioner[1]. Specific tools/scales are available to detect depression, and assess the severity/need for therapy. Anxiety state is an important factor to consider as it is an indicator of depression risk, which is highest the first 5 years after diagnosis. Studies have found positive correlations between anxiety scores and depression scores, indicating

that the two conditions are related. Anxiety has also been shown to be prominent in the period surrounding MS diagnosis disclosure, particularly in women[171,172].

People with MS must be assessed for depression during routine clinic visits, and supported to disclose symptoms or issues to their MS Nurse and/or their general practitioner.

4.9.3 Management

Pharmacologic therapy for depression should be initiated when indicated, and may commonly be with an SSRI or tricyclic antidepressant.

Adverse events with SSRI therapy include decreased appetite, somnolence or sleep disturbances, dizziness and tremor, nausea, dry mouth, constipation, diarrhoea, asthenia, increased body weight and sexual dysfunction. Rarely, a neuroleptic malignant syndrome-like event may occur when starting therapy with an SSRI. Symptoms include hyperthermia and rigidity, myoclonus and confusion.

The tricyclic antidepressants are associated with anticholinergic side effects including dry mouth, dilated pupils, hyperpyrexia, urinary retention and constipation. Other events may include dizziness, weakness and anxiety/insomnia.

4.10 Cognition

4.10.1 Background

Some degree of cognitive impairment is noted in approximately 45–65% of patients with MS[173]. The impairment may start at early stages of the disease and cognition continues to deteriorate with disease progression[174]. The main symptoms of these deficits include problems with concentration, mental exhaustion and fatigue, spurious actions, learning difficulties and forgetfulness.

4.10.2 Management

There are no approved drugs for treatment of cognitive deficits in MS. Off-label use of donepezil in 69 people with MS has been reported to have positive effects but this could not be confirmed in a larger trial[175]. A study with memantine was terminated early following evidence of treatment-related worsening of neurological symptoms[176]. Rivastigmine has shown no significant effects on cognitive problems in MS patients in smaller studies so far, but is currently being investigated in a larger multicentre study with 200 patients[177]. Because of the significant impact of cognitive impairment on every aspect of life, early referral for assessment and expert support is paramount.

4.11 Pain

4.11.1 Background

Pain is experienced by more people with MS than was previously thought[1]; the most recent estimates suggest around one-half of patients experience a range of symptoms[178] (Table 28). It is often very difficult for people with MS to articulate, or locate, their pain or discomfort.

Type	Examples and frequency	Pharmacologic Management
Acute	Paroxysmal pain	Anticonvulsants
	Trigeminal neuralgia (1.9–3%)	Anticonvulsants or antispasmodics
	Lhermitte's phenomenon (>25%)	Surgical procedures
	Dystonic spasms (10–20%)	Antispasmodics
Chronic	Low back pain	Anticonvulsants
	Dysesthetic extremity pain	Nonsteroidal anti-inflammatory drugs
	Spasms, cramps (common)	Opioid narcotics
	Complex regional pain syndrome (rare)	Nerve blocks, tricyclic antidepressants

Table 28 : Pain syndromes in multiple sclerosis[178]

Acute pain may worsen, or become more frequent as MS progresses. Paroxysmal pain may occur at any site depending on the nerve affected; **trigeminal neuralgia** may occur in up to 3% of patients[1].

Trigeminal neuralgia
Trigeminal neuralgia is characterised as an 'electric shock' like facial sensation which lasts for a few seconds to up to a minute but is experienced repeatedly through the day. It results from abnormal nerve signalling within the trigeminal nerve which is a major nerve involved in sensation in the face

4.11.2 Management

Many therapies used for pain in people with MS are based on clinical experience rather than evidence from large scale clinical trials[178], and a number of agents are used (Table 29).

Agent	Common uses in multiple sclerosis*	Common adverse effects
Anticonvulsants		
Carbamazepine	Trigeminal neuralgia Lhermitte's sign paroxysmal pain‡	Altered taste Ataxia Bone marrow depression Constipation Diplopia Dizziness Dysarthria Gastrointestinal upset Hyponatraema Impaired alertness Sedation
Lamotrigine	Trigeminal neuralgia	Ataxia Blurred vision Diplopia Dizziness Headache Insomnia Irritability
Pregabalin	Central neuropathic pain Paroxysmal pain Trigeminal neuralgia	Blurred vision and loss of visual acuity Dizziness Vertigo

