Supporting Information

Supplementary material

This appendix was part of the submitted manuscript and has been peer reviewed.
It is posted as supplied by the authors.

Appendix to: Shipley J, Beharry J, Yeh W, et al. Consensus recommendations on multiple sclerosis management in Australia and New Zealand: part 2. *Med J Aust* 2024; doi: 10.5694/mja2.52577.

Table 1. Consensus recommendations for multiple sclerosis (MS) management in Australia and New Zealand

Number	Consensus recommendation/statement[a]	Level of consensus	GRADE[b]
Disease-modifying therapy (DMT) counselling and selection			
DMT counselling			
R1	Prior to commencing DMT, patients should be counselled about the nature of the disease, what to expect, and implications for day-to-day life and life choices such as pregnancy. Patients should also be counselled about the aims of DMT, the DMTs available, the associated risks and benefits, the importance of early treatment, and modifiable risk factors for disease progression (see *Table 1* and '*general lifestyle measures*').	96.3%	GPP
R2	Where available, a second consultation with an MS nurse specialist should also occur to further discuss DMTs, mode of administration, and to address any further questions.	88.5%	GPP
R3	DMTs for MS should be initiated and supervised by a neurologist and selection individualised to the person with MS (PwMS). The choice of DMT is determined by considerations including disease phenotype, disease activity, drug efficacy, drug risk profile, John Cunningham virus (JCV) antibody status, patient comorbidities, pregnancy considerations, local accessibility, route of administration, and patients' personal preferences, values, and goals.	100%	GPP
Relapsing-remitting MS (RRMS)			
R4	In RRMS, it is recommended that DMT is started as early as possible after diagnosis to limit irreversible disease progression. 'International consensus on quality standards for brain health-focused care in multiple sclerosis' suggests the process of discussing and commencing DMT should be complete within 3 months ('core') (with approximately 5 weeks being 'achievable' and 17 days being 'aspirational').	100%	A1
R5	In Australia and New Zealand, high-efficacy therapy (particularly natalizumab, ocrelizumab, ofatumumab, or cladribine) is generally favoured as first-line DMT in people with RRMS.	96.2%	A1
R6	Following an informed discussion between the patient and consultant, there are circumstances where intermediate or low-efficacy therapy is indicated.	88.2%	B2
Progressive MS			
R7	The evidence of effectiveness of DMTs in progressive MS is limited. Therefore, when considering therapy for progressive MS, the risk of adverse effects needs to be carefully weighed against the likelihood of slowing disease progression.	100%	B1
Clinically isolated syndrome (CIS)			
R8	In individuals with CIS meeting criteria for dissemination in space on magnetic resonance imaging (MRI) but not fulfilling criteria for dissemination in time, lumbar puncture for intrathecally-restricted oligoclonal bands can be offered as a probabilistic substitute for dissemination in time. This allows the diagnosis of MS and treatment according to the recommendations for RRMS (refer to *'RRMS'*).	85.2%	B1
R9	Individuals with a first demyelinating event with MRI abnormalities typical of MS should be considered for DMT, especially those with intrathecally-restricted oligoclonal bands.	94.4%	B2
Radiologically isolated syndrome (RIS)			
R10	In general, people with RIS should be monitored for the development of clinical manifestations and new demyelinating lesions on MRI at least annually for at least 5 years.	88.4%	B2
R11	Advice from MS specialist neurologists should be sought in treatment decisions in radiologically-isolated MS.	94.1%	GPP
Evaluation prior to commencing DMT			

