

CLINICAL PRACTICE GUIDELINES

MOH/P/PAK/293.15(GU)

MANAGEMENT OF MULTIPLE SCLEROSIS



Ministry of Health
Malaysia



Malaysian Society of
Neurosciences



Academy of Medicine
Malaysia

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STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

These guidelines were issued in 2015 and will be reviewed in a minimum period of four years (2019) or sooner if new evidence becomes available. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed.

TABLE OF CONTENTS

No.	Title	Page
	Levels of Evidence & Formulation of Recommendation	i
	Guidelines Development and Objectives	ii
	Guidelines Development Group	v
	Review Committee	vi
	External Reviewers	vii
	Algorithm 1. Care Pathway for Referral and Management of MS	viii
	Algorithm 2. Disease Modifying Therapies for Multiple Sclerosis	ix
	Algorithm 3. Treatment of Relapsing-Remitting Multiple Sclerosis	x
1.	INTRODUCTION	1
2.	EPIDEMIOLOGY	1
3.	RISK FACTORS	3
4.	PATHOLOGY AND IMMUNOLOGY	4
5.	CLINICAL FEATURES	5
6.	CLINICALLY ISOLATED SYNDROME, OPTIC NEURITIS AND TRANSVERSE MYELITIS	7
7.	DIFFERENTIAL DIAGNOSIS	13
8.	NATURAL HISTORY	20
9.	DIAGNOSTIC CRITERIA	22
10.	INVESTIGATIONS	24
11.	MONITORING DISEASE ACTIVITY AND RISK OF PROGRESSION	27
12.	REFERRAL	32
13.	TREATMENT	33
	13.1 Treatment of Acute Attacks and Relapses	33
	13.2 Disease Modifying Treatment	35
	13.3 Treatment of MS-related Symptoms	53

No.	Title	Page
14.	NEUROPSYCHIATRIC PROBLEMS	72
15.	SPECIAL ISSUES	75
16.	IMPLEMENTING THE GUIDELINES	78
	References	79
Appendix 1	Example of Search Strategy	91
Appendix 2	Clinical Questions	92
Appendix 3	Differential Diagnosis of Optic Disc Swelling	93
Appendix 4	Treatment of NMO/NMOSD	94
Appendix 5	New NMOSD Diagnostic Criteria for Adult Patients	97
	2013 MS Disease Modifier Phenotypes	
Appendix 6	Kurtzke Expanded Disability Status Scale (EDSS) for Neurologic Assessment	99
Appendix 7	Neuroimaging Features in MS	100
Appendix 8	Bladder Diary	103
Appendix 9	Drug Dosages and Side Effects in MS	104
	List of Abbreviations	120
	Acknowledgement	122
	Disclosure Statement	122
	Source of Funding	122

LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II -1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

In line with the current development in CPG methodology, the CPG Unit of MaHTAS is in the process of adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of each retrieved evidence and its effect size are carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:-

- overall quality of evidence
- balance of benefits versus harms
- values and preferences
- resource implications
- equity, feasibility and acceptability

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for these Clinical Practice Guidelines (CPG) were from the Ministry of Health (MoH) and Ministry of Higher Education. There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A literature search was carried out using the following electronic databases: Guidelines International Network (G-I-N); Medline via Ovid, Pubmed and Cochrane Database of Systemic Reviews (CDSR) (refer to **Appendix 1 for Example of Search Strategy**). The inclusion criteria are all literature on multiple sclerosis regardless of study design. The search was limited to literature published in the last 15 years, humans and English. In addition, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. Experts in the field were also contacted to identify relevant studies. In certain situations, pivotal papers beyond the scope of search were used in the CPG. All searches were conducted from 30 January 2013 to 13 August 2014. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 28 February 2015 to be included. In view of evolving issues on it, pivotal papers on diagnostic criterias after February 2015 were accessed. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

Reference was also made to a CPG on multiple sclerosis developed by the National Collaborating Centre for Chronic Conditions in 2004 and National Clinical Guideline Centre in 2014 [commissioned by National Institute for Health and Care Excellence (NICE)]. The CPG was evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to them being used as references.

A total of 23 clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections. (Refer to **Appendix 2 for Clinical Questions**) The DG members met 24 times throughout the development of these guidelines. The literature retrieved was appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meetings. All statements and recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. Any differences in opinion were resolved consensually. The CPG was

based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literature used in these guidelines was graded using the US/Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation was done using the principles of GRADE (refer to the preceding page).

On completion, the draft of the CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council MoH Malaysia for review and approval.

OBJECTIVES

The objectives of the CPG are to provide evidence-based recommendations on the following:

- a. Diagnosis of multiple sclerosis
- b. Management of multiple sclerosis and its complications

CLINICAL QUESTIONS

Refer to **Appendix 2**

TARGET POPULATION

a. Inclusion Criteria

Adult patients (≥ 18 years old) with MS

b. Exclusion criteria

- Patients with other relapsing remitting central nervous system disorders not fulfilling diagnostic criteria for MS
- Paediatric groups with demyelinating disorders

TARGET GROUP/USER

This CPG is intended to guide those involved in the management of MS particularly healthcare professionals in primary and secondary/tertiary care namely:-

- a. Physicians and specialists from related disciplines
- b. Family Medicine Specialists
- c. Medical officers and general practitioners
- d. Allied health professionals
- e. Pharmacists
- f. Students (medical postgraduates and undergraduates, and allied health students)
- g. Patients and carers

HEALTHCARE SETTINGS

Outpatient, inpatient and community settings

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The draft guideline was reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

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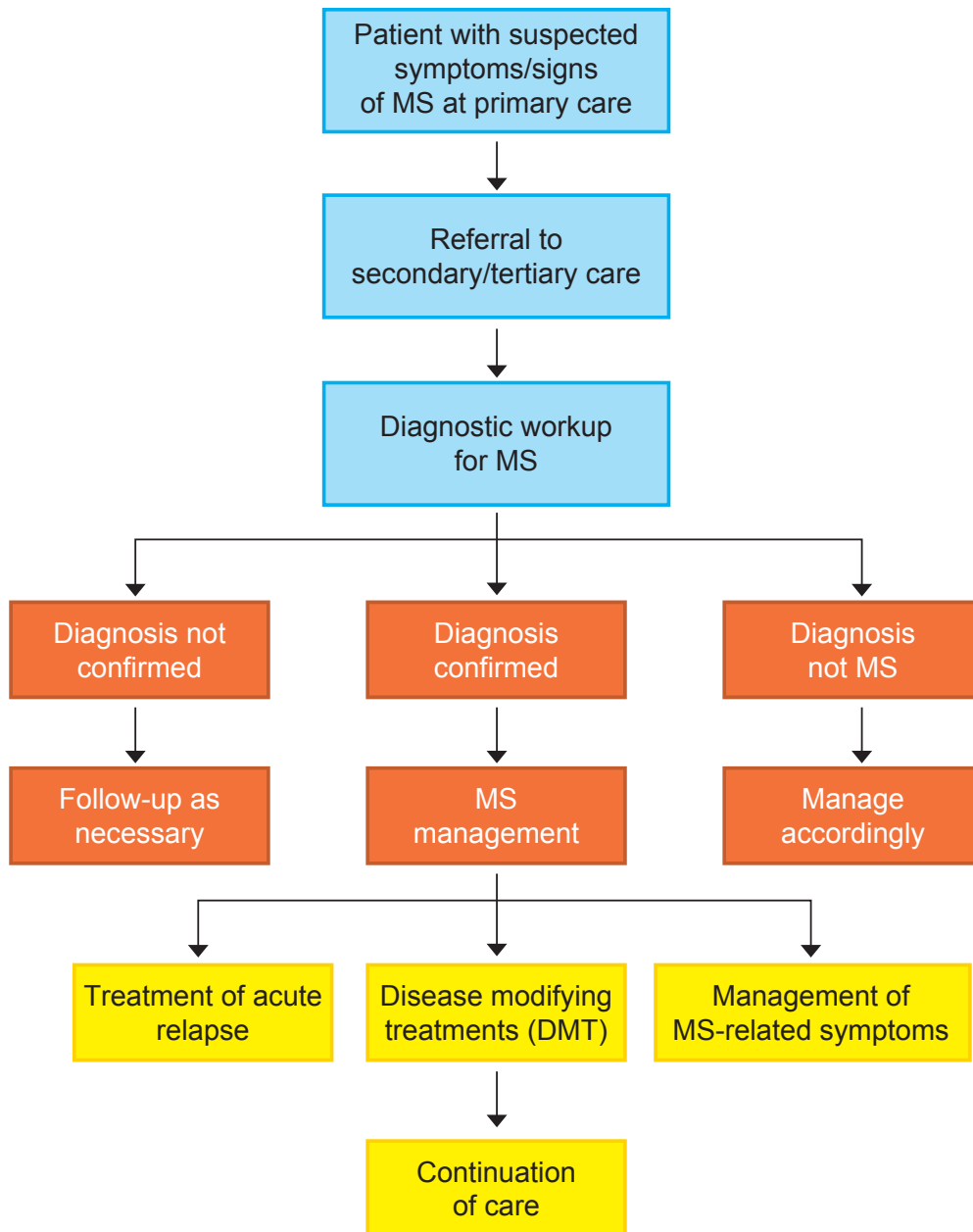
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ALGORITHM 1. CARE PATHWAY FOR REFERRAL AND MANAGEMENT OF MULTIPLE SCLEROSIS (MS)



ALGORITHM 2. DISEASE MODIFYING THERAPIES FOR MS

Level of therapy	Level of pharmacological agent	Relapsing-remitting active MS*	Highly active relapsing-remitting MS*	Rapidly evolving/ aggressive relapsing-remitting MS*	Secondary progressive MS with relapses
Initial Therapy	First-line	Interferon beta/ Glatiramer acetate**/ Teriflunomide/ Dimethylfumarate	NA	Fingolimod/ Natalizumab***/ Alemtuzumab	Interferon beta
Escalation Therapy	Second-line	Refer to section on highly active relapsing remitting MS	Fingolimod/ Natalizumab***/ Alemtuzumab		Mitoxantrone/ Cyclophosphamide
	Third-line		Mitoxantrone/ Rituximab/ Cyclophosphamide		
Relapse Therapy	First-line	Methylprednisolone			
	Second-line	Plasmapheresis			

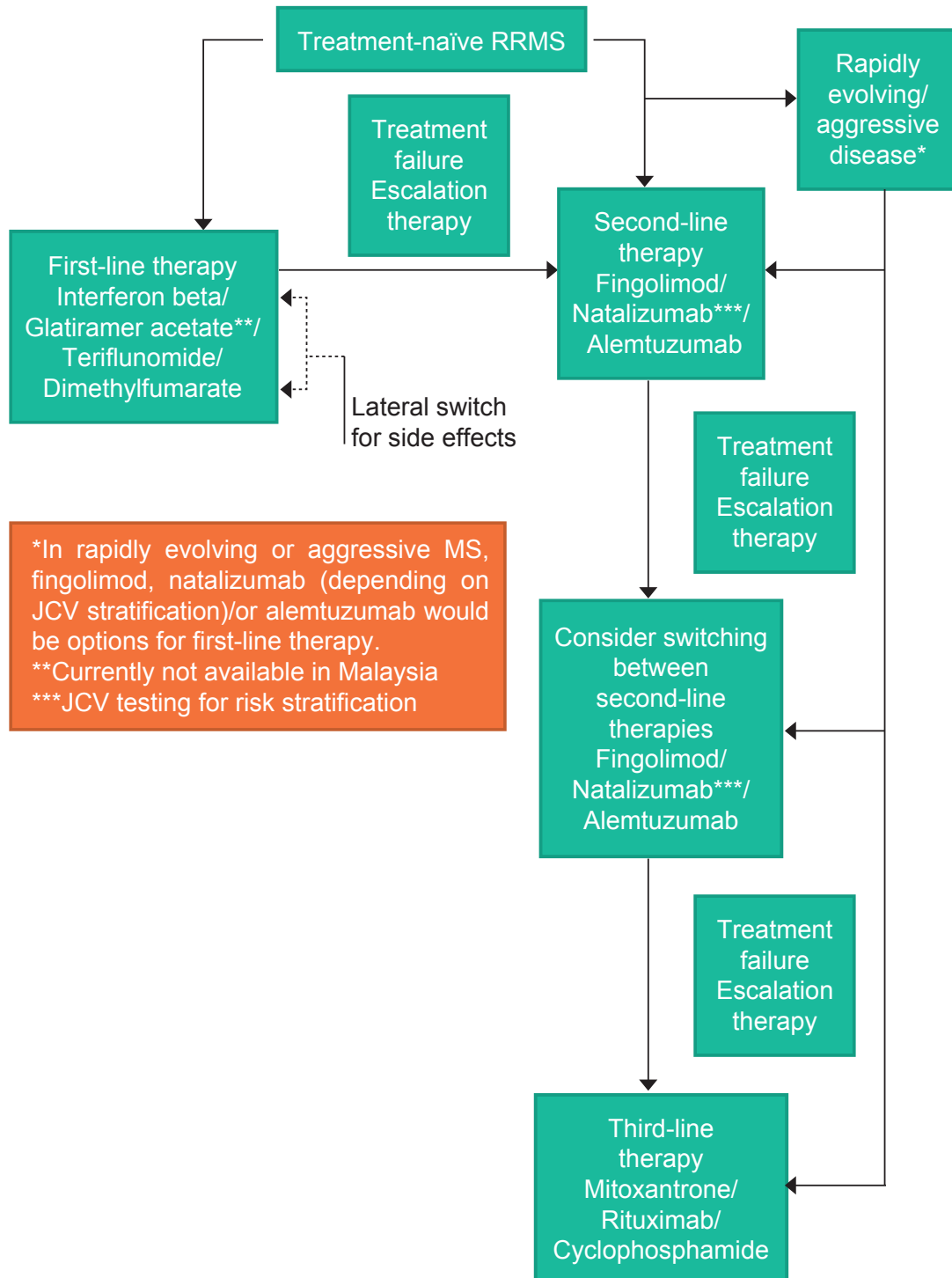
NA = not applicable

*Refer to text for definitions of active MS, highly active MS and rapidly evolving or aggressive MS

**Currently not available in Malaysia

***John Cunningham virus (JCV) testing for risk stratification

ALGORITHM 3. TREATMENT OF RELAPSING-REMITTING MULTIPLE SCLEROSIS (RRMS)



1. INTRODUCTION

Multiple sclerosis (MS) and other idiopathic inflammatory demyelinating disorders (IIDDs) especially neuromyelitis optica spectrum disorder (NMOSD) have an increasing importance in terms of diagnosis and treatment in Malaysia. MS is an inflammatory demyelinating disorder of the central nervous system (CNS) with heterogeneous presentations. It can be considered a two phase disease made up of the early predominantly inflammatory phase wherein relapses are common and a later more progressive neurodegenerative phase characterised by axonal loss.

It is important to diagnose MS during the early inflammatory phase. It is during this phase that disease modifying therapy (DMT) prevents relapses and may delay the disability and progression of disease. Initiation of early treatment in MS poses many challenges and with the recent increase in DMTs, the treatment should be individualised. As MS patients also experience diverse symptoms and disabilities, a multidisciplinary approach is ideal.

In Malaysia, the first point of contact for patients with symptoms suggestive of established MS or high risk for MS is the primary and secondary healthcare providers. Neurologists have an important role in confirming the diagnosis, ruling out NMOSD and initiating DMT in MS. To date, there have not been any local guidelines to aid in the management of MS. Hence, this CPG on Management of MS is timely, evidence-based and applicable to the local context at all levels of health care.

2. EPIDEMIOLOGY

The total number of patients with MS worldwide is estimated to be 2 - 2.5 million. The prevalence is >100 - 200/100,000 in temperate areas like United States of America, Canada, New Zealand and parts of Australia. It is <5 per 100,000 in tropical areas or Asia.^{1, level III}

In Asia, the prevalence of MS is reported to be 1 - 2/100,000 in China and 7.7/100,000 in Japan.^{2 - 3, level III} The prevalence of MS in Malaysia is estimated to range from 2 to 3/100,000.^{3 - 4, level III} However, the patient population included in these studies were a mixed group of both MS and NMOSD. In the 1980s, the prevalence of MS in India was crudely estimated to be 1/100,000 but a recent study suggested the age adjusted prevalence had increased to 7.8/100,000.^{5, level III}

Worldwide, MS is commonest among women in their 20s to 40s. It is commoner among whites and the female to male ratio varies from 2:1

to 3.8.^{3, level III} A study at the Kuala Lumpur Hospital showed a female to male ratio of 5:1 for MS. The mean age at onset was 28.6 ± 9.9 years with a mean duration of illness of 6.4 ± 5.2 years. Malay was the predominant racial group affected (52.9%), followed by the Indian (26.9%), Chinese (18.3%), and indigenous groups from East Malaysia (1.9%). Ratios of MS to NMOSD in different racial groups in Malaysia also differs i.e. Malays 38:55 (41% NMOSD), Chinese 32:19 (63% NMOSD) and Indians 7:28 (20% NMOSD).^{6, level III}

3. RISK FACTORS

The aetiology of MS is multifactorial involving both genetic and environmental factors. The disease is triggered by an autoimmune process in susceptible individuals. The risk factors can be categorised as the following:

a. Genetics

- The risk of MS in offspring of single affected parent is 2% and higher in those of conjugal pairs with MS (20%).^{7, level III} Maternal half-siblings of MS patients have twice the risk compared with paternal half-siblings.^{1, level III}
- First degree relatives have a 10 - 25 times greater risk of developing MS than the general population.^{8, level III}
- Twin studies have shown genetic susceptibility with concordance rates of 25 - 30%.^{1, level III}
- The commonest genetic risk factor is Human Leucocyte Antigen allele DRB1*1501.^{1, level III}

b. Ethnicity

- Caucasians from Scandinavia and Scotland are extremely susceptible to MS. However, it is rare in the Mongolian race, Chinese and others.^{1, level III}

c. Sex

- MS is more common in women than men.^{8, level III}

d. Migration and latitude

- Migrants moving from an area where MS is common to an area where it is less common show a decrease in the rate of MS, while migrants moving in the opposite direction tend to retain the low risk of MS as of their country of origin. Studies have shown that people born in an area with a high risk of MS who then migrated to an area with a lower risk before the age of 15 assumed the risk of their new area suggesting the effect of an environmental agent before puberty.^{1, level III}
- Within regions of temperate climate, MS prevalence generally increases with latitude.^{8, level III}

e. Environmental factors associated with increased risk of MS are:

- lack of sunlight exposure^{1, level III} and ultraviolet radiation^{9, level III}
- low serum level of 25 Hydroxycholecalciferol^{10, level II-2}
- Epstein-Barr Virus infection^{11, level II-2}
- smoking^{12, level II-2}

- Risk factors for MS are:
 - genetics
 - ethnicity
 - sex
 - migration and latitude
 - environmental factors

4. PATHOLOGY AND IMMUNOLOGY

MS is believed to be an autoimmune disease. The pathological hallmark of MS is the presence of multiple discrete areas of myelin loss within the CNS with predilection for the optic nerves, spinal cord, brainstem, cerebellum, juxtacortical, subcortical and periventricular white matter regions as well as the cortical grey matter. The affected areas are called plaques or lesions.^{13, level III}

Early MS demyelination is accompanied by inflammation and relative axonal preservation though axon loss also occurs. The lesions evolve differently during the early as opposed to the later stage of the disease. Within each phase, different plaques in different stages of demyelinating activity are evident. Histologically, inflammation, myelin breakdown, astrogliosis, oligodendrocyte injury, axonal loss and remyelination are seen.^{13, level III} In progressive MS, increasing axonal loss, neurodegeneration and failure of remyelination all play an important role.^{14, level III}

MS is an immune mediated disease. Autoreactive T and B cells are activated in the periphery and trans-migrate to the blood brain barrier (BBB) triggering an autoimmune cascade which leads to damage of the myelin sheath and axons directly within the CNS. This activating mechanism or antigen(s) has not been characterised to date.^{15 - 17, level III}

5. CLINICAL FEATURES

MS has a highly variable clinical presentation and course in different individuals. The majority of patients are young, less than 50 years old and females.^{7, level III; 18 - 19, level III} The clinical course is characterised by relapses and disease progression. An attack/relapse/exacerbation in MS is defined as an acute or subacute patient-reported symptom or objectively observed signs typical of an acute inflammatory demyelinating event within the CNS either current or historical of at least 24 hours in the absence of fever or infection.^{20, level III} This may be a new event or a worsening of a pre-existing event. Relapses may fully recover over days or weeks, or lead to persistent residual deficits.

In 85% of MS patients, a relapsing-remitting disease course is seen. Typical clinical presentations of relapses are optic neuritis (ON; the initial symptom in 20%), sensory deficits or cerebellar dysfunction.^{21, level III}

Primary progressive multiple sclerosis (PPMS) can be seen in 10 - 15% of patients. It refers to those with at least one year of disease progression (retrospectively or prospectively determined).^{20, level III} The usual clinical presentation is as follows:^{19, level III}

- The spinal cord is commonly involved and patients present with a slowly evolving upper motor neuron syndrome for the legs (chronic progressive myelopathy).
- Progressive cognitive decline, visual loss, brainstem and cerebellar ataxic syndromes, bowel, bladder and sexual dysfunction may occur.
- If accompanied by relapses, it is called progressive relapsing MS (seen in less than <5% of patients).

- The hallmark of relapsing MS is attacks or exacerbations affecting different parts of the CNS which are separated in time and space.

Pseudorelapse is defined as an acute worsening of symptoms that is typically associated with an increase in body temperature due to infection, exercise or heat exposure.^{22, level III}

Patients may experience the following clinical symptoms and signs during their disease course:^{7, level III; 18 - 19, level III; 23 - 25, level III}

a. Weakness occurs in 89% of patients:

- with cerebral involvement - monoparesis, hemiparesis or hemiplegia
- with spinal cord involvement - partial myelitis, presenting with hemiparesis/plegia and paraparesis/plegia, spasticity, stiffness, painful spasms, sensory symptoms, sphincter involvement

- b. Sensory symptoms:
 - numbness, tingling and paraesthesias can be seen in 87% of patients
 - 34% of patients complain of sensory symptoms at initial presentation
 - Lhermitte's sign (trunk and limb paresthesias elicited by neck flexion)
- c. Fatigue is a common symptom in 83% of patients.
- d. Pain, such as paraesthesias or paroxysmal pains (trigeminal neuralgia), is seen in 54% of patients
- e. Visual disturbances due to optic nerve involvement are seen in 50% of patients:
 - unilateral ON is more common (20%) than bilateral ON at onset (0.4%)
 - painful blurring of vision, visual field (VF) defects and reduced colour vision
- f. Cognitive Impairment
- g. Psychiatric symptoms such as depression, anxiety, and psychosis
- h. Cortical symptoms - aphasia/dysphasia and epilepsy rarely occur
- i. Brainstem and cerebellar disturbances - diplopia, internuclear ophthalmoplegia, dysarthria, pseudo-bulbar palsy, vertigo, ataxia, postural or action tremors and others
- j. Paroxysmal attacks of motor or brainstem phenomenon - painful tonic muscle contraction of the limbs, trunk and face
- k. Bowel and bladder involvement
- l. Other features that can occur include:
 - heat intolerance and Uhthoff's phenomenon (symptomatic worsening with increases in body temperature)
 - extrapyramidal symptoms
 - sexual dysfunction
 - headaches

6. CLINICALLY ISOLATED SYNDROME, OPTIC NEURITIS AND TRANSVERSE MYELITIS

6.1 Clinically Isolated Syndrome

Clinically isolated syndrome (CIS) is the first clinical episode, lasting ≥ 24 hours in which a patient has symptoms and signs suggestive of an inflammatory demyelinating disorder of the CNS that is at high risk of development of MS.^{26 - 27, level III}

In 85% of patients with MS, possible presentations of CIS at onset include:^{21 level III; 27, level III}

- ON (20 - 25%)
- transverse myelitis (partial) (30 - 50%)
- brainstem or cerebellar disease (25 - 30%)
- rarely cerebral hemisphere syndromes (5%)

However, only 30 - 70% of patients with CIS will convert to clinically definite multiple sclerosis (CDMS) provided all other potential diagnosis has been excluded within 2 to 5 years.^{27, level III}

The term CIS is typically applied to:^{26, level III}

- adults (aged 20 - 45 years) with an episode of subacute or acute onset, which reaches a peak within 2 - 3 weeks and
- the episode should last for at least 24 hours and occur in the absence of fever or infection, with no clinical features of encephalopathy

CIS is by definition isolated in time (monophasic) and also isolated in space (monofocal) clinically, with signs indicating a lesion in the optic nerve, spinal cord, brainstem or cerebellum, or a cerebral hemisphere. Occasionally, it is multifocal.^{26, level III}

The presentation of CIS affects the disease course and prognosis as shown in **Table 1**.^{27, level III; 28, level II-2}

Table 1. Features of CIS affecting prognosis

Good prognosis	Bad prognosis
Young	Older age at onset
Female sex	Male sex
Good recovery from first attack	Poor recovery from first attack
ON, isolated sensory symptoms	Efferent systems affected (motor, brainstem, cerebellar etc.)
Long interval to second relapse	High relapse rate in the first two to five years
No disability after five years	Substantial disability after five years
Normal magnetic resonance imaging (MRI) brain/low lesion load	Abnormal MRI brain with large lesion load, brain atrophy, ≥ 2 spinal cord lesions, $\geq T1$ lesions
Cerebrospinal fluid (CSF) negative for oligoclonal bands (OCBs)	CSF positive for oligoclonal bands

Diagnosis of CDMS can be made clinically if CIS patients have another attack.^{29, level III} However a second attack is not required if McDonald 2010 MRI criteria for dissemination in space (DIS) and dissemination in time (DIT) is fulfilled at presentation.^{20, level III}

Clinical factors associated with higher risk of conversion to CDMS are:^{28, level II-2}

- younger age at onset
- female
- non-white ethnicity
- greater number of functional systems affected at onset
- higher Kurtzke Expanded Disability Status Scale (EDSS) at onset

MRI predicts risk for time to conversion of CIS to CDMS as follows:

- With the presence of asymptomatic but typical brain lesions, the long-term risk is 60 - 80%.^{26, level III}
- If MRI brain is normal apart from the symptomatic lesion, the long-term risk is 20%.^{26, level III}
- Spinal cord lesions on MRI independently predicts a higher risk and shorter time to CDMS conversion.^{30, level II-2}
- Infratentorial lesions (especially in the brainstem) have higher risk of conversion to CDMS.^{31, level II-3}
- Risk for developing MS increases from 4% to 23% with the presence of OCBs in CSF for patients who have normal MRI at presentation.^{26, level III} In patients with >than 10 lesions on brain MRI and OCB positivity, the risk of CDMS increases to 64%.^{32, level II-3}

6.2 Optic Neuritis

ON involves primary inflammation of the optic nerve. Although it may be associated with various systemic autoimmune disorders, acute demyelinating ON, which is the commonest form, is known to be associated with MS.^{33, level III}

i. Clinical Presentation

Acute demyelinating ON is a clinical diagnosis. It is more common in women (67%) and usually presents between 20 to 50 years of age. Patients with ON of the type seen in CIS or MS may present with the following clinical features:^{20, level III; 33 - 34, level III}

- eye pain
 - present in more than 90% of cases
 - worsens on eye movement and resolves within a week
- central visual loss
 - usually monocular in MS, rarely bilateral at onset (0.4%) but more commonly involves both eyes in NMOSD at onset (11 - 20%)^{35, level III}

- it typically progresses over hours to days; recovery begins within two to four weeks and visual acuity (VA) recovers to 6/6 or better by one month in 75% of patients with MS
- progression of visual loss beyond two weeks or lack of any improvement after four weeks should prompt the consideration of other differential diagnoses and the appropriate investigations
- ocular assessment reveals evidence of optic neuropathy
 - reduced VA between 6/6 to “No Perception to Light (NPL)”
 - presence of relative afferent pupillary defect
 - colour vision loss
 - VF loss (classically central scotoma)
 - reduced contrast sensitivity (CS)
- funduscopy
 - optic disc findings at presentation
 - two thirds have normal optic discs (retrobulbar neuritis)
 - one third have mild and diffuse optic disc swelling
 - optic-nerve head atrophy (disc pallor) which occurs after a few weeks in spite of VA recovery
- atypical features of ON (if baseline MRI is normal)
 - retinal haemorrhages
 - markedly swollen optic nerve
 - retinal exudates
 - absence of pain
 - NPL vision at onset
 - absence of any visual recovery by 30 days

Refer to **Appendix 3 on Differential Diagnosis of Optic Disc Swelling.**

ii. **Differential Diagnosis of demyelinating ON**^{33 - 34, level III}

- Other autoimmune conditions [such as sarcoidosis, systemic lupus erythematosus (SLE) and Sjogren’s syndrome] or infective conditions (such as syphilis, tuberculosis, viral infections, cat scratch and Lyme disease)
- Neuromyelitis optica spectrum disorder
- Compressive optic neuropathy
- Anterior ischaemic optic neuropathy
- Leber’s Hereditary Optic Neuropathy

iii. **Investigations**^{33 - 34, level III}

The following investigations are useful in the assessment of ON including to rule out the above differential diagnosis (refer to **Chapter on Differential Diagnosis**):

- MRI orbit, brain and spine
- OCBs in CSF (investigations based on suspected differential diagnosis)
- Visual Evoked Potentials (VEPs)
 - VEPs show prolonged P100 latencies and/reduced amplitudes of waveforms in 65% patients with ON

- Optical Coherence Tomography
 - Retinal Nerve Fibre Layer Thickness of $<70\ \mu\text{m}$ predicts a worse VA outcome at least three months after ON ($p=0.0193$).³⁶, level II-2

iv. **ON AND CDMS**^{33 - 34}, level III

About 15 - 20% of MS patients may first present with ON. Apart from that, ON can present during the course of MS in 50% of patients. Neuroimaging of the brain can help to stratify the risk of MS in ON (refer to yellow box below).