		Drowsiness/fatigue Mood changes Ataxia/tremor Gastrointestinal upset[179].
Gabapentin	Central neuropathic pain Lhermitte's sign Paroxysmal pain Trigeminal neuralgia	Ataxia Diplopia Fatigue Gastrointestinal upset Nystagmus Sedation Tremor
Clonazepam	Paroxysmal pain	Ataxia Dizziness Lethargy Sedation
Tricyclic antidepressants		
Amitriptyline	Central neuropathic pain	Blurred vision Constipation Drowsiness Dry mouth Sedation Urinary retention
Muscle relaxant		
Baclofen	Painful tonic spasms Trigeminal neuralgia	Dizziness Fatigue Gastrointestinal upset Seizures Transient drowsiness Weakness
* Some medications may not be available in all countries; not necessarily based on published studies. ‡ Paroxysmal pain refers to short, frequent and stereotyped pain with a sudden onset (ie. Lhermitte's sign or paroxysmal pelvic pain)		

Table 29: Drugs commonly used in the treatment of pain syndromes in MS[178]

For acute paroxysmal pain anticonvulsants represent first line therapy; examples of drugs used include carbamazepine, gabapentin, pregabalin, **levetiracetam or lamotrigine**[180].

Carbamazepine may cause leucopenia, thrombocytopenia and more rarely, agranulocytosis and anemia. Therefore a pre-treatment blood count is usually recommended[181]. Patients should also be advised to report any signs or symptoms suggestive of infection (e.g. fever, sore throat) or bruising/skin reactions to their doctor[179]. Because of the risk of liver function abnormalities it is also usual to check liver function tests and electrolytes before therapy, and periodically during therapy as carbamazepine may also cause severe hyponatriemia[179]. Patients treated with carbamazepine may suffer more adverse events than those treated with gabapentin or lamotrigine, and discontinuation may be more frequent[178].

Pregabalin is a therapy approved for peripheral and central neuropathic pain. The usual does is 150 mg per day given as two or three divided doses which can be increased to 300 mg per day after 3 to 7 days, and if needed, to a maximum dose of 600 mg per day after an additional 7-day interval. The adverse events with pregabalin are similar to gabapentin and for people with MS receiving pregabalin

it is important to consider whether any visual symptoms are adverse events of therapy, or secondary to their MS. The higher doses of gabapentin used for neuropathic pain can result in events being more frequent or severe than with pregabalin – although comparative studies have not been done in people with MS.

levetiracetam or lamotrigine
Other agents used (although not approved for neuropathic pain) also have distinct adverse event profiles. Levetiracetam is associated with nasopharyngitis, somnolence, headache, fatigue and dizziness. In addition, anorexia, mood changes (depression, anxiety, insomnia, and irritability), tremor, gastrointestinal effects and convulsions may occur182. However, pre-treatment or on-treatment blood or liver function tests are not normally required. Similarly, lamotrigine can be associated with aggression or irritability, headache, dizziness, tiredness and fatigue, skin rashes and gastrointestinal disturbances183.

Treatment of neuropathic pain in people with MS is highly individualised[1]; for acute paroxysmal pain combination therapy may be required, while trigeminal pain may be treated with anticonvulsants or antispasmodics such as baclofen or misoprostol[1,180,184]. Small studies of treatment options for trigeminal neuralgia suggest that the majority of patients may gain benefit from therapy (carbamazepine, gabapentin, lamotrigine)[178]. Tricyclic antidepressants may also be used for neuropathic pain, although adverse events can be wide ranging and significant (see section *Depression*)[185]. For those who fail to respond to pharmacotherapy, surgical procedures or microvascular decompression may be considered[178].

Overall it has been suggested approximately 50% of patients may respond to first line anticonvulsant therapy for neuropathic pain syndromes in MS, however response is highly variable between patients, and requires ongoing review and assessment[178].

Approximately 50% of patients may respond to first line anticonvulsant therapy for neuropathic pain syndromes in MS.

Lhermitte's sign is a sensation of 'electric shock' like tingling experiences throughout the body, often down the spine when the patient bends their head[1]. It may occur in one-quarter to one-third of people with MS which if troublesome can be treated with surgery[1].

Chronic neuropathic pain is also common in people with MS and, like acute neuropathic pain, anticonvulsants are the usual first-line therapy, with NSAIDs, opioids, tricyclic antidepressants or nerve block[1,180]. Dystonic spasms can cause both acute and chronic pain and antispasmodics (see section 'spasticity') can provide relief.

Depending on local clinical practice, patients with chronic pain may be able to attend a specialist Pain Clinic for assessment and management. Pain Clinics vary in the treatment/therapies offered and not all centres will have a specific pain clinic.

4.12 Role of Complementary & Alternative Medicine

Complementary and alternative medicine (CAM) refers to those forms of treatment which are not widely in use by orthodox healthcare professionals. Complementary refers to those treatments that are used in conjunction with orthodox medicine. Alternative refers to those treatments that are used instead of more conventional approaches.