Pre-immunotherapy screen			
R12	Prior to commencing DMT, perform a pre-immunotherapy screen to identify active and latent infections at risk of worsening with immunotherapy and to assess immunisation status (see *Table 2*).	100%	GPP
R13	If an important active or latent infection is identified, the patient should be referred to an appropriate specialist (e.g., infectious diseases or hepatologist) for assessment and treatment prior to initiation of DMT.	92.3%	GPP
R14	Patients with serological evidence of chronic active hepatitis B infection (HbsAg positive, HBV DNA positive) or evidence of prior exposure (anti-Hbcore Ab positive, HbsAg negative) should be referred to an infectious diseases physician or hepatologist prior to DMT commencement. The specialist will consider antiviral therapy (e.g., entecavir) for those with chronic infection and consider antiviral therapy or surveillance for those with evidence of prior exposure to minimise the risk of reactivation.	81.5%	B1
R15	Patients receiving anti-CD20 monoclonal antibodies are at highest risk of hepatitis B reactivation and anti-CD20 therapy is contraindicated without prophylaxis. Prophylaxis should continue for up to 18 to 24 months after cessation of anti-CD20 monoclonal antibodies.	85.2%	B1
Immunisations			
R16	Review the patient's immunisation history and aim to ensure that they up to date with the Australian National Immunisation Program Schedule (NIPS) or New Zealand National Immunisation Schedule, as relevant. Particular attention should be paid to varicella zoster and hepatitis B vaccinations. However, delaying DMT to complete vaccinations may not be feasible in all cases, especially in the setting of severe or aggressive MS.	84.6%	B1
R17	All indicated live and live-attenuated vaccinations should be given at least 4 to 6 weeks prior to starting certain immunosuppressant DMT (e.g., anti-CD20 monoclonal antibodies) to ensure the vaccines are safe and effective.	84.6%	B2
R18	To allow time for a vaccine response, non-live vaccines should be completed 2 to 6 weeks prior to some DMT, as per Therapeutic Goods Administration (TGA) guidelines.	80.7%	B2
Baseline laboratory tests and examinations			
R19	Perform baseline laboratory tests relevant to the particular DMT (e.g., full blood examination, creatinine, liver function tests, quantitative serum immunoglobulins, pregnancy test, urinalysis, electrocardiogram, optical coherence tomography) and relevant examinations (e.g., skin, ophthalmic, cervical smear) (see *Table 1*). These tests are not required prior to all therapies.	92.3%	GPP
Monitoring disease activity on DMT			
R20	Monitor PwMS on DMT for symptoms and/or signs of disease activity, including acute clinical relapses and progression of disability.	100%	A1
R21	Obtain a re-baselining MRI of the brain and/or spine within 3 to 6 months of treatment commencement.	92.6%	GPP
R22	If there are new lesions on the re-baselining MRI, arrange an interval MRI in 3 to 6 months to ensure radiological disease stability.	92.6%	GPP
R23	In patients with long-term disease stability and low risk of progressive multifocal leukoencephalopathy (PML), interval MRI is generally performed every 12 months (see '*progressive multifocal leukoencephalopathy'*). In patients with active disease or moderate to high risk of PML, MRI is generally performed 3- to 6-monthly.	84.5%	GPP
Switching DMT			
Indications for switching			
R24	Switching to another DMT is recommended if there is evidence of breakthrough clinical disease activity (one or more clinical relapses) or radiological disease activity (one or more new T2-	92.3%	B1