- Among patients with a first episode of ON, 38% will develop MS over ten years.
- The risk of MS within 10 years after the first episode of ON increases from 22% to 56% if at least one characteristic demyelinating white matter lesion is present on baseline MRI brain.
- Over ten years, recurrent ON will develop in 48% of MS patients compared with 24% of non-MS patients.

Recommendation 1

- All patients with isolated optic neuritis should be referred to an ophthalmologist/neurologist for further assessment.

6.3 Transverse Myelitis

Transverse myelitis (TM) is a focal inflammatory disorder of the spinal cord, resulting in motor, sensory and autonomic dysfunction. Approximately one third of patients with TM have complete recovery or minimal deficits, one third are left with moderate degree of permanent disability and another third have severe disability.³⁷, level III

TM can be divided into two subgroups based on the spinal cord involvement:

- Acute Complete TM (ACTM)
 - An acute or subacute inflammatory process of the spinal cord causing a symmetrical and moderate to severe loss of function distal to that level.³⁸
 - Usually lesions are centrally located, extending >3 vertebral segments in length, with cord oedema and gadolinium (Gd)-enhancement in acute lesions.³⁹, level III
- Acute Partial TM (APTMT)
 - Incomplete or patchy involvement of at least one spinal segment with mild to moderate weakness, asymmetrical or dissociated sensory symptoms, and occasionally bladder involvement.³⁸
 - Lesions are usually peripherally located with a predilection for lateral and posterior areas of the cord, and involvement of <2 spinal cord segments.³⁹, level III

MS-associated TM is usually a partial myelitis, milder in severity with sensory predominant symptoms.

The differential diagnoses for TM include inflammatory, infective (bacterial, viral, parasitic, and fungal), and paraneoplastic conditions.⁴⁰ level III

Figure 1 shows the differential diagnosis of demyelinating spinal cord syndrome.

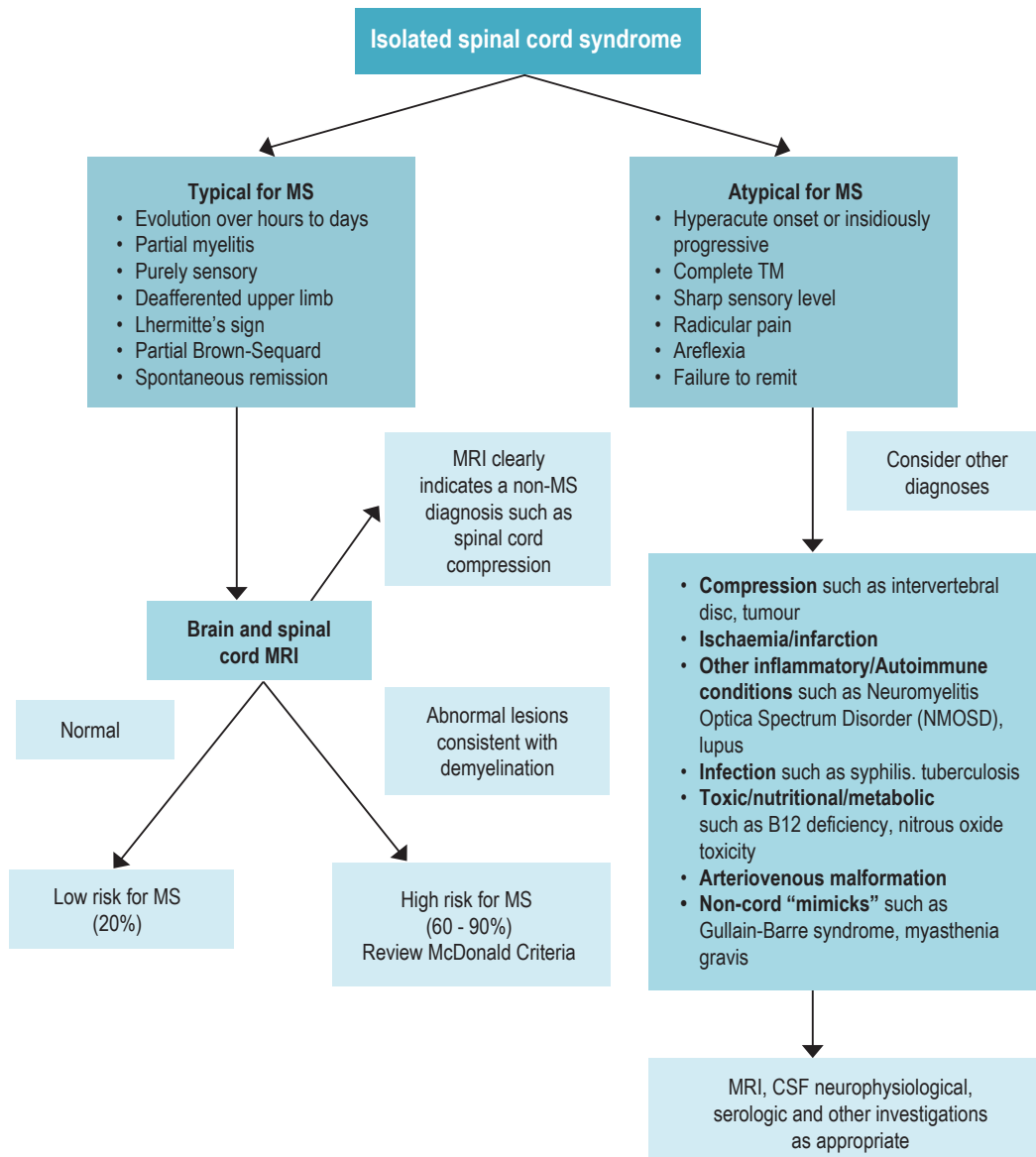


Figure 1. Differential diagnosis upon presentation with demyelinating spinal cord syndrome

Source: Miller DH, Weinshenker BG, Filippi M, et al. Differential diagnosis of suspected multiple sclerosis: a consensus approach. *Mult Scler*. 2008 Nov;14(9):1157-74

At least 13% of patients with Idiopathic Acute TM will convert to MS.

⁴¹, level II-2 The risk factors associated with conversion to MS are:

- types of TM - conversion rate of 10.3% in APTM (95% CI 4.1 to 23.6) as compared with 0 - 2% in ACTM on five years follow-up³⁸

- MS-like MRI brain abnormalities - conversion rate of approximately 80% in abnormal MRI group as compared with 10% in normal MRI group by three to five years of disease onset³⁸
- longitudinally extensive spinal cord lesions (LESCLs), defined as extending over at least three vertebral segments - LESCLs are more likely to have NMO than MS ($p=0.0036$).³⁸ Spinal cord MRI lesions in Asian patients with classical MS are similar to that of Caucasians.
42, level III
- anti-Aquaporin 4 antibody (anti-AQP4 Ab) - ACTM with LESCLs in the presence of anti-AQP4 Ab positivity is highly sensitive and specific for NMO.³⁸ In the presence of seronegative anti-AQP4 Ab, other differential diagnosis should be carefully excluded in view of the heterogeneity of this condition.^{43 - 44, level III}
- OCBs in CSF - conversion rate is 33% if OCBs are positive as compared with only 2% if it is negative. In contrast, the combination of negative OCB testing and IgG index ≤ 0.7 yields a very low likelihood of MS conversion (NPV of 100%).^{41, level II-2}

The red flags based on MRI features which are not supportive of TM are:^{39, level III; 45 - 46, level III}

- vascular cause
 - elongated “pencil-like” lesion in the anterior cord (anterior spinal artery occlusion)
 - triangular lesion in posterior cord (posterior spinal artery occlusion)
 - abnormal flow voids or tortuous vessels on the surface of the cord (arteriovenous fistulas)
 - presence of haemosiderin deposition indicating old bleed
- tumour
 - persisting Gd-enhancement months after treatment of an acute myelitis
 - cavitory lesions, leptomeningeal enhancement
 - pathological fracture of the vertebral bodies (spinal cord tumour or metastasis)
- infective cause
 - dural or leptomeningeal enhancement

• APTM, MS-like brain MRI abnormalities and OCBs positivity in CSF are associated with a higher risk of conversion to CDMS.

7. DIFFERENTIAL DIAGNOSIS

The differential diagnosis for MS and its clinically isolated syndromes can be extensive as demyelination affects any part of the CNS. In the differential diagnosis, it is important to rule out conditions that may mimic the presentation of MS.^{47 - 48, level III}

In making the diagnosis, it is necessary to:^{47 - 51 level III}

- a. determine whether patient's age, symptoms and its temporal evolution are likely/consistent with MS
- b. exclude diseases not likely to be MS such as vasculitis, stroke and others
- c. exclude other Idiopathic Inflammatory Demyelinating Diseases (IIDDs) not fulfilling criteria for MS such as:
 - NMO and its spectrum disorders (NMOSD)
 - Acute Disseminated Encephalomyelitis (ADEM)
 - Isolated ON, TM (not MS or NMO) and recurrent ON such as chronic relapsing inflammatory optic neuropathy and recurrent TM (unclassified as MS or NMO)
- d. Other rarer IIDDs: acute hemorrhagic leukoencephalopathy and variants of MS such as Marburg's disease, Balo's concentric sclerosis, tumefactive presentations and others.

- IIDDs is a term which encompasses all demyelinating diseases that includes:
 - MS
 - NMOSD
 - ADEM
 - clinically isolated syndrome suggestive/not suggestive of MS
 - recurrent ON and TM (unclassified as MS/NMOSD)
 - other rarer IIDDs (refer text above)

Other differential diagnoses for MS include non-IIDDs such as:

- vascular causes: small-vessel ischaemic disease
- connective tissue disorders: SLE, Sjogren's syndrome, Bechet's disease, antiphospholipid antibody syndrome and other types of CNS vasculitis
- granulomatous diseases: sarcoidosis
- neurodegenerative/metabolic diseases: subacute combined degeneration of the spinal cord, mitochondrial disorders, leukodystrophies and Susacs syndrome
- others: cerebral lymphomas, migraines, non-specific white matter MRI lesions

Investigations in the differential diagnosis should be tailored according to the type of IIDDs suspected and to rule out the underlying possible causes for the differential diagnosis. Refer to **Figure 2 on Steps in MS Diagnosis**.

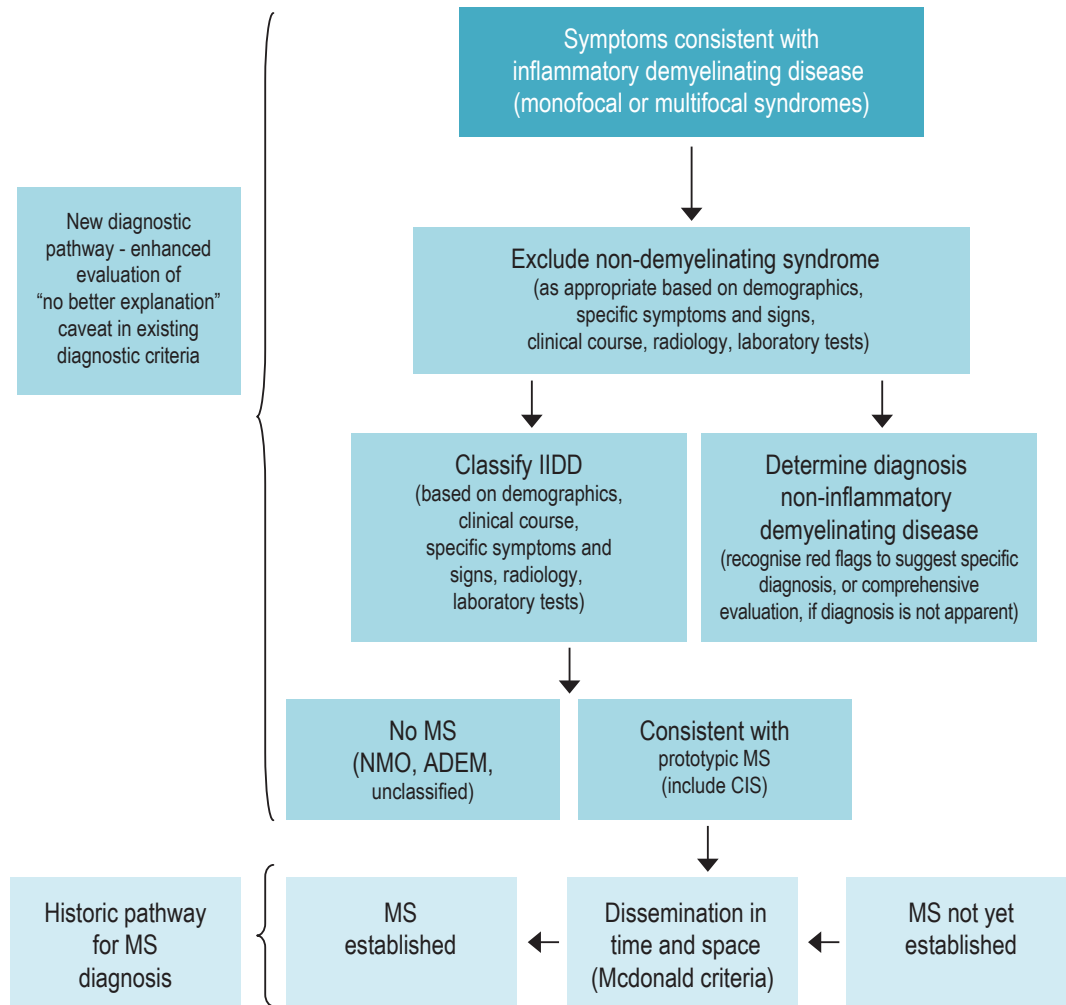


Figure 2. Steps in MS diagnosis

Source: Miller DH, Weinshenker BG, Filippi M, et al. Differential diagnosis of suspected multiple sclerosis: a consensus approach. *Mult Scler*. 2008 Nov;14(9):1157-74

- In the diagnosis of MS, it is important:
 1. to rule out other possible mimicks of MS such as inflammatory and non-inflammatory non-demyelinating diseases of the CNS
 2. to rule out other IIDDs especially NMO/NMOSD

Atypical Features for MS ("Identification of Red Flags")

Certain atypical features are inconsistent with a diagnosis of MS and recognition is important. Therefore, in the differential diagnosis identify potential "Red Flags" which are unlikely to suggest MS, based on demographics, clinical features, laboratory tests and neuroimaging.

1. The demographic and clinical "Red Flags" include:
 - onset in childhood/over 50 years of age (exceptions exist)
 - prominent family history
 - persistently normal neurological examination

- abrupt onset
 - presence of atypical clinical features such as
 - encephalopathy
 - altitudinal VF defects, persistent complete loss of vision (unilateral/bilateral) with poor recovery after one month
 - extrapyramidal symptoms, progressive ataxias or pyramidal symptoms (myelopathies)
 - area postrema symptoms and hypothalamic disturbances: intractable hiccough, vomiting, symptomatic narcolepsy
 - cortical signs: dementia, seizures, aphasia, cortical blindness
 - headaches, meningismus, loss of hearing
 - peripheral nerve symptoms, myopathy and others
 - systemic symptoms suggestive of connective tissue diseases and others
2. The laboratory and other paraclinical “Red Flags” are:
- abnormal connective tissue screens (false positives exist)
 - low serum B12 levels, raised ESR
 - serum angiotensin converting enzyme positivity, abnormal chest Xray
 - positive anti-AQP4 Ab titres
 - persistent CSF pleocytosis; white blood cells >50 cells/mm³, presence of polymorphonuclear cells, proteins >80 mg/dl
3. The neuroimaging “Red Flags” are:
- persistently normal MRI (brain and spine) or
 - atypical MRI (brain and spine) with
 - cortical, lacunar infarcts, haemorrhages, microhaemorrhages
 - meningeal enhancement, hydrocephalus
 - persistent Gd-enhancement (>3 months)/simultaneous enhancement of all lesions
 - linear medullary and periaqueductal lesions
 - chiasmal lesions (acute phase)
 - large infiltrative tumour-like cerebral/brainstem lesions
 - longitudinally extensive contiguous spinal cord lesions extending over ≥ 3 vertebral segments, centrally located in the post-acute phase
 - predominance of lesions at the cortical-subcortical junction

In the differential diagnosis of MS, clinical, demographic, paraclinical and neuroimaging “Red Flags” should be identified as they may suggest an alternative diagnosis to MS.

Neuromyelitis Optica

NMO has the following features:^{43 - 44, level III; 47, level III; 52, level II-2; 53, level III; 54, level II-3; 55 - 57, level III; 58, level II-2}

- is an autoimmune humorally mediated inflammatory demyelinating disorder of the CNS

- histopathologically, astrocytic damage, demyelination, neuronal loss and necrosis predominate
- has a different prognosis and response to immunomodulatory treatment compared with MS [refer to **Table 2** on **Differences between MS and NMO** and **Appendix 4** on **Treatment of NMO/Neuromyelitis optica spectrum disorders (NMOSD)**]
- characterised by attacks of ON and longitudinally extensive TM which are severe, often with incomplete recovery
- relapsing course in 80 - 90%, with 10% being monophasic
- females are predominantly affected
- is associated with an auto-antibody, termed as NMO-IgG or anti-AQP4 Ab, against the Aquaporin-4 water channel on astrocytic end-feet in the CNS; the discovery of this highly specific auto-antibody has allowed for the:
 - differentiation of MS and other IIDDs from NMO
 - identification of limited forms of NMO termed 'Neuromyelitis optica spectrum disorders'

It is positive in 60 - 90% of cases of NMO and 50% of cases of NMOSD, while negative in 10 - 40% of cases (seronegative NMO). However, recently in 21.1% of patients with NMOSD negative for anti-AQP4 Ab, a new autoantibody against myelin oligodendrocyte glycoprotein (anti-MOG) has been reported.

Diagnostic criteria for NMO/NMOSD

- In 2006, the diagnostic criteria for NMO was revised with the incorporation of the anti-AQP4 Ab (refer to **Table 2** and **Table 3**). It is 99% sensitive (95% CI 97 to 100) and 90% specific (95% CI 90 to 100) for the diagnosis of NMO.^{44, level III}
- In 2007, the criteria were expanded to include limited forms of NMO termed NMOSD, with the identification of the anti-AQP4 Ab in other high risk syndromes for NMO (refer to **Table 4**).^{43, level III}
- In 2015, a revision to the current diagnostic criteria has been published which awaits validation and universal use.^{59, level III} Refer to **Appendix 5**.

Table 2. Differences between MS and NMO

Features	MS	NMO
Clinical onset course	85% relapsing-remitting 15% primary progressive	80 - 90% relapsing-remitting 10 - 20% monophasic
Secondary progressive course	Often	Extremely Rare
Median age at onset (years)	29	39
Sex (Female:Male)	3 - 4:1	9:1
MRI brain	Periventricular white matter lesions, subcortical lesions (Barkhof criteria)	Usually normal or atypical for MS lesions, non-specific lesions, brainstem, diencephalon lesions, hypothalamic, peri-ependymal periventricular, corpus callosal lesions
MRI spinal cord	1 - 2 segments long, short segment lesions, peripherally located	Longitudinally extensive lesions, ≥ 3 vertebral segments, central in the post-acute phase
CSF (white cells/differential count)	$<50/\text{mm}^3$, all mononuclear	Often >50 cells/ mm^3 , polymorphonuclear and mononuclear cells
CSF oligoclonal bands	85%	Infrequent (10 - 15%)
NMO-Ig G	Negative	60 - 90% positive
Systemic-autoimmune disease	Occasional	Occasional
Severity of relapse	Usually mild to moderate	Usually moderate to severe
Recovery from relapses	Usually fair to good	Usually fair to poor
Vision	Usually unilateral, with good recovery of vision within one month	Unilateral or bilateral with poor recovery of vision

Source:

1. Morrow MJ, Wingerchuk D. Neuromyelitis optica. J Neuroophthalmol. 2012;32(2):154-66
2. Wingerchuk DM, Lennon VA, Lucchinetti CF, et al. The spectrum of neuromyelitis optica. Lancet Neurol. 2007;6(9):805-815

Table 3. Diagnostic Criteria for NMO

Absolute (at least 1 attack of each of the following)
ON
TM
Supportive (at least 2 of the following 3)
Brain MRI: Onset brain MRI normal or not meeting the diagnostic criteria for MS
Spinal cord MRI: Contiguous spinal cord lesion extending over ≥ 3 vertebral segments
NMO-Ig G seropositivity

Source: Wingerchuk DM, Lennon VA, Pittock SJ, et al. Revised diagnostic criteria for neuromyelitis optica. Neurology. 2006;66(10):1485-1489

Table 4. NMOSD

NMOSD
<p>Neuromyelitis optica</p> <p>Limited forms of NMO</p> <ul style="list-style-type: none"> • Idiopathic single or recurrent events of longitudinally extensive myelitis (≥ 3 vertebral segment spinal cord lesions seen on MRI spine) • ON (recurrent or simultaneous bilateral) <p>Asian optic spinal MS</p> <p>ON or longitudinally extensive myelitis associated with systemic autoimmune disease</p> <p>ON or myelitis associated with brain lesions typical of NMO (hypothalamic, corpus callosal, periventricular or brainstem)</p>

Source: Wingerchuk DM, Lennon VA, Lucchinetti CF, et al. The spectrum of neuromyelitis optica. *Lancet Neurol.* 2007;6(9):805-815

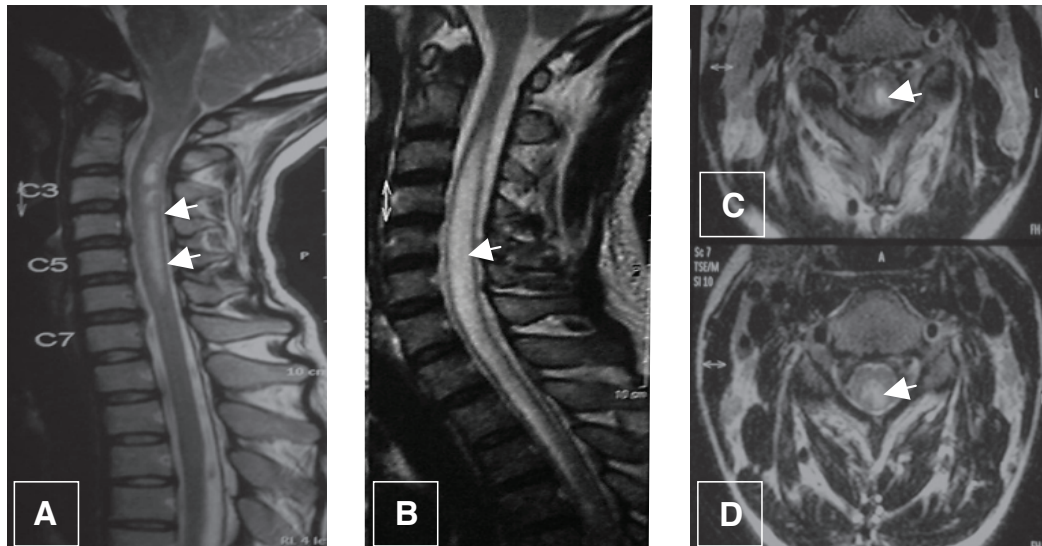
Brain involvement at onset in NMOSD:

- has now been recognised; reported in 43 - 70% of NMOSD patients at onset and 50 - 85% of patients with NMO
- may be symptomatic or asymptomatic
- MRI brain findings in NMOSD include:^{60 - 61, level III}
 - periependymal lesions surrounding the ventricular systems
 - diencephalic lesions around the third ventricle and cerebral aqueduct
 - dorsal brainstem adjacent to fourth ventricle (area postrema and nucleus tractus solitarius)
 - corpus callosal lesions (extensive, large edematous)
 - hemispheric white matter lesions
 - lesions involving the corticospinal tracts (unilateral or bilateral)
 - enhancing lesions and non specific white matter lesions

Features of spinal cord lesions in NMO/NMOSD include:^{6, level III; 62, level II-2}

- longitudinally extensive contiguous/linear lesions
- three or more vertebral segments in length
- mostly situated in the cervical/cervicothoracic region
- centrally located in the post-acute phase on axial cord scans
- associated with T1 hypointensity on sagittal scans and cord atrophy

Refer to **Figure 3** on **MRI spinal cord findings in NMOSD**.



A and B. Sagittal T2WI-Longitudinally extensive spinal cord lesion involving the cervico-thoracic region. C is axial T1WI with Gd-enhancement. D is central gray matter lesion on T2WI with Gd-enhancement.

Figure 3. Spinal cord MRI lesions characteristic of NMOSD

Acute Demyelinating Encephalomyelitis (ADEM)^{47, level III; 63, level III}

- An acute autoimmune demyelinating disease of CNS
- Triggered by viral infections and immunisations
- Usually a monophasic course
- Characterised by:
 - subacute encephalopathy evolving over one week to three months, disturbance of consciousness and/or behavioural abnormality
 - seizures or coma
 - multifocal symptoms and signs: cerebellar or cerebral
 - ON or TM
 - MRI brain shows symmetrical multifocal or diffuse brain lesions
 - supra/infratentorial
 - deep grey matter can be involved
 - simultaneous enhancement may occur
 - spinal cord lesions when present are longitudinally extensive
 - CSF pleocytosis, transient rise of CSF IgG/OCBs

8. NATURAL HISTORY

The overall course of MS can be classified into the following categories:

- a. Relapsing-Remitting Multiple Sclerosis (RRMS)^{64, level II-2; 65, level III}
 - This is defined as acute worsening of neurological function followed by a variable degree of recovery, with a stable course between attacks.
 - Approximately 85% of patients initially fall into this category.
- b. Secondary Progressive Multiple Sclerosis (SPMS)^{64, level II-2; 65, level III}
 - It is defined by an initial relapsing-remitting disease course, followed by gradual progression with or without relapses and plateaus.
 - Estimated median time to secondary progressive onset is 15 years.
 - More than 80% of patients develop secondary course after 25 years from onset of RRMS.
- c. Primary Progressive Multiple Sclerosis (PPMS)^{21, level III; 65, level III}
 - This refers to a gradual, nearly continuous worsening baseline with minor fluctuations but no distinct relapses.
 - It affects 10 to 20% of patients.
- d. Progressive Relapsing Multiple Sclerosis (PRMS)^{21, level III; 65, level III}
 - This is defined as progressive disease from onset, with subsequent relapses, with or without full recovery. The periods between relapses are characterised by continuing disease progression.
 - It affects less than 5% of individuals with MS.

The following figure illustrates the four categories of MS mentioned above:

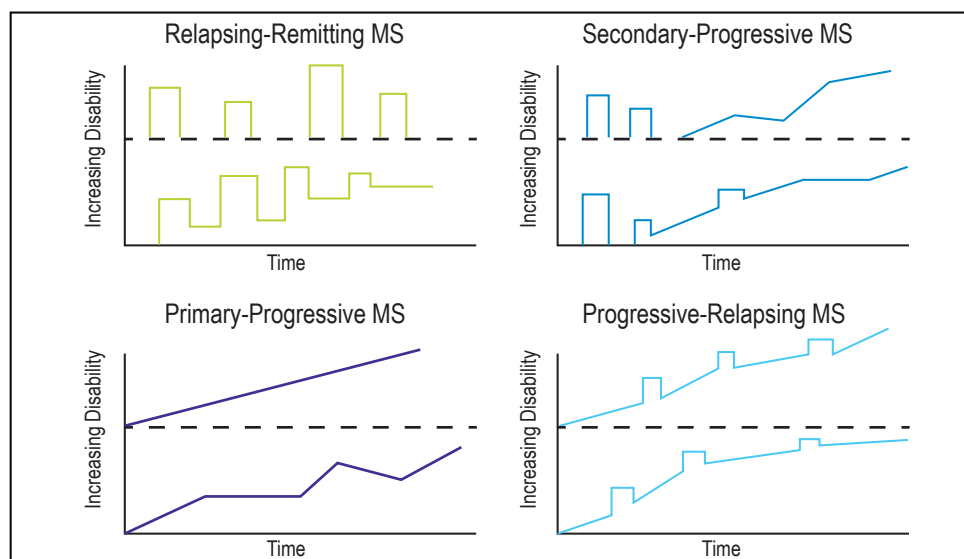


Figure 4. Categories of MS

Source: Diagnosis, Treatments, and Prognosis in MS: A Nursing Perspective. Available from: <http://www.medscape.org/viewarticle/739432>

The clinical course in MS can also be defined based on severity as below:^{65 - 66, level III}

a. Benign MS

- Patient with minimal (EDSS ≤ 3.0) or no disability 10 to 15 years after disease onset.

b. Malignant MS

- Rapid and progressive course of illness, leading to significant disability in multiple neurological systems or death in a relatively short time after disease onset.