Between one-third and two-thirds of people with MS will use complementary and alternative medicines, for many reasons and often as an adjunct to conventional therapy[186]. Many of those who use complementary and alternative medicines claim to derive benefit from these therapies including diet, omega-3 fatty acids and antioxidants[186]. Patients report most CAM use during the transition from moderate to severe impairment e.g. a reduction of the maximal walking distance. At this stage, patients may try every possible treatment for the disease or its symptoms, whereas patients in an advanced stage of disease may have resigned to the fact that they suffer from an incurable disease.[187]

A recent study found that most prevalent use of CAM was vitamins/minerals (89%, n = 24), nonvitamin, nonmineral, natural products (NP) (44%, n = 12), relaxation techniques (33%, n = 9), and special diets (30%, n = 8).[188]

There are few trials of these agents; however some have been shown to interact with conventional therapy (for example, St John's Wort taken with orthodox SSRI can cause serotonin shock syndrome) (Table 30)[186]. Patients should be given evidenced-based information on CAMS so that they can make informed choices and be advised to report use of complementary therapies to their MS Nurse or clinician, to ensure safety and prevent potentially dangerous interaction.

Between one-third and two-thirds of people with MS will use complementary and alternative medicines; individuals should be encouraged to report use to their MS Nurse or clinician.

Agent	Origin	Comments
Omega-3 fatty acids	Essential fatty acid which must be obtained in the diet (e.g. flax, soya, fish and fish oils such as mackerel and salmon).	One clinical trial has suggested a trend towards reduced EDSS scores, however there were study limitations. Appears to be safe, with mild indigestion and gastrointestinal upset reported.
Lipoic acid	Antioxidant and dietary supplement.	Has been shown in a small study to improve markers of inflammation in people with MS. Mild gastrointestinal effects and headache are the most common adverse events.
Ginkgo biloba	Traditional Chinese herbal remedy.	Although a suggested beneficial effect on cognition is controversial, there is some limited evidence of an effect in people with MS.

		Well tolerated.
Ginseng	Traditional Chinese herbal remedy.	Suggested to decrease fatigue, although effects in MS patients have not been proven. Large doses can cause adverse effects (hypertension, nervousness, irritability and insomnia).
Green tea	Suggested to have immunomodulatory effects	Limited, if any clinical studies in MS patients, but studies have been started. Generally well tolerated, although high doses used in cancer studies have caused liver dysfunction.
Vitamin D	Vitamin, produced in the skin from exposure to UV light. Low levels (both intake and serum) associated with an increased prevalence of MS in epidemiological studies.	Clinical studies to assess the effect in patients with MS are ongoing. Some centres are advocating supplementing with 1000iu per day and in particular during winter months
Cannabis	May improve pain and spasticity The active ingredient, THC, may be available as a controlled substance in some countries (e.g. to improve appetite in AIDS patients and as an antiemetic in cancer patients)	Studied in several randomised trials in MS-related spasticity. Overall therapy was well tolerated and improved patients self-reports of spasticity, however objective measures did not improve.
St John's Wort	Thought to have anti-depressant activity, and a meta-analysis reported superiority to placebo and equivalence to conventional anti-depressants[186]	Generally well tolerated, but can cause photosensitivity and also interact with other medications through cytochrome P450.
Diet	Many 'MS diets' exist, usually suggesting low-fat and/or high fish consumption.	Evidence is limited and it is important to ensure suggested diets do not impair overall nutritional status.

Table 30: Common complementary and alternative medicines[186]

An evidence-based guideline regarding the use of CAM in MS has recently been published by the American Academy of Neurology.[190] The guideline focuses on several issues including if CAM therapies reduce specific symptoms and prevent relapses or disability; if CAM use worsen MS or cause serious adverse effects; and if CAM use interfere with MS disease-modifying therapies. Some

of the recommendations include oral cannabis extract for spasticity symptoms and pain (excluding central neuropathic pain) (Level A).

4.13 Summary

- In addition to DMT, people with MS may require a wide range of therapies to improve symptoms of MS.
- If untreated these symptoms worsen quality of life and have a significant impact on the ability to maintain activities of daily living.
- The treatment options for symptom management in MS are often based on clinical experience rather than large clinical trials.
- It may be necessary to seek advice from other specialists for complex cases, for example a urologist for bladder problems.