	hyperintense lesions) after being on and adherent to a DMT for a sufficient time for it to be fully effective.		
R25	Switching DMT should also be considered if the risk of continuing outweighs the benefit or the patient develops serious or intolerable adverse effects.	96.2%	GPP
Sequential DMT selection and washout period			
R26	In addition to considerations outlined in '*DMT counselling and selection*', choice of sequential DMT is determined by considerations such as implications of previous immunosuppressive therapies and comparative drug efficacy.	100%	B2
R27	There is limited evidence to guide the optimal duration of washout periods. A washout period of more than 4 to 8 weeks should be avoided for natalizumab and sphingosine 1-phosphate (S1P) receptor modulators.	100%	A1
Autologous haematopoietic stem cell transplant (aHSCT)			
R28	aHSCT is used in a small number of carefully selected patients with severe refractory active RRMS without high levels of disability. It is generally reserved for younger adults (<65 years old) with lower baseline disability (Expanded Disability Status Scale (EDSS) ≤6.5) who have failed two or more high-efficacy DMTs due to continued clinical and radiological disease activity. Neurologists can consider referring appropriate PwMS for assessment by an MS neurologist in a major tertiary centre with experience in aHSCT for MS where cases are reviewed by the national aHSCT committee and their follow up trajectory monitored as per national standards. Appropriate PwMS in New Zealand can be referred for review by the aHSCT committee of Australia.	96.3%	C1
Discontinuing DMT			
R29	In general, it is recommended that patients with RRMS continue DMT if they are clinically stable and not experiencing significant adverse effects. For those of older age (>65 years) and at greater risk of side effects, careful consideration should be given to DMT cessation or de-escalation.	96.2%	C1
R30	For patients who decide to discontinue DMT, close clinical and radiological monitoring is recommended.	96.2%	B1
R31	In patients with progressive MS, consider discontinuing DMT if the risks outweigh the benefits or there is significant disability progression (Expanded Disability Status Scale (EDSS) ≥7).	84.7%	C2
Risk mitigation strategies during treatment with DMT			
Laboratory monitoring			
R32	Monitor relevant laboratory tests in patients on DMT, as summarised in *Table 1*. Switching DMT might be warranted if significant or serious abnormalities occur.	96.2%	GPP
Progressive multifocal leukoencephalopathy (PML)			
R33	Prior to commencing natalizumab therapy and during treatment, the risk-benefit balance of natalizumab **(**specifically the risk of PML) should be discussed.	100%	GPP
R34	To aid in quantifying the risk of PML on natalizumab, perform anti-JCV antibody testing 6-monthly and utilise established risk algorithms.	100%	A1
R352	Patients on natalizumab should be monitored for clinical and radiological evidence of PML. Therapy should be suspended immediately if there is any concern for PML and the patient should be referred to a specialist centre.	100%	A1
R36	In the setting neurological deterioration associated with immune reconstitution inflammatory syndrome (IRIS), high-dose corticosteroids (often 1g intravenous (IV) methylprednisolone for 5 days followed by tapering oral steroids) are recommended.	88.9%	C2
Mitigating infection risk			
R37	While on therapy, it is recommended that all patients are up to date with the relevant national immunisation schedule, including annual influenza vaccination (non-live formulation) and COVID-19 vaccinations in line with national guidelines.	96.2%	GPP

R38	In general, live and live-attenuated vaccines should not be administered during treatment with immunosuppressive DMTs. However, there are exceptions for which infectious diseases consultation should be sought.	94.4%	B2
Cancer screening			
R39	For all PwMS on DMT, it is recommended that standard age-appropriate national cancer screening guidelines are followed.	96.2%	A1
R40	However, in women on moderate to high-efficacy therapy in whom an oncogenic human papilloma virus (HPV) type has not been detected, cervical cancer screening with an HPV test is recommended 3-yearly instead of 5-yearly.	81.4%	C2
R41	Skins checks are recommended at least annually for patients on S1P receptor modulators.	96.3%	C1
Managing DMT in special situations			
Pregnancy			
R42	Pregnancy plans should be discussed with women of childbearing potential prior to commencing DMT and regularly thereafter to carefully plan the best approach to DMT selection and management.	100%	GPP
R43	The decision to continue or temporarily discontinue DMTs during pregnancy is individualised based on factors such as the individual's clinical and radiological disease activity and severity, DMT safety in pregnancy, the risk of rebound activity after DMT discontinuation, and personal preferences and values.	100%	GPP
R44	DMT associated with significant risks in pregnancy, including teriflunomide, fingolimod, siponimod, and ozanimod, should not be given to pregnant women or women of childbearing age who are not using highly effective contraception.	88.9%	B2
R45	If a PwMS has an unplanned pregnancy on one of these teratogenic DMTs, discontinue the DMT immediately and refer to an obstetrician for further assessment.	88.9%	A2
R46	If a PwMS becomes pregnant on teriflunomide, discontinue the drug immediately, initiate an accelerated elimination procedure (e.g., a cholestyramine washout or activated charcoal), and arrange a referral to an obstetrician for further assessment.	100%	A1
R47	Cladribine is another teratogenic DMT and should not be administered during pregnancy. Individuals can consider conception 6 months after completing the last course of cladribine. If pregnancy occurs after the year 1 course of cladribine, the second-year course should be delayed until after delivery and breastfeeding.	88.9%	B2
R48	If an individual wishes to discontinue another DMT prior to pregnancy, the risk-benefit considerations should be discussed. This includes the potential risks associated with fetal DMT exposure and the risk of MS disease activity and disability accrual with discontinuation. Following a careful risk-benefit discussion with the patient, discontinuing DMT prior to pregnancy can be considered in individual circumstances taking into consideration the personal preferences, recent disease activity, and DMT type.	96.3%	GPP
R49	In people with highly active MS, briefly delaying pregnancy to allow disease control should generally be discussed. Pregnancy outcomes are improved in women with stable disease pre-conception and therefore a period of disease stability is generally preferred prior to pregnancy. However, individualised circumstances should always be considered.	81.4%	C2
R50	In people with active disease or adverse prognostic factors who wish to become pregnant, a shared decision can be made to continue certain DMT where the risk of disease activity outweighs the risk associated with DMT exposure during pregnancy.	88.5%	B2
R51	Natalizumab can be continued until the third trimester and extended interval dosing (6-weekly) up to 30 to 34 weeks can be considered.	88.9%	B2
R52	While it was previously recommended that ocrelizumab be ceased 6 to 12 months prior to planned conception, aiming for conception 3 months after the last infusion can be considered.	88.9%	B2