Estimated median time from disease onset to EDSS 3, 6, 8 and 10 are 10, 18, 28 and 63 years respectively. The second attack usually occurs after a median of two years. The median interval from onset to EDSS 3 is approximately eight years.^{64, level II-2} Refer to **Appendix 6** on **Kurtzke Expanded Disability Status Scale**.

The factors associated with a higher conversion rate to SPMS are:^{64, level II-2}

- short first inter-attack interval
- more relapses in the first two years

This emphasises the importance of early initiation of disease modifying treatment (DMT).

In 2011, the International Advisory Committee on Clinical Trials of MS re-examined the MS disease phenotypes and revised its clinical descriptions of relapsing and progressive MS. While retaining core features above, it included assessment of disease activity based on clinical relapses, imaging findings and disease progression as the 2013 revisions. The progressive relapsing category was eliminated and it is now called primary progressive MS with disease activity. CIS is now included under the spectrum of MS.^{67, level III} Refer to **Appendix 5**.

9. DIAGNOSTIC CRITERIA

The currently accepted criteria for MS diagnosis are the Mc Donalds diagnostic criteria. The criteria includes clinical and paraclinical laboratory investigations. The criteria emphasise the need to demonstrate DIS and DIT, and to exclude alternative diagnoses. Refer to **Appendix 7 for MRI Brain Criteria on DIS and DIT**.

These criteria have resulted in an earlier diagnosis of RRMS with moderate sensitivity and specificity. The current revision of the McDonald criteria in 2010 also reinforces the importance of excluding other IIDDs such as NMOSD by doing anti-AQP4 Ab testing with validated assays.

Diagnosis of CDMS requires evidence of ≥ 2 attacks with objective clinical evidence of ≥ 2 lesions on examination. However, objective clinical evidence of one lesion, corroborated by reasonable historical evidence of a prior attack may also be used.

If the above definition for CDMS is only partially fulfilled, the diagnosis can still be made by using McDonald criteria 2010 on MRI for dissemination in space and time. The current criteria also provides for the diagnosis of PPMS. Refer to **Table 5** and **Table 6**.

Table 5. The McDonald criteria 2010 for MS diagnosis

Clinical presentation	Additional data needed for MS diagnosis
≥ 2 attacks ^a : objective clinical evidence of ≥ 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack ^b	None ^c
2 attacks ^a ; with objective clinical evidence of 1 lesion	DIS on MRI* or await a further attack implicating a different CNS site
1 attack ^a ; objective clinical evidence of ≥ 2 lesions	DIT on MRI* or await a second attack
1 attack ^a ; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Need to demonstrate both DIS and DIT on MRI or await a second attack (showing DIT and DIS)

If criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is “MS”. If criteria are not completely met, the diagnosis is “possible MS”. If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is “not MS”.

^aFor attack (refer to definition in **Chapter on Clinical Features**) - Some historical events characteristic of MS can be accepted but before a definite diagnosis can be made, at least one attack must be corroborated by findings on neurological examination, VEPs (in patients with prior visual disturbance) or MRI consistent with demyelination in the area of the CNS implicated in the historical report of symptoms.

^bReasonable historical evidence for one past attack in the absence of documented objective neurological findings can include historical events with symptoms and evolution characteristic for a prior inflammatory demyelinating event; at least one attack however must be supported by objective findings.

^cNo additional tests are required but it is desirable that the diagnosis of MS be made with access to imaging based on this criteria. If neuroimaging or other tests (CSF for OCBs) are negative alternative diagnoses must be considered.

Source: Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol.* 2011;69(2):292-302

Table 6. McDonald criteria 2010 for diagnosis of PPMS

Clinical presentation	Additional data needed for MS diagnosis
Insidious neurological progression suggestive of MS (PPMS)	One year of disease progression (retrospectively or prospectively determined) plus two or three of the following ^d : <ul style="list-style-type: none"> • Evidence of DIS in the brain [refer to Chapter on Investigations (Neuroimaging)] • Evidence of DIS in the spinal cord based on ≥ 2 T2 lesions in the cord • Positive CSF (isoelectric focusing evidence of OCBs and/elevated IgG index)

^dGd-enhancing lesions not required, symptomatic brainstem or cord lesions are excluded.

Source: Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol.* 2011;69(2):292-302

Table 7 demonstrates the moderate sensitivity and specificity of McDonald criteria 2010 applied in different populations.

Table 7. Sensitivity and specificity of McDonald criteria 2010 in different populations

Population (studies)	Sensitivity (range)	Specificity (range)	Accuracy (range)
European ⁶⁸ , level II-2 (at two years)	76.6% (64.9 - 85.3)	60.2% (53.0 - 67.0)	Not available
Spanish ⁶⁹ , level III DIS (at two years)	85.71% (73.33 - 92.90)	66.67% (43.75 - 59.26)	66.67% (43.75 - 83.72)
DIT (at two years)	52.63% (37.26 - 67.52)	75.00% (50.50 - 89.82)	59.26% (45.97 - 71.32)
Korean (DIS) ⁷⁰ , level III (at two years)	75.5% (65.0 - 84.4)	60.0% (48.6 - 69.7)	68.1% (57.2 - 77.3)

Recommendation 2

- The McDonald 2010 criteria should be used in the diagnosis of multiple sclerosis.

10. INVESTIGATIONS

The mainstay of investigations in patients with MS is neuroimaging; MRI is supported in certain situations by paraclinical tests and other investigations to rule out potential differential diagnoses (refer to Section on Differential Diagnoses, tailoring investigations according to clinical suspicion).

10.1 Neuroimaging

Since 2001, brain MRI has been included in the evaluation of patients with suspected MS by demonstrating dissemination of disease in space (DIS) and time (DIT).^{71, level III} It assists in earlier diagnosis of MS by enabling visualisation of lesions in the brain that are clinically silent. However, a diagnosis of MS should not be made simply on the basis of MRI findings without the appropriate clinical history, signs and symptoms.^{72, level III}

To date, there have been a number of revisions to the McDonald criteria (refer to **Appendix 7**). The latest revision of 2010 simplifies the MRI criteria for easier implementation in both clinical and research settings.^{20, level III}

a. Dissemination in Space

DIS on MRI is demonstrated by the presence of multiple lesions in characteristic locations, some of which can be clinically silent.

In the revised McDonald criteria 2010, ≥ 1 T2-hyperintense lesion in at least two of the four characteristic locations are required for DIS:

- juxtacortical
- periventricular
- infratentorial
- spinal cord*

*If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded from the criteria and do not contribute to lesion count. Gd-enhancement of lesion is not required for DIS. Refer to **Appendix 7**.

Characteristics of spinal cord lesion in MS:

- more common in cervical than thoracic cord
- vertical length of the lesion is less than two vertebral bodies
- asymmetric in axial section (occupies only part of the spinal cord)^{71, level III}

MRI of the spinal cord can differentiate MS from other neurological diseases (OND) which encompass various inflammatory disorders and cerebrovascular diseases. Brain images are abnormal in all MS

patients and in 65% of OND patients. Abnormal cord images are found in 92% of MS and 6% of OND patients. The combination of brain and spinal cord images increases the accuracy of MS diagnosis compared with brain images alone.^{30, level II-2; 73, level II-2}

b. Dissemination in Time

DIT on MRI can be shown by either one of the two ways based on McDonald criteria 2010:

- The presence of both Gd-enhancing and non-enhancing lesions in a single scan provided that these lesions are not due to non-MS pathology.^{68, level II-2} This single early scan must demonstrate DIS and can be performed at any time after the onset of CIS.
- The presence of new enhancing lesions or new/enlarging T2 lesions on follow-up scans. In the absence of both Gd-enhancing and non-enhancing lesions on their initial MRI, serial imaging showing a new enhancing/new T2 lesion will still be required to establish DIT.^{20, level III; 74, level III}

Refer to **Appendix 7** for images.

Table 8 compares the sensitivity and specificity of the different MRI diagnostic criteria. The McDonald criteria 2010 have a moderate sensitivity and specificity for DIS and DIT.^{20, level III; 74, level III}

Table 8. Performance of various MRI diagnostic criteria for predicting conversion of CIS into CDMS

DIS and DIT	Sensitivity	Specificity	Accuracy
McDonald 2001	47.1%	91.1%	73.1%
McDonald 2005	60.0%	87.8%	76.4%
McDonald 2010	71.8%	87.0%	80.8%

*The McDonald 2010 criteria incorporates the Swanton neuroimaging criteria

Source: Montalban X, Tintoré M, Swanton J, et al. MRI criteria for MS in patients with clinically isolated syndromes. *Neurology*. 2010;74(5):427-434

Recommendation 3

- Magnetic resonance imaging (MRI) of the brain and spine utilising the MRI Diagnostic Criteria* should be used in the diagnosis of multiple sclerosis.

*Refer to preceding text on DIS and DIT.

10.2 Paraclinical Investigations

OCBs and evoked potentials (EPs) are valuable as supportive tools in diagnosis and differential diagnosis of MS. These investigations are helpful in assessing the risk of CIS conversion to CDMS, support the

inflammatory demyelinating nature of the underlying condition, rule out alternative differential diagnosis and in the diagnosis of PPMS.^{20, level III}

a. Oligoclonal Bands

IgG OCBs represent IgG unique to the CSF and they are indicative of plasma cell immune response in the CNS.^{75, level III} The finding of OCBs in CSF but not in the serum and/elevated IgG index supports the diagnosis of MS.^{76, level III} In Caucasians, OCBs were positive in about 68% of CIS and 84 - 88% of patients with MS.^{77, level II-2} A hospital-based study in Malaysia showed positive CSF OCBs in 57.6% of patients with MS.^{78, level III}

A systematic review of MS showed that CSF OCBs had sensitivities between 69% and 91% with specificities between 59% and 94% for the diagnosis of MS. When combined with MRI, the sensitivity and specificity were further enhanced.^{79, level II-2}

Four percent of CIS patients with normal MRI and negative OCBs developed CDMS compared with 23% in those with normal MRI but positive OCBs.^{32, level II-2}

b. Evoked Potentials

EPs tests are studies to measure the electrical activity of the brain in response to stimulation of specific sensory nerve pathways, thus detecting the slowing of electrical conduction due to demyelination in the regions of the CNS which are clinically silent.^{80, level II-2}

In a systematic review of moderate quality diagnostic studies, patients suspected to have MS with abnormal VEPs were 2.5 - 9 times more likely to develop CDMS compared with patients with normal VEPs. VEPs sensitivities ranged from 25% to 83%. Somatosensory EPs were possibly useful to identify patients at increased risk for developing CDMS, but there was insufficient evidence to recommend brainstem auditory EPs.^{81, level II-2}

However, a more recent systematic review showed that the current data did not justify applying EPs to diagnose MS.^{79, level II-2}

Recommendation 4

- Cerebrospinal fluid oligoclonal bands and evoked potentials may be useful in the diagnostic workup for multiple sclerosis.

11. MONITORING DISEASE ACTIVITY AND RISK OF PROGRESSION

Disease activity and risk of progression in MS can be measured by looking at:^{82 - 83, level II-2; 84, level II-3; 85, level I}

- clinical relapses
- change in disability over a given time period assessed at two time points as measured by the EDSS
- neuroimaging (presence of new or enlarging T2-weighted lesions and Gd-enhancing lesions)

These measures help in assessing whether a patient is truly stable or a change or escalation in therapy should be considered.

a. Clinical relapses

Natural history studies have shown a modest correlation between the occurrence of relapses in the first few years (2 - 5 years) of disease onset and the risk of disability, progression to EDSS 6.0 and onset of secondary progressive MS. Later in the disease course, the association between relapses and progression is not as strong.^{64, level II-2; 86 - 87, level II-2}

b. Measuring progression

Progression in MS is the term used to define steady worsening of symptoms and signs over 6 - 12 months. The date at which progression starts is assigned retrospectively, once the required 6 - 12 months duration of continuous neurological worsening is confirmed. Disease progression in MS can be monitored clinically using the EDSS.

Kurtzke's Expanded Disability Status Scale (EDSS) is the gold standard for grading clinical impairment and disability in MS. EDSS is an ordinal and categorical assessment (refer to **Appendix 6**). Time to reach a selected level of EDSS is the best means to measure disease progression.^{7, level III; 21, level III} Refer to **Figure 5** on EDSS.

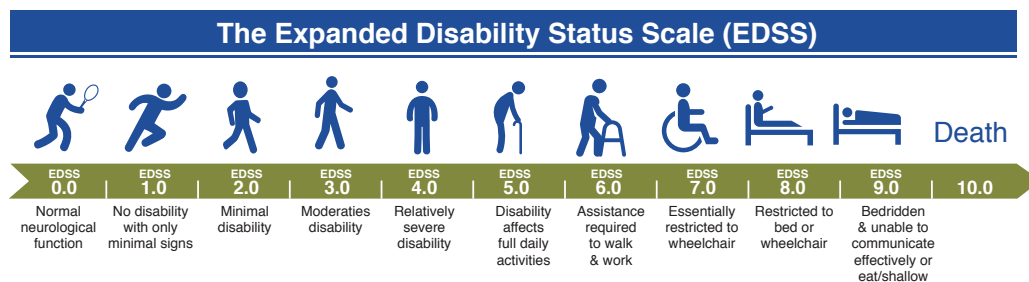


Figure 5. The Expanded Disability Status Scale

Source: My-MS.org For Information on Multiple Sclerosis (Internet communication, 16 December 2014 at <http://www.my-ms.org/ms.htm>)

Disease progression is influenced by several factors:

- Sex^{88, level II 2}
 - Males have four times risk to reach EDSS 6 compared with females (HR=4.39, 95% CI 2.13 to 9.03). More recent studies (outside our search period) had suggested males progressed faster in their EDSS in relapsing MS. But in primary progressive MS, the rate of disability accumulation was equal in both sexes.
- Age of onset^{21, level III}
 - Mean age of onset for relapsing MS is younger than progressive MS (29.6 ± 9.5 years vs 39.3 ± 11.3 years; p<0.001).
 - The time to EDSS 4 or EDSS 6 is significantly longer in relapsing MS compared with progressive MS.
- Symptoms at onset^{88, level II 2}
 - Motor and brainstem symptoms at onset are associated with an 8.1-fold and 13.1-fold increased risk to EDSS 6 respectively [HR=8.1 (95% CI 1.06 to 61.97) and HR=13.1 (95% CI 1.71 to 100.99) respectively].

Recommendation 5

- Disease progression in multiple sclerosis should be assessed clinically by using Kurtzke's Extended Disability Status Scale upon diagnosis and follow-up.

c. Neuroimaging

In MS, T2-weighted (T2WI) and Gd-enhanced T1-weighted (T1-Gd) MRI scans measure plaque burden and breakdown of the BBB respectively. These sequences are widely used outcome measures for monitoring disease activity in clinical trials and clinical practice. A number of studies have shown significant correlation between MRI activity and risk of conversion to CDMS and modest correlation with risk of disease progression especially in the early years.^{89, level II-2; 90, level III} However it cannot be denied that in some patients, clinical-radiological mismatch exists whereby an increase in MRI disease activity is not always accompanied by relapses, worsening in clinical presentation or disability and vice versa.

Brain atrophy is another promising complementary imaging biomarker of MS. However currently it has limited use in daily clinical practice and is more of a tool for research purposes or as an outcome measure in drug trials.

i. T2-lesions

In a study on CIS and CDMS patients, baseline MRI findings for the whole cohort were predictive for disability of the disease.^{89, level II-2}

In this whole cohort:^{89, level II-2}

- T2-lesion volume at all time-points (0, 5, 10, 14 and 20 years) correlated with 20-year EDSS follow-up (r_s ranging from 0.48 to 0.67)
- a significant correlation between the change in T2-lesion volume and concurrent change of EDSS was found in the first 14 years, and this correlation was strongest in the first five years [$r_s = 0.69$ (95% CI 0.41 to 0.72)]

For those who developed CDMS:^{89, level II-2}

- similar correlations were also demonstrated, where the T2 lesion volume at all time-points (0, 5, 10, 14 and 20 years) was significantly correlated with 20 year EDSS (r_s ranging from 0.53 to 0.57)
- baseline MRI findings in CIS were predictive of the development of CDMS

CIS patients with an abnormal MRI scan at presentation were more likely to convert to CDMS and had shorter median time of conversion than those with a normal scan at presentation:^{89, level II-2}

- 21% CIS patients with normal baseline MRI converted to CDMS and median time of conversion was six years
- 82% CIS patients with an abnormal baseline MRI convert to CDMS and median time of conversion was two years

ii. Gd-enhancing lesions

Contrast enhancement by using a Gd-containing agent increases the efficacy of MRI and is widely practised for the diagnosis and initial evaluation of MS.

A meta-analysis on patients with MS showed that although Gd-enhancing MRI was a predictor of relapses, it was not a strong one for cumulative impairment or disability:^{91, level II-2}

- RR for relapse was 1.2 in the first year ($p=0.020$) and 1.59 in the second year ($p=0.010$).
- Neither the initial scan nor monthly scans over six months were predictive of change in the EDSS in the subsequent 12 months or 24 months.

However more recent longitudinal studies in MS patients treated with interferons and glatiramer acetate showed that new T2 lesions and Gd-enhancing lesions was modestly associated with risks of further relapses and disability progression.^{82, level II-2; 84, level II-2; 92, level II-2} A systematic review of MS patients with poor response to interferons revealed that new Gd-enhancing lesions and ≥ 2 T2-weighted lesions increased the risks of further relapses and disability progression.^{93, level I}

- In CIS patients, abnormal baseline MRI is predictive of conversion to CDMS.

- T2-lesions on MRI brain should be monitored as it:
 - is predictive of conversion from CIS to CDMS
 - modestly correlates with risk of long-term disability (in the early years)
 - may be used to monitor treatment response, risk of further relapses and worsening of disability in patients treated with disease modifying therapies (DMTs)
- Gd-enhancing lesions on MRI brain should be monitored because it:
 - is a predictor of risk of further relapses
 - may be used to monitor treatment response as it correlates with risk of further relapses and worsening disability in patients treated with disease modifying therapies

• Cerebral and cord atrophy

Brain atrophy is a recognised clinical trial outcome measure in monitoring disease progression and evaluating the impact of new treatment strategies in MS. Both global and regional brain atrophy in MS are studied using qualitative or quantitative methods in mainly research settings. Studies have shown that the rate of brain volume loss in patients with MS is higher than normal subjects, ranging from 0.5% to 1.3% annually.^{94, level III}

Brain atrophy develops in different structures of the brain (whole brain, grey matter or white matter) and in all stages of MS including the earliest stage of the disease ie CIS.^{89, level III} Whole brain atrophy has a stronger but moderate association with physical disability. It is a stronger predictor for future disability than T1-hypointense and T2-hyperintense volume.^{95, level III} The grey matter volume is the strongest independent predictor of physical disability and cognitive impairment as measured by the EDSS and Paced Auditory Serial Addition Test respectively.^{96, level III} However, brain atrophy assessment in daily clinical practice has limited value currently due to heterogeneity in trial data, lack of consensus in both method of measurement and criteria for assessment. In the future, it may gain more importance.

Spinal cord gray matter atrophy is significantly correlated with MS disability as measured by EDSS in patients with relapsing and progressive MS.^{97, level II-2}

Recommendation 6

- Magnetic resonance imaging of the brain should be used in the monitoring of disease activity in multiple sclerosis.

• **Follow-up MRI**^{72, level III; 98, level III}

Clinical indications for follow-up MR imaging of the brain are:

- reassessment of disease burden for monitoring of disease activity and treatment response; a rational approach is baseline assessment with follow-up annually in patients on treatment to assess for subclinical disease activity^{99, level III}
- reassessment with MRI may be sooner if there are concerns about the patient's clinical activity and disease course^{99, level III}
- after switching DMT i.e. repeat MRI in six months
- assessment for DIT within 6 - 12 months in high risk CIS and 12 - 24 months in low risk CIS
- assessment of risk of progressive multifocal leukoencephalopathy (PML); every 12 months in patients with JCV negative, every 3 - 6 months in those with JCV positive and in those on natalizumab ≥18 months
- suspicion of a secondary diagnosis

Indications for MRI spine are:

- CIS with or without spinal cord symptoms (TM) especially with inconclusive MRI brain findings to support the diagnosis of MS
- strong clinical suspicion for MS but with no findings on brain MRI
- to clarify the diagnosis of possible MS in cases of non-specific white matter lesions on the brain MRI
- PPMS

On follow-up, the radiologist has to provide several measures that are of value in following lesions in the brain, which include:

- number of new or enlarging T2-hyperintense lesions
- number of Gd-enhancing lesions
- T1-hypointense lesions ('black holes')

- Neuroimaging parameters in monitoring MS disease activity are:
 - T2-weighted lesions (new or enlarging lesions)
 - Gd-enhancing T1-weighted lesions

12. REFERRAL

Patients with clinical features suggestive of MS and a high index of suspicion for CIS, in particular ON and TM, require a referral to a neurologist for further investigations. The diagnosis of MS should not be made on the grounds of MRI findings alone.¹⁰⁰ The urgency of referral should be guided by the acuteness and severity of clinical presentation.

After the diagnosis of MS is made, the frequency of follow-up depends on the clinical course of MS, taking into consideration acute relapses, response to treatment and the need for multidisciplinary intervention. A comprehensive review of all aspects of care should be done at least once a year.¹⁰⁰

Refer to **Algorithm 1 on Care Pathway for Referral and Management of MS**.

Recommendation 7

- Patients with clinical features highly suggestive of multiple sclerosis should be referred to a neurologist.

13. TREATMENT

The management of MS involves:

- treatment of acute attacks (this includes CIS and relapses in CDMS)
- prevention of relapses
- symptomatic treatment

The goals of therapy in relapsing-remitting MS are:

- to reduce the incidence and severity of relapses
- to decrease MRI disease activity
- to slow or delay disability progression

With the advent of newer therapies, there has been a paradigm shift in therapeutic objectives with the concept of “Treat to the target” and no evidence of disease activity being touted which is defined as:^{101 - 103, level III}

- no evidence of confirmed relapses
- no evidence of MRI activity (new T2/enlarging T2/Gd-enhancing lesions)
- no evidence of disease progression
- (more recently) no evidence of annual brain volume loss >0.4%

Currently, it is more of a research metric for efficacy in drug trials and the ability to achieve this as well as applicability in daily clinical practice still needs further investigation.

Refer to **Appendix 9** for **Suggested Drug Dosages and Side Effects in MS**.

13.1 Treatment of Acute Attacks and Relapses

The goal of treating MS relapses is to decrease the duration and intensity of neurological dysfunction. It is important to identify pseudo-exacerbations due to infection (commonly urinary tract infection/upper respiratory tract infection), stress, fever and heat exposure, and treat this first. Disabling relapses need treatment. Relapses such as pure sensory attacks with minimal disability may only need close observation.^{104, level III}

a. Glucocorticoids

Methylprednisolone is a synthetic corticosteroid used to treat acute attacks and relapses of MS. It is widely distributed to the tissues and able to cross the BBB. It dampens the inflammatory cascades, inhibits the activation and invasion of T cells into the CNS

In a Cochrane systematic review, steroids or adrenocorticotrophic hormone were more efficacious compared to placebo in the treatment of acute relapse in MS at one week, five weeks and one year follow-

up. The doses of intravenous (IV) methylprednisolone ranged between 500 to 1000 mg daily for three to five days. Gastrointestinal symptoms were more common but non-significantly different in IV high dose methylprednisolone than placebo.^{105, level I}

In another Cochrane systematic review on acute relapse of CDMS, oral methylprednisolone was as efficacious as IV methylprednisolone in terms of improvement of EDSS and MRI Gd-enhancement activity at four weeks. The doses of methylprednisolone (oral or IV) used was between 500 to 1000 mg daily for three to five days. Adverse events rates were comparable in both groups.^{106, level I} The need for oral tapering after IV methylprednisolone needs to be considered based on severity and type of relapse though data suggests no additional benefit for it (the CPG DG feels that this should be at the discretion of the treating neurologists). However in the Optic Neuritis Treatment Trial (ONTT) for ON, oral tapering was practiced.^{107, level I}

Recommendation 8

- Intravenous (IV) methylprednisolone should be used in acute attacks of multiple sclerosis.
 - Dose of IV methylprednisolone used is 500 - 1000 mg daily for 3 - 5 days.

Acute ON

In the treatment of acute ON, higher rate in return of vision to normal was seen with IV corticosteroids compared with placebo. However, there was no additional benefit in terms of visual outcomes (VA, CS and VF) at one month, six months and one year follow-up.^{108, level I}

The dose of IV methylprednisolone used in the ONTT was 250 mg 6-hourly for three days followed by oral prednisolone at 1 mg/kg for 11 days with a fast taper.^{108, level I}

In the ONTT, the use of oral corticosteroids alone was associated with a higher rate of new episodes of ON at two years (RR=1.89, 95% CI 1.09 to 3.27).^{109, level I}

Recommendation 9

- In acute optic neuritis, intravenous methylprednisolone should be given.

b. Plasma Exchange (Plasmapheresis)

Plasma exchange (PE) has been explored as a treatment modality in acute relapses of MS since 1980s. It is a process where 1.1 to 1.4 plasma volumes are exchanged using either 5% normal serum albumin or fresh frozen plasma as replacement solutions.^{110, level II-2; 111, level III; 112, level I} A total of five to seven exchanges are performed 14 days after

completion of high dose IV corticosteroids or earlier (seven days) if deficits continue to worsen five days after steroids administration.^{112, level I} This modality of treatment is reserved for patients with poor recovery to the initial institution of pulsed corticosteroids.^{110, level II-2; 111, level III; 112, level I}

The potential efficacy of PE was based on multiple case series and small clinical trials involving heterogeneous groups of patients with IIDD. A randomised clinical trial (RCT) showed moderate to good improvement in terms of power scores ($p=0.027$) and EDSS ($p=0.032$) after PE in 42% of patients compared with placebo. Improvement was seen in 36% of patients with pure MS.^{112, level I}

These findings were further supported in a later study where marked improvements were seen in 50% of patients with paresis and 92% of patients with ON.^{110, level II-2} The effects of PE were not sustained beyond six months.^{112, level I; 113, level II-1}

Male gender ($p=0.021$), early initiation of treatment (21 to 60 days from symptoms onset, $p=0.009$) and preserved or brisk reflexes ($p=0.019$) were significant predictors of improvement in function.^{111, level III} Improvements were seen within three exchanges in 75% of responders.^{111, level III}

Overall, PE was well-tolerated. Common adverse events were anaemia and hypotension.^{110, level II-2; 111, level III; 112, level I}

Recommendation 10

- Plasma exchange may be considered in the treatment of acute attacks of idiopathic inflammatory demyelinating disorders including multiple sclerosis patients who recover poorly after initial intravenous corticosteroids.

c. Intravenous Immunoglobulin (IVIG)

IVIG is as efficacious as IV methylprednisolone^{114, level II-1} but there is no added benefit on adding IVIG to IV methylprednisolone in treating acute relapses of MS.^{115, level I} These findings are based on moderate quality of evidence.

13.2 Disease Modifying Treatment

DMTs aim to:

- reduce relapse rates
- delay disability progression
- reduce radiologically active or new brain lesions on MRI

DMT treatment selection should be individualised based on accessibility, availability, efficacy, tolerability and safety of DMTs, prognostic factors, co-morbidities and patient's preference.^{116, level III}

The following DMTs are currently used for the treatment of RRMS:

Injectables	Oral therapies	Intravenous therapies
Interferon beta (1a, 1b)* Glatiramer acetate	Teriflunomide Dimethyl fumarate Fingolimod*	Natalizumab* Alemtuzumab Mitoxantrone* Rituximab* Cyclophosphamide*

*DMTs available currently (as of June 2015) in Malaysia.

a. Interferon beta

Two types of recombinant interferon beta (IFN β) are currently available in Malaysia, IFN β -1a and IFN β -1b. Both are administered via subcutaneous (SC) injection and have anti-inflammatory properties. At present, IM IFN β -1a is not available yet.