Symptoms	Treatment		Nursing Considerations
Fatigue	• CNS stimlus (pemoline, modafinil) • Amantadine • Selective serotonin reuptake inhibitors (SSRIs), eg fluoxetine		• Restlessness or sleep disturbance may occur • Help patients with dosing schedule, titrate dose up
Bladder dysfunction	• Anticholinergics (eg oxybutynin) • Antimuscarinics (eg tolterodine) • α-Blockers (eg terazosin)		• Determine if urinary tract infection is present • Monitor retention • Monitor fluid balance • Follow overall elimination pattern consider contribution of other medications • Provide strategies to avoid side effects eg dry mouth
Bowel dysfunction	Constipation • Stool softeners • Bulk-forming agents • Mini-enemas • Stimulants • Suppositories	Urgency/diarrhea • Bulk-forming agents • Anticholinergics • Antimuscarinics	• Provide bowel training regimens; many of the medications should not be used long-term • Consider contributory effects of their medications eg steroids or antibiotics • Consider lifestyle issues • Encourage exercise • Provide diet counselling
Pain	• Anticonvulsants (phenytoin, carbamazepine, gabapentin, lamotrigine) • Tricyclic antidepressants (amitriptyline, nortriptyline) • Duloxetine hydrochloride		• Watch for sedation • Start with low dose an titrate up • Monitor outcomes; alter treatment as necessary; supportive measures can help

Spasticity	• GABA antagonists (oral or intrathecal baclofen) • α-Agonists (tizanidine) • Anticonvulsants (diazepan, clonazepam, gabapentin) • Botulinum toxin	• Time doses to maintain therapeutic blood levels • Titrate doses up (especially with baclofen) • Watch for sedation or cognitive symptoms; may require a change in dosage or medication • Combination treatments may help • Intrathecal baclofen requires surgical insertion of a programmable pump
Depression	• SSRIs and SNPIs (eg fluoxetine, sertraline, paroxetine, citalpram duloxetine hydrochloride) • Tricyclic antidepressants (eg amitriptyline, nortriptyline) • Atypical antidepressants (eg venlafaxine, bupropion)	• Evaluate type and degree of depression • Consider contribution of medications (eg with interferons) • Assess family situation/support network • Consider suicide risk • Promote use of psychiatric services • Advise patient that medication effects may take several weeks • Advise patient not to stop medications suddenly • Reassess patient regularly • Paroxetine can be taken in the morning or at night, can help with anxiety • Monitor urinary function with venlafaxine (may cause fluid retention)

Table 31: Therapies which may be used for symptom management

- The MS Nurse should be aware of the symptoms a patient may experience, and be prepared to ask about potentially 'personal' symptoms that patients may be reluctant to raise themselves.
- This requires the nurse to build a relationship based on trust and to be aware of the potential treatment options.
- In addition patients may commonly decide to take complementary and alternative remedies; it is important the patient's MS care team is made aware of these therapies in order that appropriate advice can be given if required.

Reflective learning points

How do you assess and determine severity of symptoms in people with MS and, therefore, decide if recommendation for pharmacological intervention is required?

What strategies do you employ to ensure your patients are reporting all their symptoms and the severity of their symptoms?

What factors influence your choice of management of symptoms associated with MS?

Summary of Module

- Acute relapse management focuses on the initiation of therapy to resolve symptoms as required.
- This may include symptom management or for acute relapses/exacerbations, high dose steroid therapy (IV or oral).
- A number of DMTs are available for patients with RRMS suitable for use in those with CIS or mild disease activity, those with highly active disease, and also for those who fail first-line therapy.
- For most patients with RRMS initial therapy will be IFNβ or glatiramer. These require administration by SC or IM injection and the MS Nurse plays an important role in training patients how to self-administer their DMT, either using a syringe and needle, or an autoinjector.
- In some countries the oral agent fingolimod and natalizumab are alternatives to IFNβ or glatiramer for RRMS, while in others fingolimod and natalizumab, are used for patients who progress on first-line therapy (e.g. IFNβ) of those with highly active RRMS.
- For patients with SPMS who continue to experience relapses, IFNβ-1b has been used, and some centres will continue a patient on their existing DMT while there is clinical benefit. Mitoxantrone may also be used in SPMS, or PRMS, although due to concerns about long-term toxicity, for a defined duration of time.
- It is important to inform patients of likely adverse events, how to manage the more common events and when they should report specific events to their MS Centre or primary care physician.
- In addition, each DMT has different requirements for routine follow-up assessments and tests and it is important patients are informed and followed-up appropriately to ensure these are undertaken as required.
- In addition to DMT, people with MS may require therapy to improve symptoms of MS which are both common and troublesome.
- If untreated these symptoms worsen quality of life and have a significant impact on the ability to maintain activities of daily living.
- The treatment options for symptom management in MS are often based on clinical experience rather than large clinical trials.
- It may be necessary to seek advice from other specialists for complex cases, for example a urologist for bladder problems.
- The MS Nurse should be aware of the symptoms a patient may experience, and be prepared to ask about potentially ‘personal’ symptoms that patients may be reluctant to raise themselves.
- This requires the nurse to build a relationship based on trust and to be aware of the potential treatment options.
- In addition patients may commonly decide to take complementary and alternative remedies; it is important the patient’s MS care team is made aware of these therapies in order that appropriate advice can be given if required.