R53	Glatiramer acetate is considered safe in pregnancy.	100%	B1
R54	Treatment of MS relapses during pregnancy is only recommended when symptoms are functionally disabling. A short course of non-fluorinated corticosteroids (such as methylprednisolone) is generally considered low risk after the first trimester (refer to *'acute relapses'* for approach).	85.1%	C2
R55	If MRI is required, gadolinium contrast should generally be avoided due to potential risks associated with fetal exposure.	96.3%	B1
Postpartum and breastfeeding			
R56	Early resumption of DMT is generally recommended to reduce the risk of postpartum relapse. Timing of DMT recommencement varies based on disease activity prior to and during pregnancy, risk of rebound disease activity off DMT**,** and safety considerations surrounding breastfeeding.	100%	B1
R57	Aim to recommence natalizumab within 2 weeks after birth due to the risk of rebound disease activity after natalizumab withdrawal.	92.6%	B2
R58	The benefits of breastfeeding should be discussed with women along with safety considerations related to DMTs during breastfeeding.	100%	GPP
R59	Glatiramer acetate and interferon beta are considered safe during breastfeeding.	96.2%	B1
R60	Natalizumab is likely safe during breastfeeding, with no increased risk of adverse effects in small studies of newborns exposed to natalizumab in breastmilk.	85.1%	C2
R61	Ocrelizumab and ofatumumab are likely safe during breastfeeding, though there may be a very low risk of neonatal B-cell depletion, infection, and impaired vaccine response.	92.3%	C2
R62	In neonates with B-cell depletion from anti-CD20 therapy, live vaccines should be delayed until B-cell counts have recovered.	96.3%	C1
R63	DMTs comprised of small molecules, including fingolimod, siponimod, ozanimod, teriflunomide, and cladribine, are not considered safe in breastfeeding.	92.5%	B1
Active infection			
R64	Administration of immunosuppressive DMT should be temporarily delayed if a PwMS develops a life-threatening infection or there is poor response to initial anti-microbial therapy. However, withholding therapy provides minimal short-term protective benefit due to the long half-lives of many DMTs and the latency of the impact on white cell function and reconstitution. Risk of significant rebound disease activity as a result of suspending DMT (such as S1P receptor inhibitors) should also be carefully considered.	100%	C1
R65	In PwMS with severe or recurrent serious infections, switching to a DMT with a lower risk of infection should be considered.	96.2%	B1
COVID-19 infection			
R66	Patients should be counselled about the importance of COVID-19 vaccinations and general behavioural modification strategies to reduce the risk of COVID-19 infection.	96.2%	GPP
R67	In PwMS who are on immunosuppressive therapies and experience acute COVID-19 infection, COVID-19 specific treatments (i.e., anti-virals) should be commenced promptly as per up-to-date protocols.	96.3%	GPP
R68	In the case of severe COVID-19 infection, administration of immunosuppressive DMT should generally be delayed until the infection has resolved, although the lack of acute protective benefit from delaying DMT and the risk of rebound disease activity should be considered.	81.4%	C2
Current or previous malignancy			
R69	When a patient has a current or past malignancy, decisions regarding DMT management are made on a case-by-case basis taking into consideration factors such as the type, recency, and grade of malignancy and risk of DMT. Caution should be exercised in patients with a current or previous	100%	GPP