In two Cochrane systematic reviews on patients with RRMS, IFN β -1a and IFN β -1b significantly prevented exacerbations and progression of the disease compared with placebo at two years.^{117 - 118, level I} MRI endpoints could not be assessed due to heterogeneity in MRI assessments. Recently, subcutaneous pegylated IFN β given twice monthly has become available with significant reduction on annualised relapse rate (ARR), disability progression and MRI endpoints compared to placebo at two years ($p < 0.001$).^{119, level I}

In a Cochrane systematic review on progressive MS, IFN β was not efficacious in decreasing disability progression over 24 to 36 months when compared with placebo.^{117, level I} In another systematic review, there was limited data on effect of IFN β treatment on PPMS; however this may have been due to short follow-up period for assessment of effects on disease progression.^{120, level I}

A Cochrane systematic review on SPMS showed that IFN β significantly reduced the risk of relapses and the total lesion volume on MRI, but did not prevent 6-months disease progression over three years follow-up.^{121, level I} In another systematic review, there was no effect of IFN β treatment on PPMS.^{120, level I}

The commonest side-effects in the IFN β treatment are flu like symptoms, injection site reactions, leukopaenia and elevated liver enzymes.^{118, level I}
120, level I

Recommendation 11

- Interferon beta should be used as first-line therapy in active relapsing-remitting multiple sclerosis.

b. Glatiramer acetate

Glatiramer acetate (GA) has been approved for the immunomodulatory treatment of RRMS.^{122, level III} GA is not currently available in Malaysia.

In a Cochrane systematic review, GA was more efficacious than placebo in reducing relapses in RRMS but not disease progression over 1 - 3 years follow-up.^{123, level I}

The recently completed RCT comparing long-acting GA three times a week to placebo in RRMS showed a 34% reduction in risk of relapses ($p < 0.0001$) with modest reduction in the cumulative number of Gd-enhancing T1 (44.8%) and new or newly enlarging T2 lesions (34.7%) at months six and 12 follow-up ($p < 0.0001$).^{124, level I}

Most common adverse events were transient and self-limiting such as flushing, chest tightness, sweating, palpitations and anxiety.^{123, level I}

Recommendation 12

- Glatiramer acetate should be considered for active relapsing-remitting multiple sclerosis.

c. Teriflunomide

Teriflunomide is an oral disease modifying agent approved for patients with relapsing forms of MS. It is the active metabolite of leflunomide which has both anti-proliferative and anti-inflammatory properties. Teriflunomide is thought to selectively and reversibly inhibit dihydro-orotate dehydrogenase, leading to a reduction in proliferation of activated T and B lymphocytes thus it has selective immunosuppressant and immunomodulatory activity.

A Cochrane systematic review demonstrated low quality RCTs on the use of teriflunomide for relapsing forms of MS. However, patients on teriflunomide 7 mg and 14 mg alone showed significantly lower ARR at 108 weeks and teriflunomide 14 mg had lower proportions of sustained disability progression at 12 weeks compared with placebo.^{125, level I} An RCT comparing teriflunomide 7 mg and 14 mg with placebo showed a significant reduction in ARR (with both doses) and sustained disability progression (with the high dose of 14 mg).^{126, level I} Another RCT comparing IFN β -1a with teriflunomide 7 and 14 mg failed to show any significant differences in efficacy though treatment satisfaction was higher with the oral therapy.^{127, level I}

Short-term teriflunomide, 7 or 14 mg alone or with add-on IFN β , was safe in relapsing MS compared with placebo. Most common adverse events included hair thinning, headache, diarrhoea, fatigue, elevated alanine aminotransferase levels, influenza and back pain.^{125, level I} Teriflunomide is teratogenic, categorised as X in the United States Food and Drug Administration (US FDA) Pregnancy Risk Classification. Thus, effective contraception is advisable during treatment with it among women. Men wishing to father a child or women wishing to get

pregnant or in the event of a pregnancy during teriflunomide therapy, the medication needs to be actively washed-out with cholestyramine (8 g every 8 hours intravenously for 11 days to achieve non-teratogenic plasma concentration of <0.02 mg/L).^{128, level III}

Recommendation 13

- Teriflunomide may be considered as first-line therapy in active relapsing forms of multiple sclerosis.

d. Dimethyl fumarate

Dimethyl fumarate (DMF) is an oral fumaric acid metabolite. It is thought to have anti-oxidant and anti-inflammatory properties through activation of the nuclear-related factor 2 transcriptional pathway, thus reducing oxidative cell stress.

There are good RCTs on the efficacy of DMF 240 mg twice daily in the treatment of RRMS at two years follow-up.^{129 - 130, level I}

- reduction of ARR by 44 - 53% for twice daily dosing and 48 - 51% for thrice-daily dosing ($p < 0.001$)
- reduction in mean number of new or enlarging hyperintense lesions on T2-weighted images by 71 - 85% for twice daily dosing and 73 - 74% for thrice daily dosing ($p < 0.001$)

However, reduction of confirmed disability progression (CDP) was seen with both doses of DMF at 12 weeks in only the former RCT and failed to be replicated in the subsequent RCT.^{129 - 130, level I}

DMF was safe, with mild to moderate severity of flushing and gastrointestinal side effects which was highest in the first month of the treatment.^{129 - 130, level I} However, due to rare lymphopaenia ($<2\%$), white blood cell counts are recommended one month after treatment initiation, followed by 3 - 6 monthly monitoring. If a patient develops permanent lymphopaenia (<500 cell/ μ L at two consecutive laboratory controls 3 - 6 months apart), DMF should be stopped. PML was recently reported in treatment naïve MS patients on DMF with lymphopaenia, thus vigilance is needed in this matter.^{131, level III}

Recommendation 14

- Dimethyl fumarate may be considered as first-line therapy in active relapsing-remitting multiple sclerosis.

e. Fingolimod

Fingolimod is a new class of oral sphingosine-1-phosphate-receptor modulators that prevents the migration of potentially auto-reactive lymphocytes from lymph nodes and reduces its infiltration into the CNS.^{132 - 133, level I} Due to its mode of action, fingolimod is classified as a selective immunosuppressant.

Two good quality RCTs demonstrated the efficacy of fingolimod on clinical and neuroimaging outcomes in RRMS. The first RCT, comparing fingolimod 0.5 mg OD and 1.25 mg OD vs placebo at 24 months, showed:^{133, level I}

- relative reduction in ARR by 54% and 60% respectively ($p < 0.001$)
- reduction in confirmed disability progression after six months by 37% and 40% respectively ($p < 0.05$)
- significant reduction in mean number of Gd-enhancing lesions, higher proportion of patients with absence of Gd-enhancing lesions, free of new or enlarged T2-weighted lesions with significantly smaller percentage reduction in brain volume at one and two years

In the second RCT, comparing fingolimod 0.5 mg and 1.25 mg to placebo, similar results of significant reduction in ARR and number of patients relapse free at two years as the former trial was noted. In addition, there was also a significant reduction in new/enlarged T2 and Gd-enhancing lesions as well as a smaller reduction in mean percentage brain volume loss with both doses in the latter RCT compared to placebo.^{132, level I}

In another RCT with 12 months follow-up, fingolimod 0.5 mg OD and 1.25 mg OD vs IM IFN β -1a showed:^{134, level I}

- relative reduction in ARR by 38% and 52% respectively ($p < 0.001$)
- higher proportion of patients relapse free ($p < 0.001$)
- no significant differences in the time to confirmed disability progression
- higher proportion of patients free of new or enlarged T2-weighted and Gd-enhancing lesions ($p < 0.001$) and smaller percentage reduction in brain volume ($p < 0.001$)

Baseline characteristics of patients in all the RCTs were consistent with active or highly active RRMS and also included a subgroup of rapidly evolving MS patients who had prior DMT.^{132 - 134, level I}

Fingolimod was associated with clearly reported adverse events.^{132 - 134, level I}

- Most common adverse events were transient bradycardia (1 - 2%, majority asymptomatic) and atrioventricular block (<1%) which were noted after the first dose. Therefore, first dose hourly monitoring of the heart rate with electrocardiogram recording at baseline and at the end of six hours is important.
- Other side effects included:
 - reversible lymphopaenia (73%), seen within one month after treatment initiation
 - raised ALT (8%)
 - macular oedema (0.5%), seen within four months, reversible upon drug discontinuation
 - non-fatal herpes viral infections

- skin cancers such as basal cell carcinoma (though no causal relationship had been established)
- Two fatal cases, one of disseminated primary varicella zoster infection and herpes encephalitis were reported in the fingolimod 1.25 mg treated group in the TRANSFORMS trial. Thus, before initiating fingolimod, it is important to do varicella-zoster antibody titres and if negative, vaccination is advisable one month prior to initiation.
- Two cases of PML have been reported in fingolimod-treated patients as of 2015, so continued vigilance is necessary.^{135, level III}
- Fingolimod has teratogenic risk, thus female patients have to perform effective contraception as long as being treated with fingolimod (and another two months after stopping fingolimod).

Recommendation 15

- Fingolimod should be used for highly active relapsing-remitting multiple sclerosis patients who have failed first-line treatment or rapidly evolving aggressive disease. Close cardiac monitoring (pre- and post-treatment), varicella-zoster screening and 3 - 6 monthly laboratory monitoring of white blood cell count and liver enzymes are advisable.

f. Natalizumab

Natalizumab is a highly specific $\alpha 4$ -integrin antagonist that acts at the level of the BBB.^{136, level I} Due to its mode of action, natalizumab is classified as a selective immunosuppressant.

In a Cochrane systematic review on RRMS patients, natalizumab \pm IFN β was more efficacious than control (placebo or IFN β) at two years in:^{137, level I}

- reducing relapse rates (RR=0.57, 95% CI 0.47 to 0.69)
- reducing disease progression (RR=0.57, 95% CI 0.47 to 0.69)
- reducing Gd-enhancing lesions (RR=0.12, 95 CI 0.09 to 0.17)

Serious allergic reactions occurred only in 1% of cases.^{136, level I} Natalizumab was well tolerated over two years follow-up. However, PML due to the re-activation of the JCV was reported in two cases.^{137, level I} Therefore, factors that influence the selection of patients with RRMS for natalizumab are:

- prior immunosuppressant therapy
- JCV antibody status and index if available^{138, level II-2}
- patient's choice and type of disease activity

The Stratify Anti-JCV™ Antibody Test, a two step enzyme-linked immunosorbent assay (ELISA) to screen for the presence of JCV antibodies is used to assess antibody status prior to treatment initiation

and identify the risk of PML. JCV antibody is detected in 54% of MS patients with seroconversion rates of 2 - 3 % annually. Seropositive patients can be treated up to two years, then re-stratification for benefit vs risk of PML on whether to continue or switch therapy is needed. Anti-JCV index (where available) helps further to define PML risk in treated patients. Seropositive patients with a JCV antibody index <1.5 are considered to have a low PML risk and can be continued with natalizumab [with rigorous clinical follow-up and 3- (if on prior immunosuppressants and locally feasible) to 6-monthly MRI of the brain]. Seronegative patients should have 6-monthly anti-JCV antibody testing and biannual MRI scans.^{138 - 139, level II-2; 140, level III}

Risk stratification for natalizumab use is shown in the table below. The risk increases with:

- duration of exposure to natalizumab
- prior immunosuppressant use
- JCV seropositivity

Table 9. Stratified PML risk data associated with natalizumab therapy for JCV seropositive patients^{a, b}

Duration of natalizumab therapy (month)	Prior immunosuppressive therapy exposure	
	No	Yes
0 - 24	0.7 (0.5 - 1.0)	1.8 (1.1 - 2.7)
25 - 48	5.3 (4.4 - 6.2)	11.2 (8.8 - 14.3)
49 - 72	6.1 (4.8 - 7.8)	Insufficient data

^aRisk estimates are expressed per 1000 treated patients (95% CI) and updated on September 1, 2013.

^bThe risk of PML for JCV seronegative patients is estimated at 0.1 per 1000 patients (95% CI 0.01 to 0.35)

Source: Wingerchuk DM, Carter JL. Multiple sclerosis: current and emerging disease modifying therapies and treatment strategies. Mayo Clin Proc. 2014 Feb;89(2):225-40

If new neurological symptoms suggestive of PML occur clinically and are confirmed by CSF studies for JCV DNA and MRI brain, then natalizumab should be interrupted and plasmapheresis is instituted with care for occurrence of immune reconstitution inflammatory syndrome.

Recommendation 16

- Natalizumab should be given to patients with highly active relapsing-remitting or rapidly evolving multiple sclerosis.

g. Alemtuzumab

Alemtuzumab is a monoclonal antibody that targets CD52 antigen on the surface of most immune cells, especially lymphocytes and monocytes and possibly works by resetting the immune system.¹⁴¹

Based on three RCTs, IV alemtuzumab 12 mg or 24 mg daily for three to five days at baseline, 12 and 24 months was more efficacious than IFN β -1a in the treatment of RRMS. It significantly reduced the risk of sustained accumulation of disability (SAD) and relapse rate at two, three and five years.^{142 - 144, level I} The ARR for alemtuzumab 12 mg was 0.11 at three and five years compared with 0.36 and 0.35 for IFN β -1a at the same time points.^{144, level I} There was also significant reduction of lesion load and loss of brain volume on MRI.^{142, level I; 144, level I}

The major safety concern of alemtuzumab is its risk of further autoimmune diseases, especially thyroid events (common i.e. up to 35% of all patients), Immune Thrombocytopenic Purpura (rare i.e. <1 - 3%) and immune nephropathies (rare i.e. <1%).^{142 - 144, level I} ITP was associated with one fatal intracranial hemorrhage.^{144, level I} Given these risks, monthly laboratory monitoring is required up to 48 months after the last alemtuzumab dose. Oral prophylaxis with acyclovir 200 mg BD is recommended prior to treatment and one month after each course to reduce the risk of Herpes Simplex viral infections.^{142, level I}

Recommendation 17

- Alemtuzumab may be considered in the treatment of highly active or rapidly evolving/aggressive relapsing-remitting multiple sclerosis. However, appropriate frequent monitoring is required to detect potential serious adverse effect.

h. Mitoxantrone

Mitoxantrone is a cytotoxic agent of anthracenedione family. The postulated mechanism of action is by suppressing B cells, T cells and macrophages that attack the myelin sheath.

In a Cochrane systematic review on the efficacy of mitoxantrone in MS, it partially reduced the risk of progression (OR=0.30, 95% CI 0.09 to 0.99) and frequency of relapses (MD= -0.85, 95% CI -1.47 to -0.23) in worsening RRMS, PRMS and SPMS against placebo in a two-year follow-up.^{145, level I}

The safety profile of mitoxantrone over five years follow-up is acceptable, provided that the cumulative dose is respected (<140 mg/m²) and cardiac function [left ventricular ejection fraction (LVEF) >50%] as well as the white blood cell counts (>500/mm³) are strictly monitored.^{146 - 147, level II-2}

Severe adverse events reported include LVEF <50% (5% - 5.6%), acute congestive heart failure (0.1% - 2%), acute leukaemia (0.25% - 0.6%) and amenorrhoea (5.4% - 51% depending on age group and cumulative dose).^{146 - 147, level II-2} Cumulative dose of mitoxantrone >75

mg/m² and previous or concomitant use of oral methotrexate are risk factors for cardiotoxicity.^{146, level II-2}

Recommendation 18

- Mitoxantrone may be offered to worsening relapsing-remitting multiple sclerosis and secondary progressive multiple sclerosis with relapses provided cumulative dose, cardiac function and haematological profile are monitored closely.

i. Rituximab

Rituximab is a monoclonal antibody to CD-20 that depletes B-cells. The beneficial clinical effects in RRMS are mediated through modulation of systemic and CNS intrinsic immune responses.

There is modest evidence on the efficacy of rituximab in the treatment of RRMS. It significantly reduces ARR and total Gd-enhancing T1-weighted lesion counts at 24 but not at 48 weeks.^{148, level I}

In a large multicentre RCT on PPMS, rituximab compared to placebo failed to show significant delay in time to CDP.^{149, level I}

Rituximab is safe for a single course short-term treatment, with mild to moderate infusion related adverse event. There is no increase in incidence of any infection, infection-associated serious adverse events and clinically significant opportunistic infections.^{148, level I}

j. Cyclophosphamide

Cyclophosphamide is an alkylating drug that binds to DNA, interferes with mitosis and cell replication, thus causing suppression of cell-mediated and humoral immunity through its effects on B cells and T cells.^{150, level III}

In patients with moderate to severe, refractory and aggressive RRMS, high dose cyclophosphamide given monthly or over four days was significantly efficacious in terms of reduction in relapses, sustained disability progression and mean number of Gd-enhancing lesions over 18 and 23 months respectively.^{151 - 152, level II-3}

In a study on aggressive RRMS with treatment failure while on IFNβ-1a, pulse cyclophosphamide added to IFNβ-1a (IM weekly) was significantly efficacious in reducing the yearly relapse rates and number of Gd-enhancing lesions but not for EDSS at two years.^{153, level II-3} In rapidly worsening MS, monthly pulse cyclophosphamide added to IFNβ-1a for 12 months and then 2-monthly for six months, produced significant reductions in relapse rates, EDSS and MRI activity at three years.^{154, level II-3} However, these studies were of small sample size and subject to bias.

Another more recent Cochrane systematic review on cyclophosphamide, using direct and indirect comparisons, found an unfavourable risk benefit balance in RRMS and no efficacy in reducing disability in progressive MS.^{117, level I}

Side effects included alopecia, nausea and vomiting, amenorrhoea, infertility, major infections, leukopaenia, haemorrhagic cystitis, hypogammaglobulinaemia and malignancies.^{117, level I; 151 - 155, level II-3; 156, level I}

Recommendation 19

- Cyclophosphamide may be considered in severe refractory and aggressive relapsing-remitting multiple sclerosis.
- Cyclophosphamide should not be given in progressive multiple sclerosis as its efficacy is not established.

k. IVIG

IVIG is made up of concentrated antibodies derived from blood plasma. It is postulated to down-regulate the overactive immune system.

In a recent Cochrane systematic review on IVIG vs placebo, there was low quality evidence on disability progression and recurrence of relapse over 24 months in RRMS and progressive MS.^{117, level I}

IVIG was well-tolerated with a <5% risk of drug-related adverse events; most common were headache, nausea, fever, chills, dizziness, rash and fatigue.^{157, level I}

l. Glucocorticoids

There is poor evidence for the efficacy of steroids as a DMT in MS.^{158 -163, level I}

Steroids as add-on therapy to IFN β -1a is efficacious in reducing relapse rates when compared with placebo^{158 - 160, level I} or methotrexate^{161, level I} in active RRMS. There is inadequate data to describe the safety profile of steroids in MS.^{162, level I}

m. Methotrexate/Mycophenolate Mofetil/Azathioprine/Vitamin D

Currently, there is insufficient evidence on methotrexate, mycophenolate mofetil, azathioprine and vitamin D as maintenance treatment for the prevention of relapses and disability progression in MS.^{117, level I; 161, level I; 164 - 169, level I; 170 level II-3}

n. Indications for initiation of DMTs as preventive therapy.

• CIS

There is high quality evidence for early DMT treatment in CIS. However heterogeneity exists among the trials in terms of type and dosing of treatment, diagnostic criteria and outcome measures.

In these studies, early treatment with IFN β or GA was more efficacious in preventing conversion of CIS to CDMS compared with placebo.

- In a systematic review, OR for conversion with IFN β was 0.53 (95% CI 0.40 to 0.71) at one year and 0.52 (95% CI 0.38 to 0.70) at two years.^{171, level I}
- In a RCT comparing SC IFN β -1a vs placebo, HR for 2-year rates of conversion was 0.48 (95% CI 0.31 to 0.73) for three times a week and 0.53 (95% CI 0.35 to 0.79) for once a week dosing.^{172, level I}
- In another RCT, HR for conversion was 0.55 (95% CI 0.40 to 0.77) for GA at 36 months.^{173, level I}

IFN β was more efficacious in reducing Gd-enhancing T1 lesions and new or enlarging hyperintense lesions on T2-weighted images compared with placebo.^{171, level I} and this was significantly better seen with high dose SC IFN β 1a 44 mcg three times a week than once a week dosing.^{172, level I} Similar results were noted for MRI endpoints with GA in patients who never converted to CDMS over two years compared to placebo.^{173, level I}

IFN β and GA were safe and consistent with the well-established safety profiles.^{171 - 173, level I} DMTs have clear impact on development of CDMS, and early treatment is beneficial in eligible patients.

The CPG DG feels it is very important that all other differential diagnosis for CIS have been ruled out before initiating treatment for CIS at high risk for MS based on clinical and neuroimaging parameters.

Recommendation 20

- Patients with clinically isolated syndrome (CIS) should be stratified according to risk for clinically definite multiple sclerosis (CDMS) based on clinical and neuroimaging parameters.*
- β -interferon may be considered after stratification of risk for CDMS in CIS patients with careful consideration on the benefit risk ratio of early treatment and open discussion with the patient.

*Refer to **Figure 6** below and **Chapter on Clinically Isolated Syndrome, Optic Neuritis and Transverse Myelitis**.

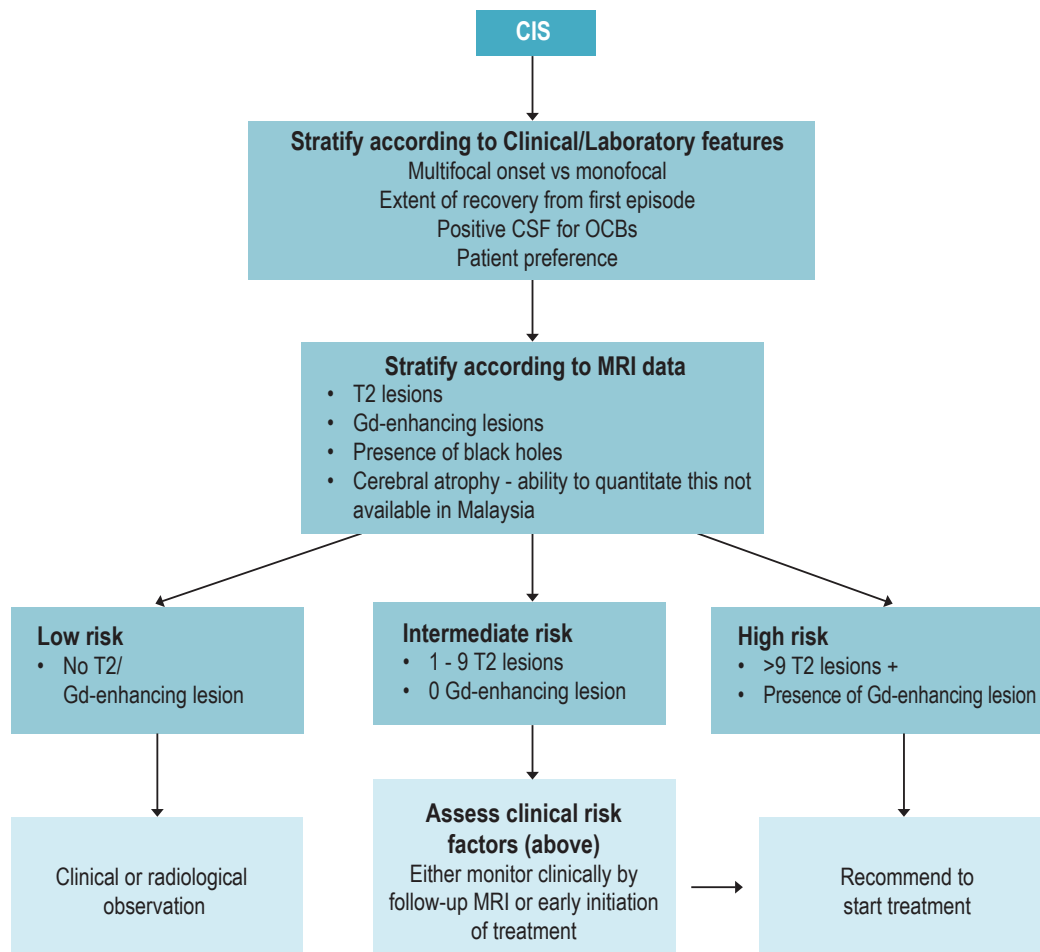


Figure 6. Risk stratification for the management of CIS

Adapted: Yamout B, Alroughani R, Al-Jumah M, et al. Consensus guidelines for the diagnosis and treatment of multiple sclerosis. Curr Med Res Opin. 2013 Jun;29(6):611-21

• RRMS

○ IFN β

IFN β is initiated as first-line treatment for patients with RRMS based on the following criteria:^{174, level III}

- ≥ 2 clinically significant relapses in previous two years (active MS)*
- able to walk ≥ 10 m**
- not pregnant or attempting conception
- aged >18 years
- no contra-indications

*Active MS is defined as more than two significant relapses in the previous two years.

**In certain situations, after careful consideration, patients who are able to walk unaided or aided between 10 and 99 metres (EDSS of 6.0 - 6.5) may still benefit from IFN β .

- GA

GA is currently not available in Malaysia and the criteria for initiating treatment as first-line therapy is similar as for IFN β

- Teriflunomide and DMF

Evidence from a number of moderate to good quality RCTs on RRMS have shown, teriflunomide and DMF compared to placebo were efficacious in reducing the relapse rates and MRI brain activity. High dose teriflunomide (in two RCTs) and DMF (in one RCT) showed modest effects on disability progression (refer to preceding sections on the specific medications).

A recent systematic review using indirect comparisons showed DMF significantly reduced ARR more than IFN β , GA and teriflunomide when compared with placebo^{175, level I}. A RCT demonstrated that teriflunomide failed to show any significant difference in clinical efficacy from IFN β though it was associated with better patient tolerability^{127, level I}.

In patients with side effects/intolerability to injectables or needle phobia, teriflunomide and DMF are options. Teriflunomide and DMF have been studied and are approved by the National Institute of Clinical Excellence, US FDA and European Medical Agency as first-line therapy in active RRMS.^{176, level III; 177 - 178, level I; 179 - 180, level III} There is a lack of evidence for the use of teriflunomide and DMF in patients with suboptimal response to first-line injectable therapy and more data with head-to-head comparisons is needed in the future.

For rapidly evolving or highly active MS, refer to **Section on Treatment failure**.

Recommendation 21

- In active relapsing-remitting multiple sclerosis,
 - interferon beta and glatiramer acetate* should be used as first-line therapy
 - teriflunomide and dimethyl fumarate may be used as first-line therapy

*GA is not available in Malaysia.

o. Treatment Failure

In a longitudinal observational study on patients with RRMS and CIS, the probability of failing initial treatment after three years was 30%.^{181, level II-2} Currently, there is no validated definition for treatment failure.^{116, level III; 182, level III}

- Treatment failure refers to patients who have failed to respond to a full and adequate course of treatment with first-line therapies after an adequate time period of one year.^{183 - 185, level III}
- It may be assessed using the following parameters:
 - clinical relapses
 - disease progression as assessed by worsening EDSS
 - MRI brain activity

Any two of the above three parameters allows identification of patients with RRMS at significant risk of disease activity in the subsequent two years.^{186, level II-3}
- However, if patients exhibit high disease activity, treatment failure is diagnosed earlier.

Therapeutic failure occurs due to the following factors:^{116, level III}

- patient factors - poor compliance and adherence to dose regimen or monitoring
- drug related factors - side effects
- lack of therapeutic efficacy - in terms of relapses and progression of disease (increase in EDSS >1 in one year)
- increase in MRI brain activity (number of new T2 lesions and Gd-enhancing lesions)

Patients with treatment failure can be divided into the following groups depending on the severity of disease activity:^{183 - 185, level III; 187, level III}

- non-responders/highly active MS
- rapidly evolving MS

Factors associated with greater risk of active/progressive disease in MS patients at diagnosis are as below:^{188, level III}

- relapse severity
 - ≥1 moderate or severe attack
 - steroids/hospitalisation required
 - severe effect on activities of daily living (ADL)
 - >1 functional system affected
 - severe motor/cerebellar/brainstem involvement
- relapse recovery - incomplete
- MRI findings
 - ≥2 Gd-enhancing, new T2 lesions or ≥2 T1 hypointense lesions
 - ≥2 spinal lesions
- older age, male sex, certain ethnicities e.g. African Americans

- Active MS refers to patients who have had two or more attacks in the last two years.

- Highly active MS/non-responders are individuals who have failed to respond to full and adequate course (one year of treatment) of DMT and have these features:
 - ≥ 1 relapse in the previous year while on treatment or
 - unchanged/increased/ongoing severe relapses compared with the previous year and
 - ≥ 9 T2 lesions on brain MRI or
 - ≥ 1 Gd-enhancing lesions on brain MRI

- Rapidly evolving/aggressive MS are those with:
 - ≥ 2 disabling relapses in the last one year and
 - ≥ 1 Gd-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared to previous recent MRI scan or
 - increase in two points in the EDSS in the past 12 months
 This can occur prior to or after initiation of first-line therapy.

Source:

1. European Medicines Agency. (Available from: <http://www.ema.europa.eu/ema/>)
2. NHS England Clinical Reference Group for Neurosciences. Clinical Commissioning Policy: Disease Modifying Therapies for Patients with Multiple Sclerosis (MS). London: NHS England; 2014
3. Río J, Tintoré M, Sastre-Garriga J, et al. Change in the clinical activity of multiple sclerosis after treatment switch for suboptimal response. *Eur J Neurol*. 2012;19(6):899-904

After treatment initiation, follow-up and evaluation are as below:^{183 - 184 level III; 189, level II-2; 190, level III; 191, level II-2}

- clinically every three months for the first year and every six months thereafter
- neurologically by EDSS compared to baseline
- radiologically via MRI brain which is usually done at baseline and 6 - 12 months after initiation of therapy with first-line agents or earlier if clinically indicated. However the frequency of neuroimaging must be tempered with local availability.

A change in treatment needs to be considered if:^{184 - 185, level III; 191, level II-2}

- relapse frequency has increased/is unchanged
- treatments are considered not acceptable to patients
- a sustained worsening of the neurological status is observed on at least two consecutive examinations (≥ 1 point on EDSS) with a six month interval between them
- an evaluation MRI done during the first 6 - 12 months of therapy shows ≥ 1 new Gd-enhancing/and ≥ 2 new or enlarging T2 lesions

It is also important to rule out pseudorelapses and non-adherence before diagnosing treatment failure. In the absence of clinical activity but in the presence of MRI activity, close clinical monitoring is needed as increase in relapses or disability scores may indicate a need for change in therapy.

In addressing treatment failures in MS, the treatment modalities include:

- escalation therapy
- induction therapy
- rescue therapy - escalation to third-line therapy

Refer to **Algorithm 3** on **Treatment of RRMS**.

Escalation therapy (to second-line therapy)

- There is no RCT to support the use of any drug as escalation therapy in patients with suboptimal response to first-line therapies.^{116, level III; 182, level III; 192 - 193, level III}
- Escalation therapy refers to the initial sequential use of first-line drugs with the best risk-benefit ratio and then adopting second-line drugs with increasing strength but potentially more side effects to control the more aggressive highly active disease.^{116, level III; 189, level II-2; 190, level III}
- Drugs used in escalation therapy include fingolimod, natalizumab and alemtuzumab.

Natalizumab

- In a systematic review (using direct and indirect comparisons), natalizumab was most efficacious in preventing clinical relapses compared with IFN β /GA, mitoxantrone and other immunosuppressants.^{117, level I}
- In a RCT, combination of natalizumab and IM IFN β -1a was more efficacious than IM IFN β -1a alone in clinical and MRI outcomes.^{194, level I}
- Observational studies on patients with suboptimal response to IFN β or GA who were switched to natalizumab showed beneficial results on clinical and MRI endpoints.^{189, level II-2; 195 - 197, level II-3}
Recently, observational studies from real world datasets using propensity matched statistics showed switching to natalizumab compared to interferon/GA in patients relapsing on interferon/GA was associated with superior outcomes in terms of 65 - 75% reduction in ARR at year one (p<0.001).^{197, level III}

Fingolimod

- There is no head to head trial to support the efficacy of fingolimod in patients with therapeutic failure on first-line treatments.
- In a RCT comparing fingolimod to IM IFN β -1a which included patients who had prior treatment with IM IFN β and GA, fingolimod

0.5 mg significantly reduced ARR, mean number of Gd-enhancing lesions, number of new or newly enlarged T2 lesions compared with IFN β -1a alone.^{198, level I} Subgroup analysis of patients with highly active disease despite IM IFN β -1a from the same trial showed a significant reduction in ARR by 61%.^{134, level I} In another study, relapse rates were not higher in patients switching from natalizumab to fingolimod compared to other therapies to fingolimod.^{199, level III}

JCV antibody stratification with the JCV StratifyTM antibody test kit is important in deciding between natalizumab and fingolimod due to the risks of PML.^{116, level III; 182, level III}

- If JCV is negative, natalizumab is an option but close monitoring is needed with 6-monthly or annual MRI and 6-monthly JCV antibody testing.
- If JCV is positive, fingolimod followed by alemtuzumab in the event of suboptimal response to fingolimod would be the other second-line options (refer to text below).
- If seropositive and considering natalizumab, the risk and benefits of starting or continuing natalizumab need to be discussed with the patient including more frequent clinical and MRI brain monitoring. Refer to Chapter on DMT (Natalizumab).

If switching from natalizumab to fingolimod is required, a washout period of 6 - 8 weeks is sufficient for risk of rebound disease activity.^{200, level III} For switching from IFN β to second-line therapy, no washout period is needed.

Alemtuzumab

Alemtuzumab is more efficacious than IFN β -1a in reducing relapse rates and sustained accumulation of disability in patients with refractory RRMS failing first-line treatment with IFN β /GA at two and five years.^{142 - 143, level I} In a study on active RRMS not controlled by IFN β -1a, alemtuzumab reduced relapse rates and improved disability scores in those who continued to relapse.^{201, level II-3} Alemtuzumab is an option in active RRMS patients with intolerance/lack of response to fingolimod or natalizumab.^{182, level III; 189, level II-2; 190, level III}

Moderate quality evidence from systematic reviews, RCTs and observational studies suggested that fingolimod, natalizumab and alemtuzumab were efficacious in highly active MS/rapidly evolving aggressive RRMS.^{100; 142 - 143, level I; 180, level III; 182, level III; 201, level II-3}

Recommendation 22

- In patients with highly active multiple sclerosis (MS) who experience treatment failure with first-line therapies, fingolimod, natalizumab or alemtuzumab may be used*.
- In patients with rapidly evolving aggressive/severe MS, fingolimod, natalizumab or alemtuzumab may be considered as first-line treatment*.

*The choice of switching depends on stratification according to John Cunningham virus (JCV) antibody, cardiac, thyroid and haematological status

- If JCV antibody is positive prior to initiation or while on natalizumab, switch to fingolimod may be an option.
- If there is lack of response or intolerability to fingolimod, natalizumab or alemtuzumab may be used.
- Alemtuzumab is an option in highly active/aggressive RRMS with issue of lack of response/intolerability to fingolimod or natalizumab.

Rescue therapy (escalation to third-line therapy)

Rescue therapy refers to the use of drugs with limited evidence for patients not responding to the approved drugs mentioned above (third-line therapy).^{189, level II-2}

Mitoxantrone significantly reduces relapse rates, prolongs time to confirmed disease progression and reduces MRI activity in patients with worsening or aggressive RRMS and secondary progressive MS.^{117, level I; 192, level III; 202, level III; 203 - 204, level II-3} However, benefit:risk ratio in terms of cardiotoxicity (2% heart failure) and treatment-related leukaemia (0.6%) needs to be considered.^{205, level III} **Refer to Chapter on DMT (Mitoxantrone).**

Open label and observational studies showed the efficacy of rituximab and cyclophosphamide in the treatment of refractory and rapidly deteriorating MS.^{151, level II-3; 153 - 154, level II-3; 189, level 2; 206, level II-3; 207, level I}

Refer to Chapter on DMT (Rituximab and Cyclophosphamide).

Induction therapy

Induction therapy represents a more aggressive approach in which powerful immunosuppressants/DMT are used right from the start to tackle the disease process hard and early, followed by long-term maintenance treatment with less powerful DMT.^{190, level III; 191, level II-2; 202, level III} Fingolimod and natalizumab are indicated for aggressive MS.

There is limited evidence on mitoxantrone followed by IFN β in patients with highly active/aggressive MS. Monthly IV mitoxantrone

for six months followed by IFN β is efficacious in terms of clinical and neuroimaging endpoints in patients with aggressive MS.^{204, level II-3; 208 level II-2}

Induction therapy in aggressive MS with cyclophosphamide or alemtuzumab is another option. Induction therapy with natalizumab runs the risk of rebound disease activity.^{142 - 143, level I; 153 - 154, level II-3; 189, level II-2; 201, level II-3; 202, level III}

p. Treatment for Progressive MS

• Treatment for PPMS

Based on a high quality systematic review, currently there is lack of evidence on any disease modifying agent or immunosuppressants in the treatment of PPMS.^{117, level I}

• Treatment for SPMS

- IFN β -1b shows some benefits in SPMS with relapses. Refer to Chapter on DMT (IFN β).^{121, level I} Indications for starting IFN β -1b in SPMS are:^{174, level III}
 - ≥ 2 disabling relapses in two years
 - able to walk ≥ 10 m
 - minimal increase in disability due to gradual progression over the past two years
 - disease progression by < 2 EDSS points over last year
- In a large multicentre RCT, mitoxantrone 12 mg/m² was efficacious compared with placebo in significantly reducing clinical exacerbations, Gd-enhancing lesions and progression of disability over two years.^{209, level I}

Recommendation 23

- Interferon beta (IFN β) may be given as first-line therapy in active secondary progressive multiple sclerosis (SPMS) with relapses.
- Mitoxantrone may be given in active SPMS with relapses especially if failing IFN β .

13.3 Treatment of MS-related Symptoms

a. Rehabilitation Programmes

• General Rehabilitation

Rehabilitation is a 'problem-solving educational process aimed at reducing disability and handicap experienced by someone as a result of disease or injury'.^{210, level I}

Rehabilitation involves multidisciplinary interventions focusing on reducing symptoms and limitations at the level of activity and participation. This is done through interventions which include personal and environmental factors, to achieve the highest possible independence

and the best quality of life (QoL) of MS patients within the limits of the disease.^{210, level I}

Rehabilitation settings may include:^{210, level I}

- inpatient settings
- ambulatory/outpatient settings
- home-based settings

• **Multidisciplinary Rehabilitation**

Multidisciplinary rehabilitation (MDR) in MS is a co-ordinated delivery of intervention by two or more disciplines (physiotherapy, occupational therapy, social work, psychology, nursing and others) under medical supervision (neurologist and rehabilitation physician). It is designed to be patient-centred, time-based and functionally-oriented using a biopsychosocial model.^{210, level I}

A Cochrane systematic review showed strong evidence to support inpatient MDR in producing short-term gains at the levels of activity (disability) and participation in patients with MS.^{211, level I}

• **Physical Therapy**

Up to 79% of patients with MS experience loss of mobility. Within 10 years of diagnosis, 38% of the patients will need walking aids and these increases to 83% after 30 years.^{212, level III}

MS is associated with a reduction in physical activity as a result of the disease per se and/or a sedentary lifestyle. It leads to increased incidence of osteoporosis, depression, fatigue, loss of muscle strength and death from cardiovascular diseases.^{213, level I}

Physical therapy aims at improving motor functions, balance and gait, and reducing spasticity through passive and active exercises training. Types of exercise that can be used includes resistance, endurance and combination training.^{213 level I}

A Cochrane systematic review on MS reported:^{214, level I}

- strong evidence for exercise-based rehabilitation in improving muscle power, exercise tolerance and mobility-related activities
- moderate evidence for improving mood

Both group exercise therapy^{215, level I} and home-based therapy^{216, level I} improve some functions compared to no exercise in MS patients.

Robot-driven gait orthosis significantly improves walking endurance and knee strength compared with conventional walking training in MS patients with severe walking disabilities (EDSS 6.0 - 7.5).^{217, level I}

- **Occupational therapy**

The key components of occupational therapy (OT) in MS are restoration and maintenance of functional independence, modification of environment and use of adaptive or assistive devices.

MS patients experience limitations in their ability to undertake a variety of activities needed to live independently referred to as ADL which include personal, domestic and community ADL.

Patients with MS who experience limitation in ADL should receive a comprehensive multidisciplinary assessment and, individualised and goal-directed programme of interventions with the aim of increasing and maintaining independence wherever possible.²¹⁸

Mobility Assistive Technology (MAT) is useful to maintain or improve mobility. These are devices that:^{219, level II-2}

- reduce activity limitations and participation restrictions
- prevent or reduce fatigue by energy conservation
- improve QoL

MAT includes gait aids, orthoses and wheelchairs.

Arm or upper extremity function is important in performing ADL. This requires motor coordination, dexterity and precise collaboration between both hands. Treatment can be divided into training and compensatory approaches. The former aim to maximise arm function while the latter focuses on correct positioning of the affected upper limb and prevention of contracture.^{212, level III}

Recommendation 24

- Patients with multiple sclerosis (MS) should be assessed on MS-related symptoms.
- Multidisciplinary rehabilitation should be offered to MS patients in all health care settings.

b. Ataxia

Cerebellar ataxia refers to deficits in temporal and spatial coordination caused by lesions or degeneration in the cerebellum and/or brain stem in patients with MS.^{212, level III}

A Cochrane Review on treatment of ataxia revealed a lack of RCTs on ataxia. Physical training programmes may bring some benefit.^{220, level I} The use of weights for ataxia with specific weighting placement on the trunk has effects on functional ambulation outcome measures.^{212, level III}

c. Fatigue

Fatigue is defined as a subjective lack of physical and/or mental energy, perceived by the individual or caregiver to interfere with usual and desired activities. It has been reported in 60 - 95% of patients with MS and has a significant impact on ADL, social life and ability to work.^{210, level III; 212, level III}

Treatment of fatigue should be multi-dimensional and tailored to the medical and functional status of each patient.^{210, level III; 212, level III}

• Treatment

Rehabilitation interventions should be the initial treatment of choice for fatigue.^{221, level I} These include energy conservation strategies, education for patient and family (avoid heat but use air-conditioners/cooling gel vests) and address lifestyle factors (avoid physical activity at mid-afternoon).^{210, level III}

Energy conservation management utilises strategies or assistive technologies to reduce fatigue by pacing, modifying and delegating activities.^{222, level I} This can be achieved by individually adapting the structure of private & work life such as having “power-naps”.

In a Cochrane systematic review of five RCTs on amantadine, there was a small and inconsistent improvement of fatigue in MS. The side effects were generally mild such as hallucinations, nausea, dizziness, hyperactivity, anxiety and insomnia observed in 10% to 57% of patients.^{223, level I}

There is insufficient evidence to support the use of carnitine^{224, level I} while modafinil is not efficacious in the treatment of fatigue in MS.^{225, level I}

In a recent meta-analysis on non-pharmacological treatment, energy conservation management based on Packer course was more effective than no treatment in reducing the impact of fatigue in the short-term.^{222, level I} However, more evidence is needed on this matter before it can be recommended.

Recommendation 25

- In multiple sclerosis patients with fatigue:
 - energy conservation management should be used
 - amantadine may be offered

d. Spasticity and Paralysis

Spasticity

About 60% of patients with MS experience spasticity complications.^{226, level III} Spasticity is defined as a disordered sensori-motor control, resulting from an upper motor lesion, presenting as intermittent or sustained involuntary activation of muscles.^{227, level III} In some instances, spasticity

may be beneficial by counteracting muscle weakness. However, disabling spasticity should be treated as it may lead to pain, pressure ulcer, spasms, reduced mobility, restricted joint range of motion and contractures.

• Clinical Evaluation

In every MS patient, a detailed history should include symptoms of spasticity such as muscle stiffness/spasms or tightness in or around the joints. For more severe symptoms, painful spasms may be enquired. Modified Asworth Scale is a commonly used clinical tool to assess severity and monitor treatment outcome of spasticity.^{228, level I}

• Treatment

Treatment of spasticity in MS should be individualised with the aim to achieve reduction of symptoms, improvement of functions and prevention of complications such as contractures. Elimination of triggers that may exacerbate spasticity such as urogenital infection, constipation, pressure ulcer and pain are also important.

Treatment of spasticity in MS involves non-pharmacological, pharmacological and surgical intervention. In principle, localised spasticity is amenable to physical therapy, splinting and Botulinum Toxin (BTX) injection. Conversely, oral drugs and at a later stage intrathecal intervention may be considered for generalised spasticity.^{226, level III}

i. Non-pharmacological intervention

There is minimal evidence to support non-pharmacological intervention with or without pharmacological intervention in the management of spasticity and paralysis in MS.

• Physical therapy

- Daily range of motion exercise performed at least 2 - 3 times/day is an integral part of spasticity treatment as it may prevent contractures in MS.^{229, level III}
- Daily stretching and strengthening exercises minimise the risk for muscle shortening and reduce the risk of progressive weakening of spastic muscles respectively in MS.^{230, level III}
- Hydrotherapy^{230, level III} and swimming in cold pools^{231, level III} actively stretch spastic muscles and maintain/build endurance in MS. Local applications of cold may provide temporary relief of localised muscles spasm and spasticity.^{230, level III}
- Four sessions of unloaded arm and leg cycling exercise 20 minutes every 2 - 3 days reduces spasticity in MS ($p < 0.001$).^{232, level II-3}
- Treadmill training with partial body weight support, combined with physiotherapy, reduces spasticity in MS.^{231, level III}
- BTX A followed by daily physiotherapy for 15 days decrease spasticity at two weeks and 12 weeks compared with BTX A alone in MS ($p < 0.01$).^{228, level I}

- Physical modalities
 - Functional electrical stimulation causes a significant reduction of spasticity in MS.^{231, level III}
 - Transcutaneous electrical nerve stimulation (TENS) applied eight hours daily for two weeks improves muscle spasm ($p=0.038$) and pain ($p=0.008$) in MS.^{228, level I; 231, level III}
 - Daily sessions of repetitive magnetic stimulation for two weeks improves spasticity in MS ($p<0.05$).^{228, level I}
- Splints and orthotic device
 - Splints and orthotic devices can be used to reduce tone, prevent contractures and reduce pain in MS. Orthotic device may also control joint instability and improve ambulation such as ankle foot orthoses. Serial plaster casting every seven to 10 days may also be used to gradually improve range of motion and thus correct mild soft tissue contracture.^{229, level III}
- ii. Pharmacological intervention
 - Baclofen
 - Oral baclofen improves spasticity, passive range of motion, painful spasms and clonus compared with placebo in MS.^{226, level III; 229, level III; 233, level I}
 - Intra-thecal baclofen via an implantable pump may be an option for MS patients who do not achieve adequate control of their spasticity or unable to tolerate side effects of oral medication.^{226, level III; 229, level III}
 - Tizanidine
 - Tizanidine reduces mean total Ashworth score from baseline after nine weeks of treatment MS ($p=0.004$).^{233, level I}
 - Oral and sublingual tizanidine is more efficacious compared with placebo in reducing spasticity in MS by Ashworth score ($p=0.002$). Sublingual tizanidine given on night significantly reduces somnolence effect.^{234, level I}
 - Benzodiazepines (diazepam and clonazepam)
 - Benzodiazepines are efficacious in reducing spasticity from spinal and cerebral complications of MS. These drugs however are preferably given at bed time due to drowsiness side effect.^{226, level III; 229, level III}
 - Cannabinoids
 - Cannabinoids significantly improves pain, spasms and spasticity in terms of severity and frequency compared with placebo.^{228, level I}
 - Oral cannabinoids are more efficacious in relieving muscle stiffness after 12 weeks compared with placebo in MS (OR=2.26, 95% CI 1.24 to 4.13).^{235, level I}
 - BTX A
 - BTX A injection improves spasticity lasting for 1 - 3 months in MS.^{233, level I} It also induces muscle relaxation and prevents contractures in affected muscles.^{226, level III; 229, level III}

iii. Surgical intervention

Orthopedic procedures such as tenotomies, tendon transfers and tendon lengthening can be considered in the management of focal spasticity and contractures in MS.^{229, level III}

In extreme refractory cases of spasticity, neurosurgical procedures such as selective dorsal rhizotomy, myelotomy or cordectomy may be indicated.^{229, level III}

Paralysis

Patients with MS are commonly affected by weakness and paralysis in consequence to deconditioning as well as the neurological disease itself. This often results in impaired mobility and abnormal gait pattern. Physiotherapy intervention and the use of walking aids can compensate for weakness, alleviate pain, improve posture, correct gait abnormality and thus enable people to walk further and more safely. Fampiridine^{226, level III} and extended-release dalfampridine^{236, level III} have shown positive results on walking ability in some patients with MS.

Recommendation 26

- In multiple sclerosis (MS) patients with disabling spasticity:
 - non-pharmacological interventions may be offered as initial treatment
 - pharmacological intervention may be offered in severe spasticity refractory to non-pharmacological management
 - orthopaedic and neurosurgical procedures may be offered for extreme spasticity, when conservative management fails
- In MS patients with weakness and paralysis resulting in abnormal gait pattern, physiotherapy intervention, use of walking aids and pharmacological treatment may be offered.

e. Visual Problems

MS patients with visual disturbances may benefit from the low-vision rehabilitation utilising low-vision aids, illumination and training to maximise participation in independent living. These aids include magnifiers, prisms, telescopes, electronic devices and large-text reading material. MS patients with oscillopsia may benefit from Gabapentin.^{100; 218} Rehabilitation services for the blind assist in personal, domestic and community ADL.^{7, level III; 210, level III}

f. Swallowing and Speech Difficulties

Swallowing Difficulty

Oropharyngeal dysphagia affects between 30% and 65% of MS patients. Dysphagia is associated with increased morbidity and mortality due to complications such as malnutrition and bronchopneumonia.^{212, level III}

- Treatment

Dysphagia evaluation comprises of bedside swallowing assessment, formal swallowing evaluation (such as videofluoroscopy or flexible endoscopy) and in specific situations, oesophageal manometry.^{212, level III}

The aims of treatment for dysphagia are to preserve or to restore patients with MS to a normal diet, to improve the nutritional status and to decrease the morbidity and mortality associated with aspiration pneumonia.^{212, level III}

Evidence of efficacy of dysphagia therapy in MS is limited. This includes.^{212, level III}

- restorative interventions
 - oromotor stimulation and exercise
 - head elevation exercise
- compensatory strategies
 - postural manoeuvres
 - special swallowing techniques such as double swallow, effortful swallow and Mendelsohn manoeuvre
- adaptive strategies
 - diet adaptation and modification of fluid consistency
 - positioning of body and head, take up time for eating, breaks, empty one's mouth before next bite and regular swallowing of saliva

Other swallowing therapies:

- pharmacological agents
 - BTX A injection is safe and may benefit dysphagic MS patients associated with upper oesophageal sphincter hyperactivity.^{237, level II-3}
- tube feeding
 - Enteral feeding tubes are used when oral intake is insufficient in MS. If the need is short term, nasogastric tube feeding is utilised, whereas percutaneous gastrostomy is preferred in chronic cases.^{212, level III}

Recommendation 27

- Dysphagia therapy maybe offered in multiple sclerosis (MS) with swallowing difficulty.
- Botulinum toxin A injection may be offered in dysphagic MS patients with upper oesophageal sphincter hyperactivity.

Speech Difficulty

Slurred speech (dysarthria), including spastic and ataxic components, occurs in 40% to 50% of MS patients.^{212, level III} It occurs because of difficulty in controlling the quality of the voice and in articulating words

due to motor impairment in the muscles controlling speech, insufficient subglottal pressure and weakened expiratory and/or laryngeal muscles.^{238, level II-I}

Language disturbance (aphasia) is rare in MS but may occur mostly in the context of severe cognitive impairment.^{212, level III} or rarely in the context of a relapse caused by a subcortical MS plaque and perilesional edema. Cognitive and behavioural impairment, fatigue, pain and emotional disturbances, and common drugs in MS (such as benzodiazepines, baclofen and tizanidine) may impair speech.^{212, level III}

- **Treatment**

The main goals of the intervention are to increase speech intelligibility and functional communication, depending on the stage of dysarthria.^{212, level III}

The type of speech therapy interventions used to improve the respiratory and phonatory functions in MS patients include the intensive Lee Silverman Voice Treatment. Other interventions are expiratory muscle strength training, breath control exercises, accent method and breath pattering, and music therapy.^{212, level III}

A variety of techniques has been used to improve rate, prosody and articulation with some success, including external pacing devices, computer training, behavioural instructions and biofeedback.^{212, level III}

Other augmentation methods include using letter or communication boards and microcomputers with synthetic voice output.^{212, level III}

Recommendation 28

- Speech therapy interventions maybe offered in multiple sclerosis with speech difficulty.

g. Bladder Dysfunction

About 75% of patients with MS have bladder dysfunction.^{239, level III} The symptoms may vary according to the severity of the neurological disability. Symptoms of incontinence are reported to occur in 49%, urgency and frequency in 32% and hesitancy-retention in 19% of MS patients with bladder dysfunction.^{240, level III}

Although there is no strong evidence on management of bladder dysfunction, CPG DG agrees that this issue is crucial and has to be addressed based on expert opinion when evidence is limited.

- **Clinical Evaluation**

In every MS patient, a detailed clinical history (especially in those with clinical or MRI spinal cord involvement) should include symptoms of bladder dysfunction such as urgency, frequency, incontinence,

hesitancy, retention and nocturia. The aetiology of bladder dysfunction (neurogenic or non-neurogenic; detrusor versus sphincter origin or combination of both) should be determined.

A bladder diary is a useful tool for clinical assessment in symptomatic patients. Relevant investigations include urine analysis, culture and sensitivity, and post-void residual volume (PVRV) assessment. In patients with severe symptoms who are refractory to conservative management, ultrasound KUB and video-urodynamic studies may be considered.

239 - 241, level III

Refer to **Appendix 8 on Bladder Diary**.

Recommendation 29

- Bladder diary, urine analysis and culture, and post void residual volume should be performed in patients with multiple sclerosis and symptoms of bladder dysfunction.
 - Ultrasound kidney-urether-bladder and video-urodynamic studies may be considered in those with severe refractory symptoms.

• Treatment

Treatment of bladder dysfunction in MS should be individualised with the aim to achieve adequate urinary continence, prevent medical complications and tailored to the severity of symptoms and disability, and results of investigations. Possible causes of clinical exacerbation such as urinary tract infection should be treated.

Treatment of bladder dysfunction in MS involves:

- i. non-pharmacological intervention
- ii. pharmacological intervention
- iii. neuromodulation
- iv. surgical intervention

i. Non-pharmacological intervention

• Behavioural therapy

Fluid management should be individualised according to the bladder diary. Generally, intake of 1 - 2 litres a day is recommended. Avoidance of caffeinated drinks may reduce the symptoms of urgency and frequency. The use of external collection devices such as incontinence pads or condom catheter may also be offered. Bladder retraining and pelvic floor muscle exercises (Kegel exercise) can reduce symptoms of both urge and stress incontinence by improving the strength of pelvic floor muscles.^{226, level III; 239 - 240, level III}

- Catheterisation

In MS patients with bladder symptoms and PVRV >100 ml, complete emptying via clean intermittent self-catheterisation or clean intermittent catheterisation by caregiver is indicated. This can be done 4 - 6 hourly.

In those with refractory urinary symptoms, indwelling catheterisation may be considered. Suprapubic catheterisation is preferred over urethral catheterisation due to risk of severe urethral erosions and damage.^{226, level III; 239, level III}

Recommendation 30

- In multiple sclerosis patients with bladder dysfunction:
 - fluid management, avoidance of caffeinated beverages, timed voiding and pelvic floor muscles exercises may be offered as initial management.
 - clean intermittent catheterisation 4 - 6 hourly should be advised in those with high post void residual volume (>100 ml).
 - suprapubic catheterisation is preferred in those with severe refractory urinary symptoms not responding to conservative management.

ii. Pharmacological intervention

- Anti-cholinergic medications

Anti-cholinergic agents such as oxybutinin, tolterodine tartarate, propiverine hydrochloride and solifenacin succinate are available locally.

In a Cochrane systematic review, oral oxybutinin was more efficacious than oral propantheline in reduction of frequency symptoms with MD=0.7 (95% CI 0.17 to 1.23). Although there is no significant difference in the efficacy, oral oxybutinin caused more dry mouth compared with intravesical atropine [OR=9.0 (95% CI 4 to 22)]. The trials in this review were of poor quality.^{242, level I}

Side effects of anti-cholinergic agents include drowsiness, constipation and urinary retention.^{239 - 240, level III; 243, level III}

- Alpha blockers

The use of alpha adrenergic blockers may be of benefit to improve the flow rate and reduction of PVRV in MS patients with obstructive urinary symptoms.^{226, level III; 239, level III}

- Desmopressin

A meta-analysis showed that desmopressin either orally or intranasally administered was efficacious compared with placebo for day frequency and nocturia in MS. Hyponatraemia was reported in 5% of cases, thus

this medication need to be prescribed with caution and not be used more than once in 24 hours.^{244, level I} Locally, desmopressin may be considered for those with nocturnal diuresis refractory to conservative measures.