	malignancy and specialist advice sought. People at high risk of skin cancers should avoid S1P receptor inhibitors.		
General lifestyle measures			
Exercise			
R70	PwMS are recommended to participate in regular exercise, including aerobic and resistance training, to a minimum weekly total of 2.5 hours.	100%	B1
R71	At higher disability levels, guidance from allied health clinicians such as physiotherapists, occupational therapists, and exercise physiologists with experience in MS is recommended to develop individualised exercise programs that are safe and effective.	96.3%	GPP
Smoking cessation			
R72	PwMS should be strongly counselled and supported to cease and avoid smoking, including vaping.	100%	B1
Vitamin D supplementation			
R73	While there is no benefit in modulation of disease activity, maintaining adequate serum vitamin D levels is recommended to promote bone health through adequate safe sun exposure and vitamin D supplementation where required.	85.1%	C2
Acute MS relapses			
Pseudorelapses			
R74	When a patient presents with neurological symptoms suggesting a clinical relapse of MS, assess for causes of a pseudorelapse such as infection that might explain the deterioration. However, differentiating relapses and pseudorelapses can be difficult. A comprehensive assessment, including a thorough history, neurological examination, and in some instances imaging, is required for accurate differentiation.	100%	GPP
R75	Manage a pseudorelapse by treating the underlying cause.	100%	GPP
MS relapses			
R76	After infection or other intercurrent medical illness is excluded, acute or subacute symptomatic neurological episodes with functionally disabling symptoms lasting more than 24 hours are treated with IV or oral methylprednisolone 1g for three to five days. Mild relapses, particularly those characterised by isolated sensory symptoms, generally do not warrant steroid treatment.	100%	B1
R77	In severe refractory relapses, a second course of methylprednisolone or plasma exchange can be considered.	96.2%	C1
R77	Acute clinical relapses should be evaluated with MRI of the brain or spine with gadolinium contrast, but treatment need not be delayed for this.	84.7%	C2
Symptomatic treatments			
R79	Support from a multidisciplinary team of allied health clinicians with experience in MS, such as physiotherapists, occupational therapists, continence specialists, exercise physiologists, speech pathologists, dieticians, psychologists, and neuropsychologists, is important in managing specific symptoms in select individuals with MS.	92.6%	GPP
R80	Clinicians should exclude other causes of symptoms such as fatigue (e.g., infection, depression, anaemia, iron deficiency, and thyroid dysfunction) and consider non-pharmacological approaches (e.g., exercise therapy for fatigue) prior to prescribing pharmacological therapy.	96.3%	GPP

a Please see main text for additional context and references to supporting evidence for each of the recommendations

b Recommendations were graded using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. The quality of the supporting evidence was defined as high (A), moderate (B), or low (C) and the strength of the recommendations was classified as strong (1) or conditional (2). Where specific evidence is lacking and recommendations are based on best-practice standard of care, consensus recommendations were designated as Good Practice Points (GPP). Based on the GRADE framework, high quality evidence (A) was assigned when it was assessed that 'further research is very unlikely to change our confidence in the estimate of effect', moderate (B) when 'further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate', and low (C) (combining the 'low' and 'very low' categories of the standard GRADE system) when 'further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate' or 'any estimate of effect is very uncertain'.