- **BTX Type A**

In a systematic review which included MS patients, BTX A was significantly more efficacious than control in decreasing daily urinary incontinence at week 2 and 24 post-treatment and significantly improved urodynamic parameters. No significant adverse reaction were reported.^{245, level I}

Recommendation 31

- In multiple sclerosis, the following medication may be considered:
 - anti-cholinergics for frequency and urge incontinence.
 - alpha blockers for high post-voiding residual volume and urinary retention.
 - desmopressin for nocturnal diuresis refractory to conservative measures.
 - botulinum toxin type A intravesical injection for urinary incontinence refractory to conservative measures.

iii. Neuromodulation

Given the likely neurogenic cause of voiding dysfunction in MS, neuromodulation may potentially alleviate symptoms. Neuromodulation is defined as the alteration of nerve activity through the delivery of electrical stimulation or chemical agents to targeted sites of the body.

A minimally invasive neuromodulation technique using Posterior Tibial Nerve Stimulation is significantly efficacious compared with control in both clinical symptoms and urodynamic parameters of bladder dysfunction in MS after 12 weeks.^{246, level II-3}

Sacral neuromodulation with electrical stimulation of the S3-nerve root can be considered in detrusor overactivity unresponsive to BTX A.^{226, level III}

iv. Surgical intervention

Surgical intervention such as bladder augmentation surgery and urinary diversion can be offered for patients with intractable urge incontinence, renal compromise from low compliance or reflux, or those with irreversible complications of long-term catheterisation.^{226, level III; 239, level III; 241, level III}

Augmentation ileocystoplasty is efficacious in improving bladder capacity compared with baseline in MS.^{247, level II-3}

Recommendation 32

- Neuromodulation may be considered for the treatment of severe detrusor overactivity refractory to conservative treatment in multiple sclerosis (MS).
- Bladder augmentation surgery or urinary diversion may be offered in the treatment of severe detrusor overactivity refractory to conservative treatment in MS.

A summary of bladder dysfunction management in MS is shown the following **Figure 7**.

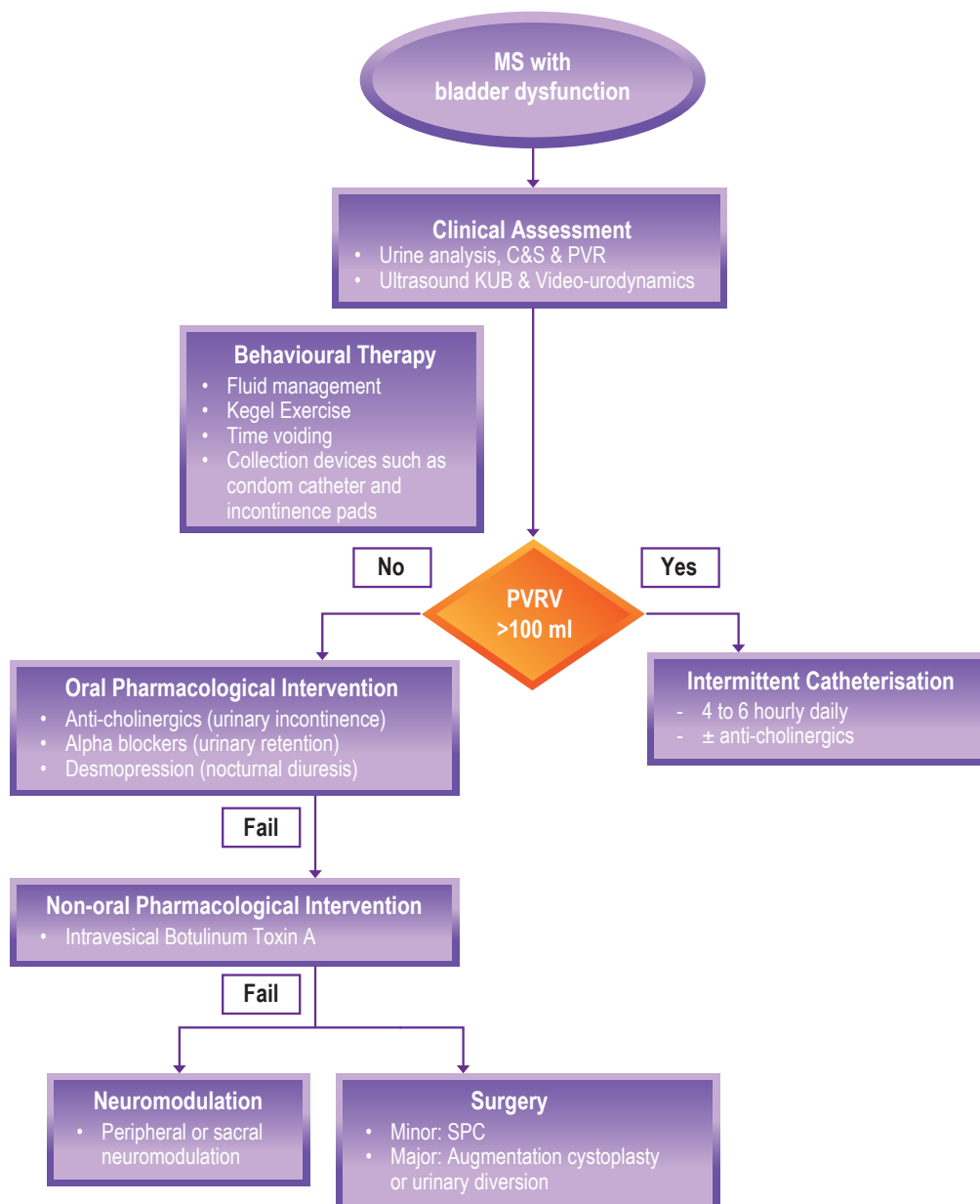


Figure 7. Management of Bladder Dysfunction in MS

h. Bowel Problem

Bowel dysfunction (constipation and faecal incontinence) has been reported in up to 70% of MS patients.^{212, level III} This results from autonomic and rectal dysfunction.^{210, level III} Management of bowel dysfunction in MS is predominantly based on expert opinion.^{212, level III}

• Treatment

An effective bowel management programme involves:^{210, level III; 212, level III}

- a regular schedule:
 - completed within 60 minutes from beginning of insertion of rectal stimulant to bowel evacuation
 - timing ideally should be postprandial to induce gastrocolic reflex
 - should be daily or alternate day which is designed to meet specific requirements of patients and carers
- optimisation of stool consistency
 - achieved by adequate oral intake, a high fibre diet and laxatives
 - laxatives may include bulking agents such as fibre supplement (psyllium seed husks) and stool softener such as liquid paraffin
- facilitation in the movement of bowel contents
 - abdominal massage increases the frequency of defecation^{248, level I}
 - laxatives including osmotic agents (such as lactulose) and oral colonic stimulants (such as bisacodyl)
- bowel evacuation
 - digital rectal stimulation increases motility in reflex neurogenic bowel dysfunction
 - manual evacuation of faeces involves using a single gloved and lubricated finger to remove faeces from the rectum
 - rectal stimulants [suppositories (such as bisacodyl) and enemas] are used to stimulate reflex evacuation at the time chosen for bowel care; enemas are to be avoided except in faecal impaction due to adverse effects on sacral reflexes from excessive distention of the rectum^{7, level III}

If the bowel management programme is insufficient, transanal irrigation can be used by passing water or other liquids via the anus.^{212, level III}

The Malone Antegrade Continence Enema is a safe and effective treatment when conservative and transanal irrigation are unsuccessful or inappropriate. Other treatment options available are electrical stimulation of the pelvic floor and sacral anterior root stimulation.^{212, level III}

Surgery (elective colostomy or ileostomy) should only be performed if all medical and conservative options have failed especially when faecal incontinence is associated with severe pressure ulcers.^{212, level III}

Recommended 33

- Bowel management programme may be offered in multiple sclerosis patients with bowel dysfunction.

i. Pain

The prevalence of pain (acute and chronic) in MS is 83%.^{249, level I} The underlying mechanisms of pain in MS are unclear and have been linked with the differentiation and disinhibition of central and peripheral pain pathways.^{210, level III}

Pain in MS can be classified into:^{250, level III}

- central neuropathic pain
 - most common pain syndromes associated with MS^{251, level III}
 - constant burning sensation, usually affecting lower limbs, more frequently distally than proximally^{251, level III}
 - caused by demyelinating lesions in the CNS^{250, level III}
- non-neuropathic pain^{250, level III}
 - such as musculoskeletal pain and painful tonic spasms
 - due to indirect consequence of the disability associated with MS
- mixed neuropathic and non-neuropathic pain^{250, level III}
 - such as headache, painful muscle spasms and spasticity

Pain is co-related with anxiety, depression, and fatigue, and is aggravated by sleep disturbance and spasticity.^{250, level III}

• Treatment

To date, few clinical trials have examined the pain management in MS. In a systematic review on this issue:^{249, level I}

- Anticonvulsants
 - Gabapentin and pregabalin reduced pain, with adverse events including mental cloudiness, somnolence and nausea.
 - Lamotrigine was efficacious in reducing the worst and least pain in comparison to placebo. Nausea was the most common adverse event.
 - Levetiracetam was significantly efficacious in reducing pain when compared with placebo. Common adverse events were tiredness, dizziness and mental changes.
- Antidepressants
 - Nortriptyline was as efficacious as TENS in reducing pain. Common adverse effects included drowsiness, constipation, urinary retention and hypotension.
 - Duloxetine was efficacious in reducing pain compared with placebo in central neuropathic pain. Common side effects included nausea, somnolence and dizziness.
- Cannabinoids
 - Dronabinol improved pain when compared with placebo.

- Nabiximols (an oromucosal spray) was significantly efficacious in reducing central pain but not mixed pain when compared with placebo.
- Dizziness was most common adverse event. Others included fatigue, somnolence, vertigo and headaches.
- Dextromethorphan/Quinidine
 - Dextromethorphan/quinidine, originally intended for pseudobulbar affect, improved pain when compared with placebo. Most common adverse events were non-vertiginous dizziness, nausea and headache. This drug is currently not available in Malaysia.
- Opioids
 - IV morphine reduced pain when compared with saline placebo. Most common adverse effects were constipation, sedation, nausea, dizziness and vomiting.

NICE 2004 recommends the use of anticonvulsants (such as carbamazepine or gabapentin) or antidepressants (such as amitriptyline) for the treatment of neuropathic pain in MS.²¹⁸

However in a 3-year cohort study, a significantly higher incidence of adverse effects in patients treated with carbamazepine was noted, with a high rate of discontinuation at low dosages and episodes of neurological worsening compared with gabapentin or lamotrigine.^{252, level II-2}

In central pain of MS, opioids have minimal use and seem effective only at very high doses. Neuropathic pain is poorly responsive to opioids. On another note, The International Association for the Study of Pain rates cannabis use in MS pain as second-line treatment due to lack of long-term safety data.^{250, level III}

• **Chronic low back pain**

In MS, chronic low back pain:

- is the most common type of somatic nociceptive pain and may be due to degenerative changes and excessive burden of joints and muscles from incorrect posture and/or abnormal gait, prolonged wheelchair use and ill-fitting use of aids^{251, level III}
- pharmacological treatment (non-steroidal anti-inflammatory drugs or opioids) should follow the same strategies as those for non-MS-related pain^{251, level III}
- high-frequency TENS is more efficacious for pain relief at six weeks while the low-frequency TENS produces a more sustained effect at 32 weeks although not statistically significant^{253, level I}

Recommendation 34

- Anticonvulsants or antidepressants may be offered for central neuropathic pain in multiple sclerosis.

j. Paroxysmal Symptoms

Paroxysmal manifestations of MS are cluster of brief symptoms that appear suddenly, frequently and are often stereotyped.^{7, level III} In MS, paroxysmal symptoms which cause severe discomfort affect 10% of patients.^{254, level II-3} Paroxysmal symptoms are likely due to abnormal transient electric discharges spread throughout demyelinated axons.^{255, level II-3}

Paroxysmal symptoms include:

- trigeminal neuralgia (TN)
 - TN occurs 20 times more common in MS than in the general population. It is typically unilateral.^{250, level III}
- painful tonic spasms
 - Painful tonic spasms is an abrupt abnormal posturing of extremities. It can be described as cramping, pulling pain, clawing of a hand or arm, or kicking out of a leg.^{250 - 251, level III}
 - It is distinct from pain related to spasticity and is estimated to occur in 11% of the MS population.^{251, level III}
- Lhermitte's sign
 - This is a transient paroxysmal electric shock-like sensation radiating down the spine to the lower extremities which is elicited by neck flexion or extension.^{251, level III}
 - It is experienced by 40% of patients with MS.^{250 - 251, level III}
- other paroxysmal manifestations of MS are paroxysmal paraesthesiae, paroxysmal itching, dysarthria, diplopia, akinesia and ataxia.^{7, level III}

- **Treatment**

Despite of lack in RCTs, carbamazepine is being used in the treatment of paroxysmal symptoms in MS.^{7, level III; 210, level III}

Gabapentin reduces or completely resolves paroxysmal symptoms (TN and PTS) with mild side effects within three months of therapy and sustains for subsequent months ($p=0.005$).^{255, level II-3}

Pregabalin reduces paroxysmal painful phenomena ($p<0.05$) with well-tolerated side effects.^{254, level II-3}

Recommendation 35

- Carbamazepine, gabapentin or pregabalin may be used in multiple sclerosis with paroxysmal symptoms.

k. Sexual Dysfunction

Sexual dysfunction in MS due to neurogenic lesions is common during the disease course and affects approximately 70% of patients (refer to **Table 10**). Underlying psychological dysfunction and side effects of medication may also play a role.^{240, level III}

Table 10. Common symptoms of sexual dysfunction in MS

Men	Women
Decreased libido	Decreased libido
Difficulty in achieving or maintaining erection	Orgasmic dysfunction
Delayed ejaculation or loss of ejaculatory function	Decreased vaginal lubrication
Impaired genital sensation	Decreased vaginal sensation

• Clinical Evaluation

Sexual dysfunction in MS is commonly diagnosed on clinical basis alone. If needed, serum testosterone level can be helpful to exclude hormonal deficiency in men.^{240, level III; 256, level III}

• Treatment

- Counseling is offered to address psychosocial relationship concerns.^{240, level III; 256, level III}
- Relevant interventions offered to patients with recognised specific symptom.
 - For female patients:^{240, level III; 256, level III}
 - oral or topical estrogens for vaginal dryness due to decreased lubrication
 - methyl-testosterone to increase libido
 - vibratory stimuli to improve arousal
 - variation in sexual positioning to reduce fatigue
 - For male patients:
 - sildenafil citrate improves ability to achieve and maintain erection thus enhancing vaginal penetration and completion of intercourse (RR=2.72, 95% CI 1.40 to 5.28). Significant side effects include visual disturbance, rhinitis, flushing, dyspepsia and headache.^{164, level I}
 - other interventions include:^{226, level III; 240, level III; 256, level III}
 - stimulation therapy - alternative erogenous zones, erotic visual, audio aids and olfactory stimulation
 - local injectable therapy - intra-urethral or intra-cavernosal prostaglandin E1
 - physical intervention such as physical therapy - vacuum pump with constriction bands or manual/vibratory stimulation
 - surgical intervention - inflatable, rigid or semi-rigid penile prostheses

Recommendation 36

- Sexual dysfunction in multiple sclerosis (MS) should be enquired and addressed. Management strategies may be offered to provide symptomatic relief and improve the quality of life of MS patients.

14. NEUROPSYCHIATRIC PROBLEMS

a. Epidemiology

Neuropsychiatric manifestations are very common in MS in all subtypes and stages. The prevalence rates of cognitive impairment in MS ranges from 43 to 70%. MS negatively affects various aspects of cognitive functioning including attention, information processing abilities, new learning and memory functioning.^{257, level I} Cognitive impairment is detected as early as in CIS (20 - 30%) progressing over time, and most frequent and severe in SPMS.^{258, level III}

Among individuals with MS, relative to the general population, lifetime prevalence rates are elevated for major depressive disorder (36 - 54% vs 16.2%), bipolar disorder (13% vs 1 - 4.5%) and psychotic disorders (2 - 3% vs 1.8%).²⁵⁹

b. Treatment

• Cognitive Problem

A Cochrane systematic review reported a low level of evidence for the positive effects of neuropsychological rehabilitation in MS. Cognitive training improved memory span (SMD=0.54, 95% CI 0.20 to 0.88) and working memory (SMD=0.33, 95% CI 0.09 to 0.57).^{260, level I}

Another systematic review found some benefits for attention training, executive functions, learning performance and memory although the evidence was limited due to methodological problems of the included studies.^{257, level I}

- Cognitive training may be beneficial in the rehabilitation of multiple sclerosis patients with cognitive impairment.

• Memory Problem

In a Cochrane systematic review, donepezil, rivastigmine, memantine and ginkgo biloba were not efficacious when compared with placebo in the treatment of memory problem in MS. Nevertheless, no serious adverse events were attributed to the above treatments.^{261, level I} In a recent Cochrane meta-analysis of cholinesterase inhibitors in MS with cognitive impairment, donepezil and rivastigmine were not efficacious when compared with placebo in objective cognitive improvement and activities of daily living in short and medium terms treatment, but showed significant improvement in the clinicians' impression of cognitive change (OR=1.96, 95% CI 1.06 to 3.62).^{262, level I}

- There is no evidence to support any specific pharmacological intervention in memory problem in MS.

- **Depression**

In a Cochrane systematic review, desipramine and paroxetine showed a trend towards efficacy in depression in MS at short term compared with placebo, however it was not statistically significant. Desipramine reduced Hamilton Depression Rating Scale (HAM-D) score at least by 50% at five weeks, and paroxetine reduced HAM-D score at least by 50% at 12 weeks.^{263, level I} Fluvoxamine improves depression based on Montgomery-Åsberg Depression Rating Scale scores in RRMS with major depression disorder.^{264, level II-3}

In another Cochrane systematic review on psychological interventions in MS patients, there was some evidence that cognitive behavioural therapy (CBT) might improve depression and help in adjustment and coping with MS.^{265, level I} Telephone-administered-CBT provides significantly greater quality of life benefits compared with telephone-administered supportive emotion focused therapy by improving depression and positive affect.^{266, level I} Stress management also significantly improves depressive symptoms in MS compared with control group (ES=0.53, p=0.02).^{267, level I} A recent systemic review on mindfulness-based intervention in MS showed significant improvement in depression post-intervention (ES=0.65, p<0.001) and six months later (ES=0.36, p<0.05).^{268, level I}

In the absence of strong evidence that depression in MS is different from depression in general psychiatry, the CPG on Management of Major Depressive Disorder should be used in managing this group of patients.²⁶⁹

Recommendation 37

- Antidepressants, cognitive behavioural therapy, mindfulness-based intervention or stress management may be offered in multiple sclerosis with depression.

- **Bipolar disorder and pseudobulbar affect**

Dextromethorphan/quinidine (DM/Q) is efficacious compared with placebo in treatment of pseudobulbar affect (pathological laughing and crying) in MS based on Center for Neurologic Study-Lability Scale scores (p=0.0001) at all clinic visits (days 15, 29, 57 and 85). This treatment is well-tolerated.^{270, level I}

In the absence of strong evidence that bipolar disorder in MS is different from bipolar disorder in general psychiatry, the CPG on Management of Bipolar Disorder in Adults should be used in managing this group of patients.²⁷¹

Recommendation 38

- Dextromethorphan/quinidine may be considered in the treatment of multiple sclerosis with pseudobulbar affect.

- **Psychosis**

Based on two systematic reviews, there was insufficient evidence to determine the efficacious treatment of psychosis in MS.^{226, level III; 259} Therefore the management of these patients should follow the management of psychosis in general psychiatry.^{226, level III}

Recommendation 39

- Psychosis in multiple sclerosis should be managed as in general psychiatry.

15. SPECIAL ISSUES

15.1 Pregnancy-related Issues

MS is most common among women during their child-bearing age and this poses extra challenges for women, their families and health providers. However, MS is not a hereditary disorder.^{272, level III}

- **Conception**

MS appears to have no physiological effect on fertility although sexual dysfunction affecting individuals with MS may impact conception.^{273 - 274, level III}

- **Pregnancy Management**

It is unusual for MS to present or relapse during pregnancy. A meta-analysis found that the relapse rate decreased during pregnancy in relation to the preceding year but increased in the first three months after delivery ($p < 0.0001$).^{275, level II-2} A large cohort study showed that during the first three months postpartum, the relapse rate rebounded to 70% above the pre-pregnancy state and reduced to the pre-pregnancy rate thereafter.^{276, level II-2} This risk of postpartum relapse is higher in those who have high relapse and disability in pre-pregnancy and relapse during pregnancy period than those without.^{272, level III; 276, level II-2}

Prenatal care of MS patients is similar to that of non-MS patients but some may have aggravation of pre-existing urinary or bowel dysfunction. They may be prone to urinary tract infection and possibly pyelonephritis if untreated.^{274, level III}

- **MS Therapies in Pregnancy**

There is lack of evidence on the safety of steroids in pregnant MS patients.^{272, level III} Based on a few case-control studies, steroids were associated with an increased risk of cleft lips and palate when used in the first trimester of pregnancy.^{277 - 278, level II-2} Therefore the risk:benefit ratio needs to be weighed carefully before giving steroids for acute relapses that occur during pregnancy especially during the first trimester. Alternatives such as IVIG may also be considered.^{279, level III}

Currently there is no evidence to suggest that DMT is not teratogenic or safe in pregnancy. No uniform guidelines exist to direct the stopping of a DMT before trying to become pregnant. Pregnancy counselling and planned withdrawal of DMT is usually discussed with women with MS in advance. The risks of teratogenicity and pregnancy losses are usually balanced with an open discussion on the time frame of DMT withdrawal and when the patient should start to try conceiving. For DMT like IFN β , GA and DMF one month is sufficient for withdrawal of therapy prior to try conceiving and two months for fingolimod. Although three months have been recommended for natalizumab, it may be that one month is

sufficient. Teriflunomide should always be washed out prior to planned conception.^{272, level III} In the event of unexpected pregnancy, treatment interruption is advisable and patient is closely followed up. Refer to **Appendix 9**.

Symptomatic therapies should be evaluated for potential teratogenic risks and thus minimised in pregnant MS patients. Only those absolutely necessary are used at the minimum effective dose. Alternative non-pharmacological strategies are encouraged.

- **Pregnancy Outcome**

A recent meta-analysis showed that there was a relatively higher prevalence of abortions, caesarean sections, prematurity and low birth-weight babies among women with MS. However, these rates did not reach levels that would signify great concern.^{275, level II-2} Therefore patients can be advised that MS has no negative impact on pregnancy and its outcomes.

- **Post-partum Issues**

- i. **Delivery Issues**

MS has no impact on the mode of delivery and the choice of anaesthesia in pregnancy.^{272, level III}

- ii. **Breastfeeding**

DMT is not advisable during lactation. Two meta-analyses showed that breastfeeding significantly prevented postpartum relapses although the findings were limited by heterogeneity, methodological issues and small studies.^{280 - 281, level II-2}

- iii. **Restart Therapy**

DMT can be started immediately postpartum as long as the patient is not breast-feeding.^{272, level III}

- **Contraception**

There is no evidence that oestrogen at doses contained in the combined oral contraceptive pill (OCP) has an adverse effect on MS. Some drugs used in treating MS symptoms such as carbamazepine may decrease the effectiveness of OCP. MS patients with decreased mobility should be warned about the risk of thrombosis with OCPs. Therefore, alternative methods of birth control should be discussed.^{273 - 274, level III}

Recommendation 40

- Pre-pregnancy counselling should be given to women with multiple sclerosis (MS) in the childbearing age.
- Steroids should be avoided in the first trimester of pregnancy of MS patients; however the benefit and risk need to be carefully assessed. Methylprednisolone may be offered to MS patients with acute relapse in second and third trimesters.
- Disease Modifying Therapy should not be used in MS patients who are pregnant or breast-feeding.

15.2 Anaesthesia

Currently, there is lack of evidence on the effect of anaesthesia in MS patients. Therefore, general principles on the use of anaesthesia should be applied pre-, intra- and post-operatively. DMT used in MS needs to be reviewed during pre-operative anaesthetic consultation. There is no evidence to suggest one route (spinal, epidural or general anaesthesia) or any particular agent of anaesthesia is preferable or may lead to MS exacerbation.^{282, level III}

15.3 Immunisation

Tetanus^{283, level II-2} and Hepatitis B vaccines^{284, level II-2} do not increase risk of developing MS. Hepatitis B, influenza, tetanus and diphtheria-tetanus/diphtheria-tetanus-pertussis vaccines do not increase the risk of relapse of MS.^{285, level II-2} No evidence is available for other vaccines.

Caution needs to be exercised in patients on fingolimod, natalizumab and mitoxantrone when considering the use of live attenuated vaccines.

16. IMPLEMENTING THE GUIDELINES

It is important to standardise the management of MS at all healthcare levels in Malaysia by using an evidence-based CPG. This aims to prevent long-term morbidity and mortality.

16.1 Facilitating and Limiting Factors

Existing facilitators for application of the recommendations in the CPG include:

- i. wide dissemination of the CPG to healthcare providers (hardcopies and softcopies)
- ii. regular MS update for healthcare providers

Existing barriers for application of the recommendations of the CPG are:

- i. poor understanding/limited knowledge of MS issues among patients/carers and healthcare providers
- ii. insufficient resources in the management of MS particularly in the expertise (doctors and allied health) and diagnostic tools
- iii. variation in treatment practice and preferences
- iv. lack of active involvement of government and non-governmental organisations
- v. lack of co-ordinated referral and follow-up system

16.2 Potential Resource Implications

To implement the CPG, there must be strong commitment to:

- i. ensure widespread distribution of the CPG to healthcare providers
- ii. initiate training (with adequate funding) of healthcare providers ensuring information is up-to-date
- iii. ensure availability of highly specialised diagnostic tools and trained manpower in MS management including multidisciplinary team at different levels of healthcare
- iv. ensure availability of drugs to treat MS
- v. ensure widespread distribution of updated patient education materials

To assist in the implementation of the CPG, the following is proposed as **clinical audit indicator for quality management**:-

$$\text{Percentage of RRMS patients prescribed with IFN}\beta \text{ as first-line treatment} = \frac{\text{Number of RRMS patients prescribed with IFN}\beta \text{ as first-line treatment in a period}}{\text{Total number of RRMS patients in the same period}} \times 100\%$$

Implementation strategies will be developed following the approval of the CPG by MoH. They are such as a Quick Reference and a Training Module.

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Appendix 1

Example of Search Strategy

The following MeSH terms or free text terms were used either singly or in combination, search was limit to English, human and 1998 to current:-

1. Multiple Sclerosis/
2. (multiple adj1 sclerosis).tw.
3. 1 or 2
4. Recurrence/
5. recurrence*.tw.
6. relapse*.tw.
7. 4 or 5 or 6
8. acute.tw.
9. 7 and 8
10. 3 and 9
11. Methylprednisolone/
12. Methylprednisolone.tw.
13. Methylprednisolone acetate.tw.
14. 11 or 12 or 13
15. Prednisolone/
16. Prednisolone.tw.
17. 15 or 16
18. Plasma Exchange/
19. (plasma adj1 exchange*).tw.
20. 18 or 19
21. Plasmapheresis/
22. plasmapheresis.tw.
23. 21 or 22
24. Immunoglobulin/
25. immunoglobulin*.tw.
26. (immune adj1 globulin*).tw.
27. 24 or 25 or 26
28. 10 and 14 or 17
29. limit 28
30. 10 and 20 or 23
31. limit 30
32. 10 and 27
33. limit 32

Appendix 2

Clinical Questions

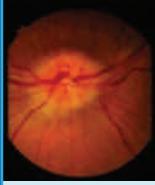
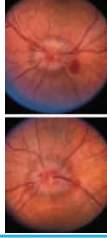
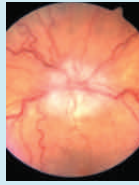
1. What is the epidemiology of MS?
2. What are the risk factors for MS?
3. What is CIS, acute relapse in MS and in MS?
4. What is the natural history/progression of MS?
5. What are the clinical features of MS?
6. What is optic neuritis and transverse myelitis?
7. In the diagnosis of MS, what is the sensitivity/specificity of:
 - McDonald criteria
 - oligoclonal bands/evoked potentials
8. What are the differential diagnoses of MS?
9. What is the sensitivity/specificity of anti-aquaporin 4 in diagnosing NMO?
10. What is the effectiveness of MRI brain and spine in:
 - diagnosing MS
 - predicting conversion of CIS to CDMS
11. How is disease progression in MS monitored?
12. In acute relapse of MS, are the following medication effective and safe:
 - high dose IV steroids
 - high dose IV steroids compared with oral steroids
 - plasma exchange
 - IVIG
13. In MS, are the following medications effective and safe as DMT:

- interferons beta	- fingolimod	- rituximab
- methotrexate	- glatiramer	- natalizumab
- cyclophosphamide acetate	- mycophenolate mofetil	
- teriflunomide	- alemtuzumab	- IVIG
- azathioprine	- dimethyl fumarate	- mitoxantrone
	- steroids	- vitamin D
14. What are the indications for starting DMT in MS?
15. What is the effectiveness and safety of DMT in CIS?
16. What are effective and safe therapies for treatment failure in MS?
17. What is the effective and safe treatment for progressive MS?
18. In MS, what is the effective and safe treatment for the following MS-related symptoms:

- rehabilitation programmes	- visual problems	- pain
- ataxia	- swallowing and speech difficulties	- paroxysmal symptoms
- fatigue	- bladder dysfunction	- sexual dysfunction
- spasticity and paralysis - bowel problem		
19. Is rehabilitation programmes effective and safe in MS?
20. What is the epidemiology and treatment for cognitive impairment/memory problem/depression/bipolar disorder/psychosis in MS?
21. Does MS or its treatment affect pregnancy/breastfeeding in women?
22. Is anaesthesia/immunisation safe in MS?
23. When should patients with suspected MS/relapsed MS be referred and followed-up?

Appendix 3

Differential Diagnosis of Optic Disc Swelling

Diagnosis	Visual Acuity	Colour Vision	RAPD	Visual Field Defect	Optic Disc Appearance	Retinal Veins	Peripapillary Retinal Haemorrhages	Symmetry	Picture
ON	Markedly decreased	Red-green defect	+	Central or centrocaecal scotoma	Hyperaemic, blurred margins	Normal or slightly dilated	+/-	Usually unilateral	
Papilloedema	Normal or mild blurring of vision	Normal	-	Normal or enlarged blind spots	Hyperaemic, swollen, blurred margins Peripapillary retinal folds	Loss of venous pulsation; dilated and tortuous	++	Bilateral	
Anterior Ischaemic Optic Neuropathy	Markedly decreased	Red-green defect	+	Altitudinal defects	Segmental disc oedema with pallor	Focal dilated vessels	+	Usually unilateral	

Adapted: Agarwal PC, Gupta S, Thakur A, et al. Optic disc oedema: a diagnostic dilemma. BMJ Case Rep. 2011 Oct 4;2011 . pii: bcr0720114473

Appendix 4

Treatment of NMO/NMOSD^{53, level III; 286 - 287, level II-3; 288; 289, level III}

1. Treatment of acute relapses
2. Prevention of relapses
3. Management of symptoms and rehabilitation (similar to symptomatic management in MS)

Treatment of acute relapse

- IV methylprednisolone 1 g daily for 5 days followed by 1 mg/kg body weight for a month, and then gradual tailing off over 6 - 12 months.
- Refractory relapses benefit from early plasmapheresis usually initiated in the second week (after high dose steroids) if no recovery is seen and deficits are severe. Five to seven exchanges over a 2-week period has been tried.

Prevention of relapses

In NMOSD, prevention of relapses is usually achieved by immunosuppressants, though there is limited high quality evidence for this. Table below shows the common immunosuppressants used in achieving stabilisation of disease by relapse prevention in NMOSD. After a relapse, steroids are given at 1 mg/kg/day from up to 1 - 3 months, then slowly tapered over 6 - 12 months. However, some patients need a low dose of maintenance steroids between 10 - 20 mg to maintain remission.

Disease modifying therapies such as interferons, fingolimod and natalizumab should not be used in patients with NMOSD as it has been shown to produce an exacerbation of the disease.^{290 - 292, level IIII}

Therapy	Drug Name	Regimen	Monitoring/Side effects
First-line therapy	Azathioprine	2 - 3 mg/kg/day oral	Thiopurine methyl-transferase activity, mean corpuscular volume monthly, LFT for first 6 months then twice yearly, maintain absolute neutrophil counts >1000 cells/ μ L (switch to rituximab/MMF if side effects not tolerable or treatment failure)
	or MMF	1 - 3 g/day oral	Monthly LFT for first 6 months then twice yearly, target absolute lymphocyte count 1 - 1.5 K/ μ L (switch to rituximab if treatment failure)
With or without	Prednisolone (\pm immunosuppressants azathioprine/MMF)	1 mg/kg/day 1 - 3 months, tapered over 6 - 12 months, then switched off OR maintenance of 10 - 30 mg/day daily and taper after one year	Refer to drug table below
	Rituximab	1) IV 375 mg/m ² weekly for 4 weeks OR 2) 1000 mg infused twice, with 2 week interval in between 3) Repeated every 6 months	Each pair can be given every 6 months without monitoring of CD 19 counts or by following CD 19 counts and redosing when it exceeds 1%. Monthly CD 19 counts starting immediately post-infusion. Early relapses do not mean failure of treatment. (switch to azathioprine/MMF if treatment failure)
Second-line therapy	Methotrexate	7.5 - 17.5 mg weekly	Check for liver toxicity every 3 months Folate supplementation
	Cyclophosphamide*	7 - 25 mg/kg every month for 6 months (especially with SLE/SS)	Refer to drug table below.
	Mitoxantrone*	IV 12 mg/m ² monthly for 6 months, followed by 12 mg/m ² every 3 months for 9 months	Refer to drug table below (*switch to azathioprine/MMF /rituximab if treatment failure) or go to third-line therapies

Therapy	Drug Name	Regimen	Monitoring/Side effects
Third-line therapy	Tocilizumab	IV 4 mg/kg once every 4 weeks	Neutropaenia, risk of infections e.g. herpes, raised liver enzymes Monitor for meningococcal meningitis (meningococcal vaccination 2 weeks before first dose), paroxysmal nocturnal haemoglobinuria and allergic reactions
	Eculizumab	<ul style="list-style-type: none"> • 600 mg weekly for first 4 weeks, followed by • 900 mg for fifth dose 1 week later, then • 900 mg every 2 weeks thereafter 	
	Combination therapy*	*Combination therapy refers to rituximab and methotrexate/IVIG or induction with mitoxantrone followed by azathioprine or MMF or intermittent PE with immunosuppressants	-

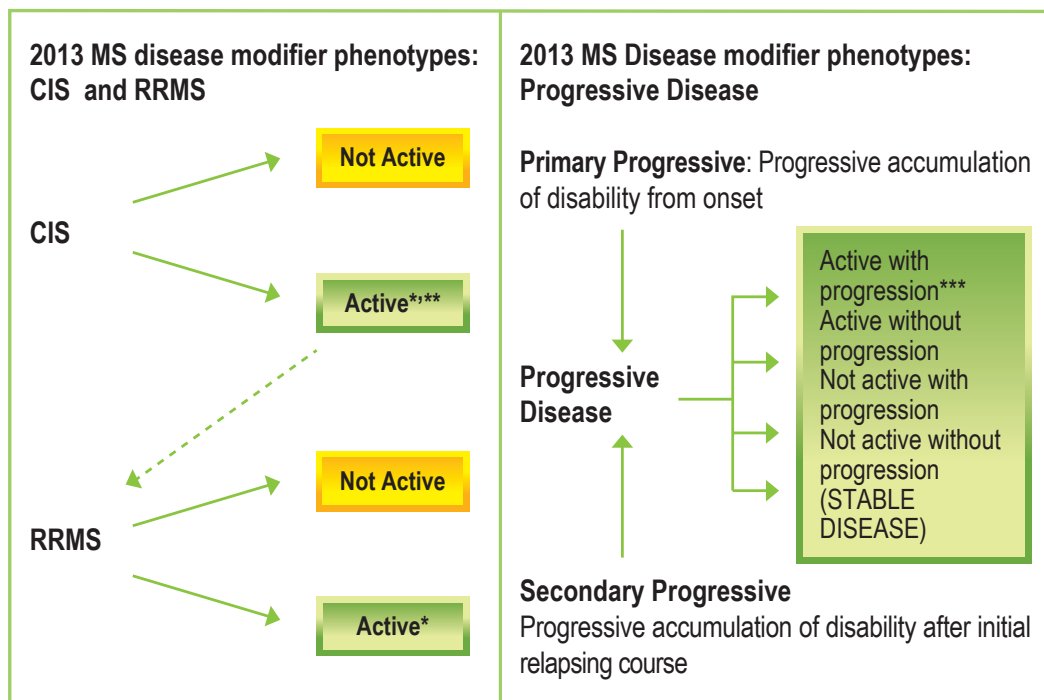
Appendix 5

New NMOSD Diagnostic Criteria for Adult Patients

Criteria for NMOSD with AQP4-IgG positive	<ol style="list-style-type: none"> 1. At least one core clinical characteristic 2. Positive test for AQP4-Ig G using best available detection method (cell based assay strongly recommended) 3. Exclusion of alternative diagnoses
Diagnostic criteria for NMOSD without AQP4-Ig G or NMOSD with unknown AQP4-IgG status	<ol style="list-style-type: none"> 1. At least two core clinical characteristics occurring as a result of one or more clinical attacks and meeting all the following requirements: <ul style="list-style-type: none"> - at least one core clinical characteristic must be ON, acute myelitis with LETM or area postrema syndrome - dissemination in space (≥ 2 different core clinical characteristics) - fulfilment of additional MRI requirements as applicable 2. Negative tests for AQP4-IgG using best available detection method or testing unavailable 3. Exclusion of alternative diagnoses
Core clinical characteristics	<ol style="list-style-type: none"> 1. ON 2. Acute myelitis 3. Area postrema syndrome: episode of otherwise unexplained hiccups/nausea and vomiting 4. Acute brainstem syndrome 5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic lesions 6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions.
Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status	<ol style="list-style-type: none"> 1. Acute optic neuritis: requires brain MRI showing: <ul style="list-style-type: none"> - normal findings or only non specific white matter lesions - OR optic nerve MRI with T2-hyperintense lesion or T1-weighted Gd-enhancing lesion extending $> \frac{1}{2}$ optic nerve length or involving the optic chiasm 2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥ 3 contiguous segments (LETM) or ≥ 3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis 3. Area postrema syndrome- requires dorsal medulla/area postrema lesions 4. Acute brainstem syndrome: requires associated periependymal brainstem lesions

Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85(2):177-189

2013 MS Disease Modifier Phenotypes



*Activity is determined by clinical relapses and/or MRI activity (contrast-enhancing lesions; new or enlarging T2 lesions assessed at least annually); if assessments are not available the activity is "indeterminate".

**CIS if clinically active and fulfils current MS diagnostic criteria becomes RRMS.

***Progression measured by clinical evaluation, assessed at least annually. If assessments are not available, activity and progression "indeterminate".

Source: Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014 Jul 15;83(3):278-86

Appendix 6

Kurtzke Expanded Disability Status Scale (EDSS) for Neurologic Assessment

Scale	Description
0	Normal neurological exam [all grade 0 to Functional system (FS)]
1.0	No disability, minimal signs in one FS (i.e. grade 1)
1.5	No disability, minimal signs in one FS (more than one FS grade 1)
2.0	Minimal disability in one FS (one FS grade 2, other 0 or 1)
2.5	Minimal disability in two FS (two FS grade 2, others 0 to 1)
3.0	Moderate disability in one FS (one FS grade 3, others 0 to 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 to 1)
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps, able to walk without aid or rest some 500 metres
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance: characterised by relatively severe disability usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps, able to walk without aid or rest 300 metres
5.0	Ambulatory without aid or rest for about 200 metres; disability severe enough to impair full daily activities (e.g. to work a full day without special provisions). (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0.)
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0.)
6.0	Intermittent or unilateral constant (cane, crutch, braces) required to walk about 100 metres with or without resting. (Usual FS equivalents are combinations with more than two FS grade 3+.)
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 metres without resting. (Usual FS equivalents are combinations with more than two FS grade 3+.)
7.0	Unable to walk beyond approximately five metres even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone.)
7.5	Unable to take more than a few steps; restricted to wheelchair, may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorised wheelchair. (Usual FS equivalents are combinations with more than one FS grade 4+.)
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms. (Usual FS equivalents are combinations generally grade 4+ in several systems.)
8.5	Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions. (Usual FS equivalents are combinations generally 4+.)
9.0	Helpless bed patient can communicate and eat. (Usual FS equivalents are combinations generally 4+.)
9.5	Totally helpless bed patient; unable to communicate effectively or eat or swallow. (Usual FS equivalents are combinations almost all grade 4+.)
10.0	Death due to MS

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory and the precise step number is defined by the Functional System score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation and usual equivalents in Functional Systems scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS. (For Functional System score, please look at source reference below)

Source: Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983 Nov;33(11):1444-52

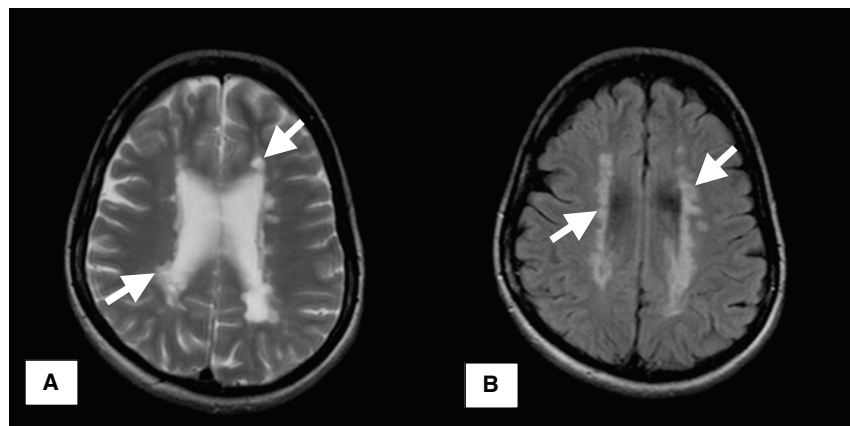
Appendix 7

Neuroimaging Features in MS

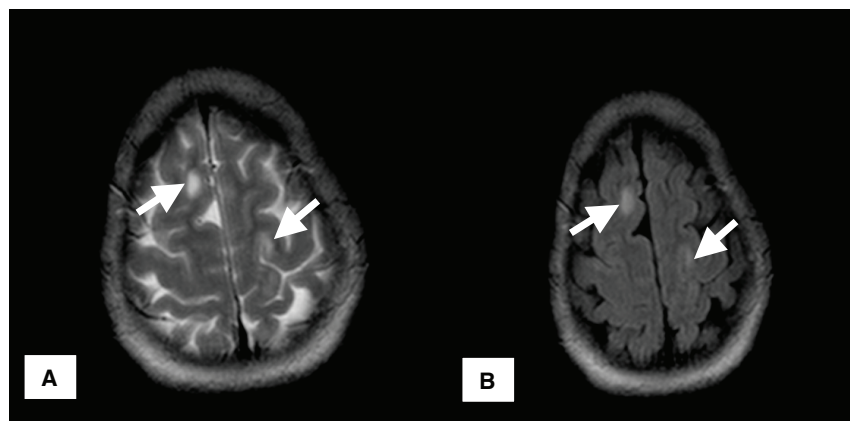
a. DIS

Types of Focal Lesions based on Location in the Brain^{Joost et al., 2002, level II-2}

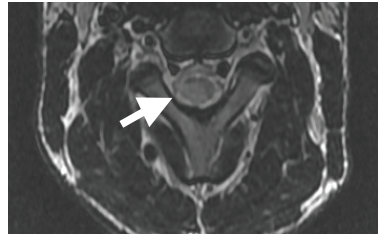
Location	Definition
Juxtacortical	Lesion touches or extends into the grey matter of the cortex
Periventricular	Lesion is adjacent to ventricles or is less than 1 cm from them as measured from the centre of the lesion
Infratentorial	(self explanatory)
Deep white matter	Lesions that do not fulfil one of the previous criteria



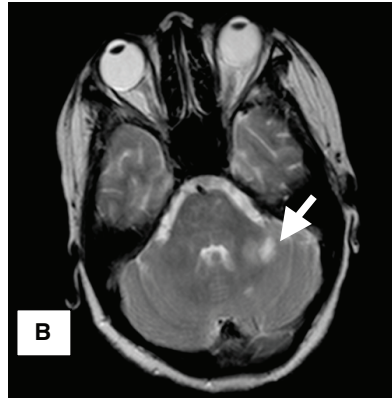
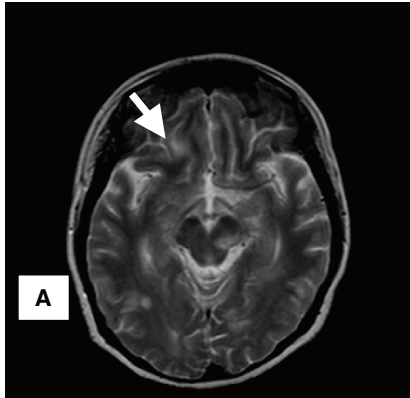
Axial T2 (A) and Axial FLAIR (B) images showing multiple periventricular lesions which are touching the ventricular borders



Axial T2 (A) and axial FLAIR (B) images: Arrows pointing to juxtacortical lesions.

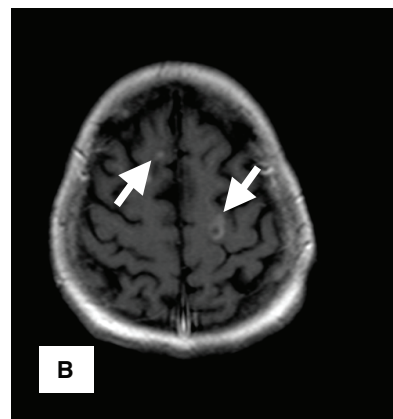
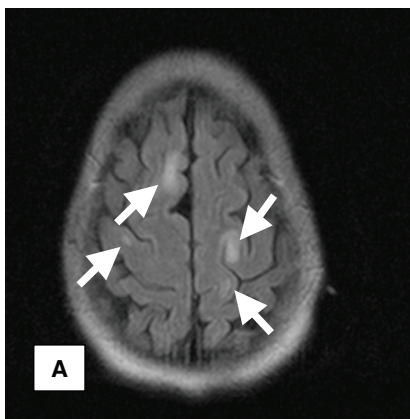


Sagittal T2 (A) image demonstrates lesion within the spinal cord (arrow). The same lesion as seen on the axial T2 (B) image, occupying only part of the spinal cord.



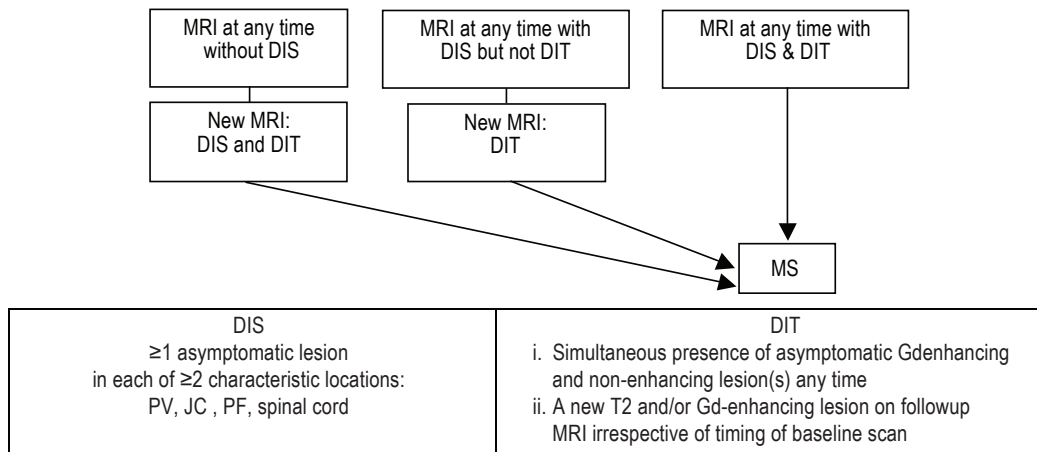
Axial T2 image shows (A) an infratentorial right midbrain lesion (arrow) and (B) a left middle cerebellar peduncle lesion.

b. DIT



Axial FLAIR (A) images show the presence of four lesions (two on the right and two on the left side). On axial Gd-enhanced T1 (B) image only two lesions show enhancement (arrowheads) whereas the other two do not. This presence of enhancing, as well as non-enhancing lesions in a single MRI indicates dissemination in time.

Diagnostic Algorithm of Patients with Typical CIS



This algorithm only applies to patients with typical CIS, aged 14 to 50 years and after having performed a complete diagnostic work up.

PV=periventricular; JC=juxtacortical; PF=posterior fossa

Source: Montalban X, Tintoré M, Swanton J, et al. MRI criteria for MS in patients with clinically isolated syndromes. *Neurology*. 2010 Feb 2;74(5):427-34

MRI Criteria for Dissemination in Space and Time for MS

DIS/DIT	McDonald 2005	McDonald 2010
DIS (on either baseline or follow-up MRI)	3 or more of :	≥1 lesion in each of ≥2 characteristics location:
	≥ 9 T2 lesions or ≥1 Gd-enhancing lesions	PV
	≥ 3 PV lesions JC	JC
	≥ 1 JC lesions PF	PF
	≥ 1 PF lesions or spinal cord lesion	Spinal cord
	Any number of cord lesions can be included in the total lesion count	All lesions in symptomatic regions excluded in BS and SC syndromes
DIT	1) ≥ 1 Gd-enhancing lesion at least 3 months after the CIS onset (if not related to CIS)	1) Simultaneous presence of asymptomatic Gd-enhancing and nonenhancing lesions at any time
	2) A new T2 lesion with reference to a baseline scan obtained at least 30 days after CIS onset	2) A new T2 and/or Gd-enhancing lesion on follow-up MRI irrespective of timing of baseline scan

Abbreviation: BS = brainstem; DIS = dissemination in space; DIT = dissemination in Time; Gd= gadolinium; JC= juxtacortical; PF= posterior fossa; PV= periventricular; SC= spinal cord

Appendix 8**Bladder Diary**

Name:.....

Registration No:.....

Mode of bladder management:.....

Bladder medications:.....

Date	Time (am/pm)	Fluid intake (mls)	Voided volume(mls)	Leaking (mls)	Comment

Appendix 9

Drug Dosages and Side Effects in MS

Acute Treatment					
Drug	Indication	Dosages	Side Effects	Contraindications	Precautions and Monitoring
IV methylprednisolone Pregnancy category: C	Acute relapse	500 - 1000 mg od for 3 - 5 days (15 - 30 mg/kg)	Transient leucocytosis, oedema, hypertension, infections, gastrointestinal (GI) effects, muscle weakness, hirsutism, acne, hyperpigmentation, arthralgia, osteoporosis	Serious infections Administration of live virus vaccines.	Tuberculosis Hypertension Congestive heart failure Liver failure Renal failure Diabetes mellitus Osteoporosis Glaucoma Severe affective disorders Epilepsy Peptic ulcer disease Thyroid disease History of steroid myopathy
		500 mg od for 5 days			
Oral methylprednisolone Pregnancy category: C					
Oral prednisolone Pregnancy category: C	ON	0.5 - 1 mg/kg/day Oral taper as per ONTT			
Maintenance Treatment (Drug Listed According To Alphabetical Order)					
Drug	Indication	Dosages	Side Effects	Contraindications	Precautions and Monitoring
IV Alemtuzumab Pregnancy category: C	Active RRMS	12 mg od for 5 consecutive days, followed by 3 days infusion at 12 and 24 months	Infusion-related reactions, idiopathic thrombocytopenia, thyroid disorder, increase risk of herpes infection, neutropaenia/lymphopaenia, anaemia/pancytopenia, renal failure (Good pastures syndrome), cardiac/respiratory events, severe myelosuppression, haematological toxicity	Active systemic infection or underlying immune-deficiency	Always pre-medicate with oral or IV corticosteroid, oral antihistamine and paracetamol before first dose and during dose increases. Anti-infective prophylaxis (IV acyclovir) is recommended from the start of the treatment till completion. Monitor full blood count (FBC), renal function test and urine analysis monthly. Monitor thyroid function test (TFT) 3-monthly. Monitor FBC and TFT for 48 months after the last infusion.

Maintenance Treatment (Drug Listed According To Alphabetical Order)																								
Drug	Indication	Dosages	Side Effects	Contraindications																				
IV Cyclophosphamide (CYC) Pregnancy category:D	Moderate to severe refractory and aggressive RRMS	700 - 800 mg/m2 monthly for the first year, and then bimonthly for the second year with re-evaluation every 6 months Max lifetime dose: 80 - 100 g First dose of CYC <table><tr><td>WBC/mm³</td><td>Dose</td></tr><tr><td>>4000</td><td>100%</td></tr><tr><td>3000 - 4000</td><td>75%</td></tr><tr><td>2000 - 3000</td><td>50%</td></tr><tr><td><2000</td><td>Skip</td></tr></table> Next dose of CYC <table><tr><td>Nadir WBC/mm³</td><td>Dose (mg/m²)</td></tr><tr><td>1500</td><td>Full dose</td></tr><tr><td>2000</td><td></td></tr><tr><td><1500</td><td>Decrease by 100 - 200 mg/m²</td></tr><tr><td>>2000</td><td>Increase by 100 - 200 mg/m²</td></tr></table>	WBC/mm ³	Dose	>4000	100%	3000 - 4000	75%	2000 - 3000	50%	<2000	Skip	Nadir WBC/mm ³	Dose (mg/m ²)	1500	Full dose	2000		<1500	Decrease by 100 - 200 mg/m ²	>2000	Increase by 100 - 200 mg/m ²	Haemorrhagic cystitis, nausea, vomiting, oral mucosal ulceration, thrombocytopaenia, leucopaenia, anaemia, non-haemorrhagic cystitis and/or bladder fibrosis, gonadal suppression, skin and nail pigmentation, alopecia, dermatitis, myelosuppression, increased risk of developing acute leukaemias, amenorrhoea	Bone-marrow aplasia Acute infection
WBC/mm ³	Dose																							
>4000	100%																							
3000 - 4000	75%																							
2000 - 3000	50%																							
<2000	Skip																							
Nadir WBC/mm ³	Dose (mg/m ²)																							
1500	Full dose																							
2000																								
<1500	Decrease by 100 - 200 mg/m ²																							
>2000	Increase by 100 - 200 mg/m ²																							
				Precautions and Monitoring																				
				Blood disorders Elderly or debilitated patients Renal/liver impairment History of cytotoxic agents use Bladder dysfunction Secondary malignancy Maintain adequate hydration and frequent micturition to reduce the risk of cystitis (3 L of fluid on the day of and the day after treatment). Premedication for cyclophosphamide as per standard pre-infusion protocol Contraception before planning cyclophosphamide and pregnancy test prior to dosing Monitor haematological profile and presence of red blood cells in urine regularly. Cystoscopy: if abnormal; yearly after 3 years of treatment Seminal fluid analysis when accumulative dose >300 mg/kg Induction 5 µg/kg/day for 4 days with Granulocyte-Colony Stimulating Factor coverage if absolute neutrophil count <1.0 x 10 ⁹ /L.																				

Maintenance Treatment (Drug Listed According To Alphabetical Order)					
Drug	Indication	Dosages	Side Effects	Contraindications	Precautions and Monitoring
Oral Dimethyl fumarate Pregnancy category:C	RRMS	Initial, 120 mg bd for 7 days, then increase to 240 mg bd	Flushing (dose-related), rash, abdominal pain, diarrhoea, nausea, vomiting, lymphocytopenia	Hypersensitivity	PML (1 case reported in Oct 2014, caution in patients with persistent lymphopaenia) Pre-medication, consider non-enteric-coated aspirin up to 325 mg orally 30 minutes prior to DMF to reduce flushing Take with food to decrease flushing. Swallow capsule whole; do not cut, chew or sprinkle on food. Monitor FBC with lymphocyte count; at baseline, after 1 month, then every 3 to 6 months.
Oral Fingolimod Pregnancy category: C	RRMS	0.5 mg od	Bradycardia, reversible lymphopaenia, increased liver enzymes, infections (influenza, herpes-varicella zoster virus (VZV), hypertension, macular oedema, decrease forced expiratory volume in 1 second FEV ₁ , alopecia	Patients who in the last 6 months experienced myocardial infarction (MI), unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalisation or class III/IV heart failure Mobitz type II 2 nd - or 3 rd -degree atrioventricular (AV) block or sick sinus syndrome (unless patient has a functioning pacemaker) Baseline QTc interval	Cardiology consultation if risk factors or abnormal baseline electrocardiogram (ECG) results Ophthalmological evaluation prior to treatment initiation and at 3 - 4 months and patients with uveitis and diabetes mellitus (DM) require more frequent examination Varicella Zoster Vaccination prior to initiation of treatment in VZV antibody negative patients postpone treatment for 1 month after VZV vaccination. Lymphopaenia may continue up to 2 months after discontinuation of therapy (precaution if reinitiate). First dose observation Perform ECG prior to first dose and

Maintenance Treatment (Drug Listed According To Alphabetical Order)					
Drug	Indication	Dosages	Side Effects	Contraindications	Precautions and Monitoring
				<p>≥500 ms.</p> <p>Treatment with class Ia beta blockers or class III antiarrhythmic drugs</p>	<p>end of 6-hours observation period (continuous ECG monitoring if post-dose symptomatic bradycardia occurs).</p> <p>Monitor heart rate and blood pressure hourly during the 6-hours observation period.</p> <p>Extended monitoring for at least 2 hours if heart rate is lowest at 6 hours after first administered dose or <45 beats/minute</p> <p>Monitoring should continue overnight or until problem has resolved for patients developing bradycardia, QTc interval ≥500 ms or new onset second degree or higher grade AV block.</p> <p>Isoproterenol and atropine are recommended in symptomatic bradycardia.</p>
IV Mitoxantrone Pregnancy category: D	SPMS RRMS	<p>12 mg/m² by IV infusion over 5 - 15 min</p> <p>Initially, dose may be given once every 3 month provided neutrophil count is >1500 cells/mm³ and LVEF >50%</p>	<p>Urinary tract infection, upper respiratory tract infection, infection/sepsis, headache, nausea, anorexia, fatigue, weakness, alopecia, amenorrhoea, haematologic disorders (leukaemia), elevated liver function test (LFT),</p>	<p>LVEF <50% or clinically significant reduction in LVEF</p> <p>Discontinue if extravasation occurs</p>	<p>Pre-existing myelosuppression</p> <p>Perform periodic blood counts.</p> <p>Hepatic impairment</p> <p>Monitor cardiac function - ECG before starting and yearly up to 2 - 5 years for delayed cardiotoxicity.</p>

Maintenance Treatment (Drug Listed According To Alphabetical Order)					
Drug	Indication	Dosages	Side Effects	Contraindications	Precautions and Monitoring
IV Natalizumab Pregnancy category:C	RRMS	Total lifetime cumulative dose: <140 mg/m ² 300 mg infused over 1 hour, given at 4-weekly intervals	blue urine, increased blood urea nitrogen and creatinine, diarrhoea Infusion reactions, hepatotoxicity, anaphylaxis, PML, immune reconstitution syndrome, herpes virus infection of CNS	Hypersensitivity	Encephalitis and meningitis (caused by herpes simplex and varicella zoster) - discontinue if confirmed Dose interruptions (recommencing therapy may increase risk of hypersensitivity reactions) Monitor patients for any new sign or symptom that may be suggestive of PML and discontinue therapy at the first sign or symptom suggestive of PML. Increased risk of PML if <ul style="list-style-type: none"> • anti-JCV antibody positive • prior antineoplastic or immunosuppressant therapy use • immunocompromised • prolonged duration of therapy with natalizumab beyond 2 years Baseline FBC and LFT monitoring, then every 6 months JCV serology and brain MRI every 6 months in seronegative patients Seropositive patients or patients who are possibly symptomatic for PML, brain MRI every 3 months

Maintenance Treatment (Drug Listed According To Alphabetical Order)					
Drug	Indication	Dosages	Side Effects	Contraindications	Precautions and Monitoring
IV Rituximab Pregnancy category:C	RRMS	1 g at day 1 and 1 g at day 15 every 6 - 12 months Initial infusion: Start at 50 mg/hour, increase rate by 50 mg/hour every 30 min till 400 mg/hour Subsequent infusions provided that initial infusion is tolerated: Start at 100 mg/hour, increase rate by 100 mg/hour every 30 min till maximum rate 400 mg/hour	Infusion-related reactions, flushing, fever, pruritus, headache, rigors, bronchospasm, angioedema, transient hypotension, skin rashes, dyspnoea, thrombocytopaenia, neutropaenia, anaemia, renal failure, exacerbation of heart failure and angina pectoris, reversible interstitial pneumonia and interstitial fibrosis, reactivation of hepatitis B virus	Hypersensitivity to murine proteins Patients with active, severe infections Severely immunocompromised state Concomitant use with live viral vaccines	Pre medication before giving rituximab with IV methylprednisolone 125 mg, IV chlorpheniramine 10 mg, tablet paracetamol 1 g Monitor FBC regularly or hepatitis in hepatitis B carriers. Discontinue therapy if viral hepatitis develops. Cardiac monitoring should be performed during and after all infusions. Pre-existing pulmonary conditions should be closely monitored for possible infusion-related toxicity. Monitor renal function Toxic epidermal necrolysis (TEN) Stevens-Johnson syndrome (SJS) Severe mucocutaneous reactions
Oral Teriflunomide Pregnancy category X	RRMS	7 or 14 mg od	Hair thinning, diarrhoea, nausea, increased liver enzymes, influenza, hypertension, SJS, TEN, neutropaenia, agranulocytosis, pancytopenia, thrombocytopaenia, liver failure, peripheral neuropathy, raised serum creatinine	Severe hepatic impairment Concomitant use with other hepatotoxic drugs may increase risk of liver injury Pregnancy or potential for pregnancy Pregnancy must be avoided during teriflunomide treatment or prior to the completion of the drug	Pre-existing liver disease Major birth defects may occur if used during pregnancy. Do not initiate treatment in patients with active acute or chronic infections. Concomitant use with immunosuppressive or immunomodulating therapies may increase risk of haematologic toxicity. Concomitant use of live vaccines is not recommended during or

Maintenance Treatment (Drug Listed According To Alphabetical Order)					
Drug	Indication	Dosages	Side Effects	Contraindications	Precautions and Monitoring
				elimination procedure after treatment	potentially following completion of therapy. Increased blood pressure have been reported; monitor blood pressure (including baseline) regularly Baseline and regular FBC every 6 months Baseline and monthly LFT for 6 months, then every 6 months Baseline pregnancy test and tuberculosis Refer to Chapter on Treatment (Teriflunomide) on wash-out period and issues related to pregnancy.
IM Interferon beta-1a Pregnancy category: C	RRMS	30 µg once weekly	Injection site reactions, flu-like symptoms, fever, fatigue, headache, leukopaenia, depression, vomiting, nausea, abdominal pain, increased liver enzymes, myalgia, arthralgia, rigors, asthenia, hypertonia-increase spasticity, pruritus, rash, neutropaenia, lymphopaenia, thrombocytopaenia, anaemia, thyroid dysfunction, chills,	Severe depressive disorders and/or suicidal ideation Hypersensitivity to natural or recombinant interferon beta	Caution when used in patients with depression or psychiatric disorders, or other CNS diseases, poorly controlled thyroid dysfunction, pulmonary disease, DM, renal or hepatic impairment, cardiac disorders, myelosuppression, auto-immune diseases, coagulation disorders, or a history of these conditions Pre-medicate with paracetamol 30 minutes before administration. Topical methods to treat injection site reactions if necessary Dose titration needed during initiation.
SC Interferon beta-1a Pregnancy category: C	RRMS	44 µg 3 times/week			
SC Interferon beta-1b Pregnancy category: C	RRMS	250 µg every alternate day			
SC Pegylated interferon beta-1a Pregnancy category: C	RRMS	125 µg every 2 weeks			

Maintenance Treatment (Drug Listed According To Alphabetical Order)					
Drug	Indication	Dosages	Side Effects	Contraindications	Precautions and Monitoring
			peripheral oedema, insomnia		Monitor hepatic and renal function regularly. Monitor FBC and LFTs at baseline at 1, 3 and 6 months, then periodically. If abnormal, temporarily discontinue treatment rechallenge at lower dose.

Symptomatic Treatment (Drug Listed According To Indication)					
Drug	Indication	Dosages	Side Effects	Contraindications	Precautions and Monitoring
Oral Amantadine Pregnancy category: C	Fatigue	100 mg od, then increased to 100 mg bd after a week or more Titrate according to response Max dose: 400 mg daily	Hallucinations, confusion, ataxia, orthostatic hypotension, blood dyscrasias, urinary retention, GI disturbances, livedo reticularis, congestive heart failure, convulsions	Hypersensitivity Epilepsy or other seizure disorders Severe renal impairment Gastric ulceration	Cardiovascular disease Liver/renal impairment Recurrent eczema Elderly Withdrawal of the drug should be gradual
Oral Baclofen Pregnancy category: C	Spasticity	Initially, 5 mg tds for 3 days, may increase 5 mg per dose every 3 days, until either 20 mg tds is reached or until desired effect is obtained Max: 80 mg daily	Sedation, ataxia, dizziness, headache, confusion, hallucinations, GI symptoms	Hypersensitivity	Seizure disorder Confusional/psychotic states Respiratory depression Hepatic impairment Renal impairment Elderly Avoid sudden withdrawal
Oral Tizanidine Pregnancy category: C	Spasticity	Initially 2 mg on night, then titrate according to response, 2 - 4 mg tds Max dose: 36 mg/day (limited experience with dose > 24 mg/day)	Somnolence, hypotension, dizziness, fatigue, headache, anxiety, nausea, dryness of mouth, GI disturbances, bradycardia, transient increase in serum transaminases, hallucinations	Severe hepatic dysfunction Concomitant use with ciprofloxacin or fluvoxamine	Liver/renal insufficiency Elderly Avoid abrupt withdrawal of therapy. Monitor LFT regularly. Stop treatment if liver enzymes are raised persistently >3 times upper limit of normal range.
Oromucosal Spray Nabiximols	Spasticity	Titration period necessary	Dizziness, fatigue, anorexia, change in appetite, depression,	Hypersensitivity Known/suspected history or family history	History of epilepsy/recurrent seizures Psychiatric symptoms

Symptomatic Treatment (Drug Listed According To Indication)					
Drug	Indication	Dosages	Side Effects	Contraindications	Precautions and Monitoring
Pregnancy category: B2		<p>Number/timing of sprays will vary between patients</p> <p>Number of sprays increased daily according to Summary of Product Characteristics table, up to maximum of 12 sprays per day with minimum 15 minutes between sprays</p>	<p>disorientation, dissociation, euphoria, amnesia, balance disorder/fall, disturbance in attention, dysarthria, lethargy, somnolence, blurred vision, vertigo, constipation, diarrhoea, dry mouth, mouth ulceration, nausea, oral discomfort/pain, vomiting, asthenia, feeling drunk</p>	<p>of schizophrenia/other psychotic illness</p> <p>History of severe personality disorder/other significant psychiatric disorders other than depression associated with MS</p> <p>Do not continue spraying onto sore or inflamed mucous membrane</p> <p>Not recommended in patients with serious cardiovascular disease</p>	<p>Liver/renal impairment</p> <p>Risk of falls</p> <p>Elderly</p> <p>Reliable contraception during treatment and for 3 months after therapy discontinuation</p> <p>History of substance abuse may be more prone to abuse sativex</p> <p>Withdrawal symptoms tend to be limited to transient disturbances of sleep, emotion or appetite</p> <p>Monitor pulse rate and blood pressure following initial dosing titration.</p> <p>Perform regular inspection of oral mucosa in long-term administration and vary site of application.</p> <p>Advise patient to check legal status of medicine before travelling to other countries.</p> <p>Contains 50% volume for volume ethanol</p>
Botulinum Toxin Type A Pregnancy category: C	Spasticity	IM individualised dose based on patient size, extent, location of muscle movement, and response to prior treatment	Injection site reactions, muscle weakness, abnormal gait, fatigue, flu-like syndrome	Hypersensitivity	Subclinical or clinical evidence of marked defective neuromuscular transmission Concomitant use with aminoglycosides
	Overactive bladder	Intradetrusor: 30 injections of 6.7 units	Haematuria, urinary retention, pelvic pain, flu-like syndrome		Effects start after 2 weeks Follow-up at 2 weeks to review

Symptomatic Treatment (Drug Listed According To Indication)						
Drug	Indication	Dosages	Side Effects	Contraindications	Precautions and Monitoring	
		/ml for a total dose of 200 units per 30 ml: may consider treatment with diminishing effect but not sooner than 12 weeks from previous administration	flu-like syndrome		treatment outcome	
Oral Oxybutinin Pregnancy category: B	Detrusor overactivity	Immediate release 2.5 - 50 mg bd or tds Max: 5 mg qid if needed	Dry mouth, dry eyes, constipation, memory impairment, blurred vision, headache, dizziness, drowsiness, dry skin, rash	Urinary retention GI obstruction or atrophy Severe toxic megacolon Significant bladder outflow obstruction Glaucoma	Cognitive impairment Hepatic impairment Renal impairment Prostatic hyperplasia Hiatus hernia Reflux oesophagitis Ulcerative colitis Myasthenia gravis	
Oral Desmopressin Pregnancy category: B	Nocturnal diuresis Enuresis	200 - 400 µg at bedtime	Hyponatraemia, oedema, nausea, transient headache, nasal congestion, rhinitis, epistaxis, stuffiness, hypertension, water intoxication	Hypersensitivity Creatinine clearance <50 mL/min Decompensated cardiac failure with ongoing diuretic treatment Type IIb von Willebrand's disease and nephrogenic diabetes insipidus	Fluid and electrolyte imbalance Cardiovascular diseases Oedema Hypertension Cystic fibrosis	

Symptomatic Treatment (Drug Listed According To Indication)					
Drug	Indication	Dosages	Side Effects	Contraindications	Precautions and Monitoring
Oral Carbamazepine Pregnancy category: D	MS pain	Initial: 100 mg 1 - 2 times/day, may increase slowly Maintenance: 400 - 800 mg/day in 2 - 4 divided doses Max: 1200 mg/day	Dizziness, drowsiness, ataxia, blurred vision, nausea, vomiting, anorexia, leucopaenia, hyponatraemia, aplastic anaemia, hepatic failure, SJS, TEN	Hypersensitivity Bone marrow depression Porphyria	History of blood disorders or haematological reactions to other drugs Cardiovascular diseases Hepatic impairment Renal impairment Elderly
Oral Dronabinol Pregnancy category: C	MS pain	10 mg od	Euphoria, hypotension, palpitations, vasodilatation, abdominal pain, nausea, vomiting, dizziness, somnolence, hallucinations, ataxia, depression	Hypersensitivity to dronabinol, cannabinoid, sesame oil or any other components	History of substance abuse and risk of dronabinol abuse Cardiac disorders (hypotension, hypertension, syncope, tachycardia) Elderly May impair cognitive and motor performance May exacerbate psychiatric illness (mania, depression, schizophrenia) May lower the seizure threshold
Oral Duloxetine Pregnancy category: C	MS pain	Initially 30 mg od for 1 week, then increase to 60 mg od as tolerated Max dose: 120 mg od	Headache, somnolence, fatigue, dizziness, nausea, dry mouth, insomnia, diarrhea, decreased appetite, erectile dysfunction, hyperhidrosis, elevated liver enzymes	Concomitant use with MAOIs Hepatic impairment Severe renal impairment	Seizures Uncontrolled hypertension Renal impairment Concomitant use with antidepressants Hyponatraemia Hepatitis/increased liver enzymes Elderly Monitor for suicidal ideation/behaviour Monitor blood glucose

Symptomatic Treatment (Drug Listed According To Indication)					
Drug	Indication	Dosages	Side Effects	Contraindications	Precautions and Monitoring
Oral Gabapentin Pregnancy category: C	MS pain	300 - 3600 mg/day in divided doses Dose may increase in increments of 300 mg every 2 - 3 days	Dizziness, somnolence/sedation, ataxia, fatigue, peripheral oedema, fever, nervousness, rash, leucopaenia, visual disturbances, weight gain	Hypersensitivity	Not recommended for patients who need to sleep during daytime and remain awake at night Abrupt withdrawal may cause rebound seizures Renal impairment and to those undergoing haemodialysis Monitor for signs of suicidal ideation and behaviours
Oral Lamotrigine Pregnancy category: C	MS pain	25 mg od for 2 weeks, followed by 50 mg od for 2 weeks Thereafter, increase dose by max 50 - 100 mg every 1 - 2 weeks until optimal response Maintenance: 100 - 200 mg daily in 1 - 2 divided doses	Skin rash, SJS, TEN, nausea, insomnia, dizziness, nystagmus, headache, irritability, drowsiness, tremor, ataxia, diplopia	Hypersensitivity	Avoid abrupt withdrawal (reduce dosage over a period of 2 weeks) unless serious skin reaction occurs Hepatic impairment Renal impairment History of allergy or rash to other antiepileptic drugs Women who are starting or stopping hormonal contraceptives Patients at high risk of suicide in bipolar disorder
Oral Levetiracetam Pregnancy category: C	MS pain	Starting dose: 250 mg bd Increase dose to 500 mg bd after 2 weeks Dose can be further increased by 250 mg bd every 2 weeks depending upon the clinical response Max: 1500 mg bd	Somnolence, dizziness, headache, anorexia, tremor, pruritus, rash, haematological disorder, GI disturbances, cognitive disturbance	Hypersensitivity	Avoid abrupt withdrawal Renal impairment Severe hepatic impairment May affect ability to drive or operate machinery Elderly

Symptomatic Treatment (Drug Listed According To Indication)					
Drug	Indication	Dosages	Side Effects	Contraindications	Precautions and Monitoring
Oral Oxcarbazepine Pregnancy category: C	MS pain	Initially, 600 mg daily in 2 divided doses Increase at a max increments of 600 mg daily at weekly intervals depending on response Maintenance: 600 - 1200 mg daily May titrate up to 2400 mg daily	Rash, SJS, TEN, dizziness, somnolence, headache, ataxia, fatigue, vertigo, vomiting, nausea, hyponatraemia	Hypersensitivity	Cross-sensitivity to carbamazepine may occur. Renal impairment Hepatic impairment Patients at risk of hyponatraemia May impair ability to drive or operate machinery Anaphylaxis Monitor for signs and symptoms of depression, suicidal tendencies and unusual behaviour
Oral Pregabalin Pregnancy category: C	MS pain	Initially, 150 mg/day in 2 - 3 divided doses May be increased to 300 mg/day after 3 - 7 days Max: 600 mg/day after an additional 7 days interval	Peripheral oedema, dizziness, somnolence, diplopia, increased appetite, increased weight, confusion, irritability, ataxia, attention disturbances, tremor, vertigo, constipation	Hypersensitivity	Renal impairment Diabetes Congestive heart failure May affect ability to drive or operate machinery Elderly >65 year old Monitor for signs and symptoms of depression, suicidal tendencies and unusual behaviours
Oral Dextromethorphan/quinidine Pregnancy category: C	MS pain Pseudo-bulbar affect	Dextromethorphan 20 mg/quinidine 10 mg od for the first 7 days Then, dextromethorphan 20 mg/quinidine 10 mg bd Reassess periodically for spontaneous	Peripheral oedema, diarrhea, vomiting, asthenia, dizziness, cough, prolonged QT interval, immune-mediated thrombocytopenia, hepatitis	Heart failure Complete AV block without implanted pacemaker or high risk of complete AV block Concomitant use with: 1. Drugs containing quinidine, quinine or mefloquine	Immune-mediated thrombocytopenia CYP2D6 poor metabolisers Left ventricular dysfunction or hypertrophy Hepatitis Myasthenia gravis QTc prolongation Torsade de pointes dysrhythmia Dizziness and risk of falls

Symptomatic Treatment (Drug Listed According To Indication)					
Drug	Indication	Dosages	Side Effects	Contraindications	Precautions and Monitoring
		improvement and the need for continued treatment		<p>2. Drugs that both prolong the QT interval and are metabolised by CYP2D6 (e.g. thioridazine, pimozide)</p> <p>3. Monoamine oxidase inhibitors or their use within 14 days (serotonin syndrome)</p> <p>Hypersensitivity to quinine, mefloquine, quinidine or dextromethorphan/quinidine with a history of thrombocytopenia, hepatitis, bone marrow depression or lupus-like syndrome</p> <p>Prolonged QT interval</p> <p>History of torsades de pointes</p>	<p>Concomitant use with</p> <ul style="list-style-type: none"> strong and moderate CYP3A inhibitors drugs that undergo extensive CYP2D6 metabolism selective serotonin reuptake inhibitors
Oral Sildenafil Citrate	Erectile dysfunction	50 mg od, taken 1 hour before sexual activity The dose may be increased to 100 mg or decreased to 25 mg	Headache, flushing, dizziness, dyspepsia, nasal congestion, altered vision, hypotension, insomnia, epistaxis, rhinitis	<p>Hypersensitivity</p> <p>Co-administration with nitrates in any form</p>	<p>Hypotension (<90/50 mmHg)</p> <p>Severe cardiovascular disorders (e.g. unstable angina, cardiac failure)</p> <p>Recent history of stroke or MI</p> <p>Anatomical deformation of the penis</p> <p>Conditions which may predispose to</p>

Symptomatic Treatment (Drug Listed According To Indication)				
Drug	Indication	Dosages	Side Effects	Contraindications
		Max: 100 mg od Elderly >65 years Initially 25 mg, may increase to 50 - 100 mg based on efficacy and tolerability		
				<p>priapism (sickle cell anaemia, multiple myeloma or leukaemia) Patients with bleeding disorders, active peptic ulceration or untreated proliferative diabetic retinopathy Known hereditary degenerative retinal disorders (retinitis pigmentosa) Renal impairment Hepatic impairment</p>

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LIST OF ABBREVIATIONS

µg	microgramme
µL	microlitre
µm	micrometre
ACE	angiotensin converting enzyme
ACTM	acute complete transverse myelitis
ADEM	acute disseminated encephalomyelitis
ADL	activities of daily living
ANA	anti-nuclear antibody
ANCA	anti-neutrophil cytoplasmic antibody
anti-AQP4 Ab	anti-aquaporin 4 antibody
anti-dsDNA	anti-double stranded deoxyribonucleic acid
anti-MOG	autoantibodies against myelin oligodendrocyte glycoprotein
APTM	acute partial transverse myelitis
ARR	annualised relapse rate
AV	atrioventricular
BBB	blood brain barrier
bd	twice daily
BTX	botulinum toxin
CBT	cognitive behavioural therapy
CDMS	clinically definite multiple sclerosis
CDP	confirmed disability progression
CI	confidence interval
CIS	clinically isolated syndrome
cm	centimetre
CNS	central nervous system
CPG(s)	clinical practice guidelines
CSF	cerebrospinal fluid
CS	contrast sensitivity
CT	computerised tomography
CYC	cyclophosphamide
DG	development group
DIS	dissemination in space
DIT	dissemination in time
dL	desilitre
DMF	dimethyl fumarate
DM	diabetes mellitus
DMT(s)	disease modifying treatments
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EDSS	Extended Disability Status Scale
EPs	evoked potentials
ES	effect size
FBC	full blood count
FLAIR	fluid attenuation inversion recovery
FS	functional system
g	gramme
GA	glatiramer acetate
Gd	gadolinium
GI	gastrointestinal
HAM-D	Hamilton Depression Rating Scale

HR	hazard ratio
IIDD(s)	idiopathic inflammatory demyelinating disease(s)
IFN β	β -interferons
Ig	immunoglobulin
IM	intramuscular
IV	intravenous
IVIG	intravenous immunoglobulin
JCV	John Cunningham virus
kg	kilogramme
L	litre
LFT	liver function test
LVEF	left ventricular ejection fraction
m	metre
MAT	mobility assistive technology
max	maximum
mcg	microgramme
MD	mean difference
MDR	multidisciplinary rehabilitation
mg	milligramme
MI	myocardial infarction
ml	millilitre
mm	millimetre
mm ³	millimetre cube
MMF	mycophenolate mofetil
MoH	ministry of health
MR(I)	magnetic resonance (imaging)
MS	multiple sclerosis
NICE	National Institute for Health and Clinical Excellence
nm	nanometre
NMOSD	neuromyelitis optica spectrum disorder
NNT	number needed to treat
NPL	no perception to light
NPV	negative predictive value
OCBs	oligoclonal bands
OCP(s)	oral contraceptive pill(s)
od	once daily
ONTT	Optic Neuritis Treatment Trial
OR	odds ratio
OT	occupational therapy
PE	plasma exchange
PML	progressive multifocal leukoencephalopathy
PPMS	primary progressive multiple sclerosis
PRMS	progressive relapsing multiple sclerosis
PTS	painful tonic spasms
PVRV	post-void residual volume
qid	four times a day
QoL	quality of life
r _s	spearman's rank correlation coefficient
RC	review committee
RCT(s)	randomised controlled trial(s)
RRMS	relapsing-remitting multiple sclerosis
RR	relative risk

SC	subcutaneous
SE	spin echo
SJS	stevens-johnson syndrome
SLE	systemic lupus erythematosus
SPMS	secondary progressive multiple sclerosis
T1-Gd	gadolinium-enhanced T1-weighted
T2WI	T2-weighted imaging
tds	three times daily
TEN	toxic epidermal necrolysis
TENS	transcutaneous electrical nerve stimulation
TFT	thyroid function test
TM	transverse myelitis
TN	trigeminal neuralgia
UTI	urinary tract infection
US FDA	United States Food and Drug Administration
VA	visual acuity
VZV	varicella zoster virus
VEPs	visual evoked potentials
VF	visual field
vs	versus

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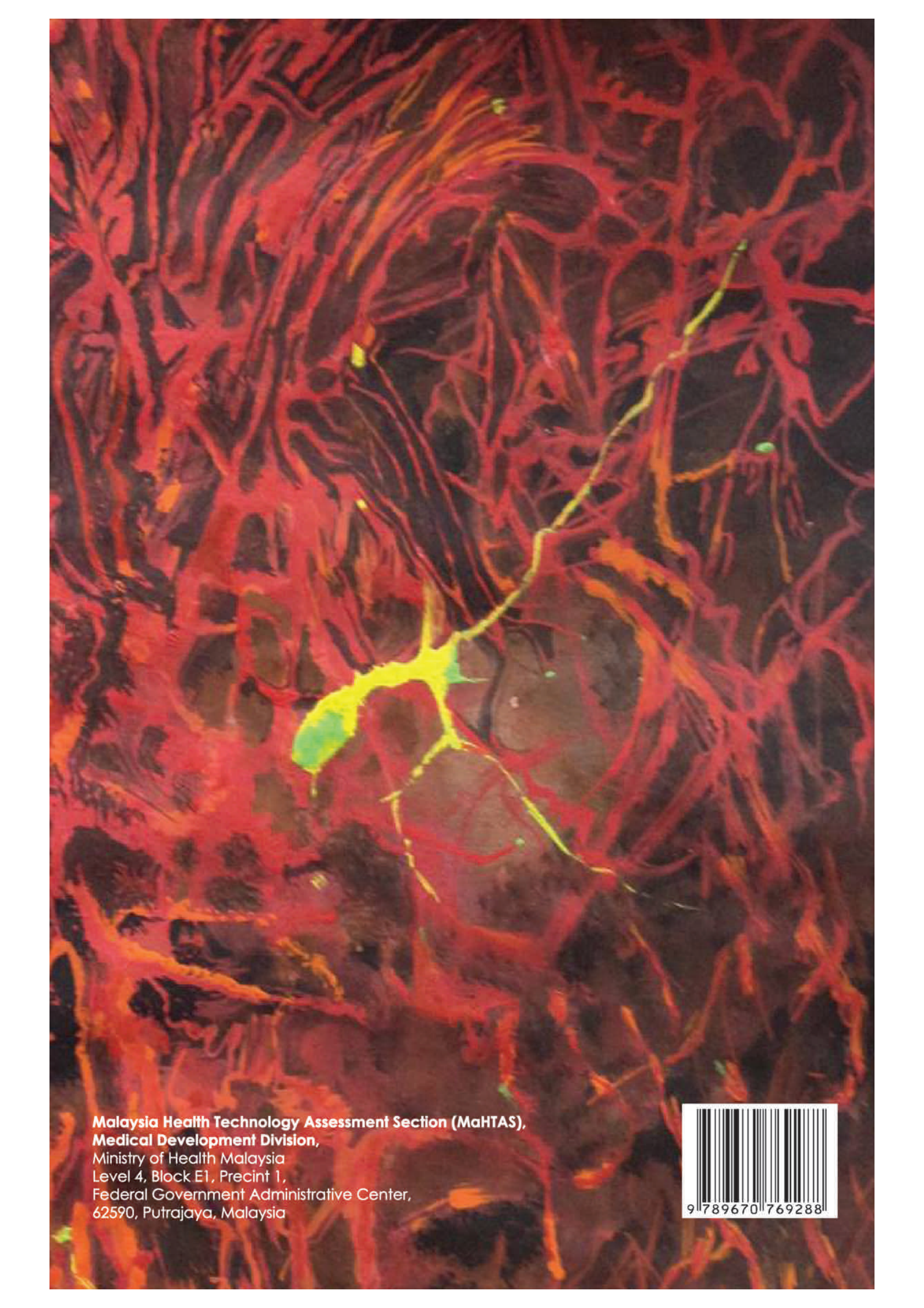
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