Recommendations were assigned as strong (1) when a ‘guideline panel is confident that the desirable effects of an intervention outweigh its undesirable effects’,[1] and conditional (or weak) (2) when ‘the desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention) but appreciable uncertainty exists’.[2] The strength of the evidence and recommendations was determined through consideration of the balance of benefits and harms, level of certainty, quality of the supporting evidence, associated costs, resource implications, and patients’ personal values and preferences.

Table 2. Conditional probability (per 1000 patients) of developing natalizumab-related progressive multifocal leukoencephalopathy (PML) in each year of treatment

JCV antibody status	Prior immunosuppressant use	Natalizumab exposure (months)	Index ≤0·9	Index 0.9-1.5	Index >1.5
Negative[a]	0.07				
Positive[b]	No	1-12	0.01	0.1	0.2
		13-24	0.05	0.3	0.9
		25-36	0.2	0.8	2.6
		37-48	0.4	2.0	6.8
		49-60	0.5	2.4	7.9
	Yes	1-12	0.3		
		13-24	0.4		
		25-36	3.6		
		37-48	8.3		
		49-60	8.4		

JCV: John Cunningham virus

Based on data from Ho et al. (2017):

a Estimated from pooled cohort of 13,996 anti-JCV antibody-negative patients

b Estimated from pooled cohort of 21,696 anti-JCV antibody-positive patients[1]

Table 3. Malignancies associated with multiple sclerosis (MS) disease-modifying therapies (DMTs)

DMT	Malignancies diagnosed in pivotal clinical trials	Malignancy incidence rate (IR) compared to reference MS or general population
Alemtuzumab (Lemtrada®)	• CAMMS223: Three cancers including non–Epstein-Barr virus (EBV)-associated Burkitt's lymphoma, breast cancer, and cervical cancer in situ were reported in the alemtuzumab arm (*n*=223)[2] • CARE-MS I: Of those on alemtuzumab (*n*=376), two developed thyroid papillary carcinoma[3] • CARE-MS II: Five cancers were diagnosed in patients on alemtuzumab (*n*=596), including two cases of basal cell carcinoma and one of thyroid cancer, vulval cancer and colon cancer[4]	TOPAZ extension study: A nine-year follow up study of alemtuzumab did not show an increase in the malignancy IR compared to the background population[5]
Natalizumab (Tysabri®)	AFFIRM: Five cancers were diagnosed in patients on natalizumab (*n*=627), including three cases of breast cancer, one cervical cancer, and one metastatic melanoma[6]	• Tysabri Observational Program (TOP): A 10-year interim analysis did not demonstrate an increase in cancer IR compared to the background European or global rates[7] • No increased risk of invasive cancer compared to the general population in a Swedish nationwide register-based cohort study[8]
Ocrelizumab (Ocrevus®)	• OPERA I and II: Four cases of malignancy were diagnosed in patients on ocrelizumab (*n*=827) over two years, including two cases of invasive ductal breast carcinoma, one renal cell carcinoma, and one malignant melanoma. In the open-label extension study, two cases of breast cancer, two basal cell carcinoma, and one malignant melanoma were detected[9] • ORATORIO: In ORATORIO, a study of ocrelizumab (*n*=488) vs. placebo in PPMS, breast cancer was diagnosed in four patients on ocrelizumab, basal cell carcinoma in three, and endometrial adenocarcinoma, anaplastic large-cell lymphoma, pancreatic carcinoma, and fibrous histiocytoma in one each[10]	A seven-year study of ocrelizumab safety did not demonstrate an excess IR of malignancy in patients exposed to ocrelizumab compared to the MS or general population including no statistically significant excess risk of breast cancer[11]
Ofatumumab	ASCLEPIOS I and II: Five cancers in the ofatumumab arm (*n*=946)	Long-term incidence studies lacking

(Kesimpta®)	including two cases of basal cell carcinoma and one case each of malignant melanoma in situ, recurrent non-Hodgkin's lymphoma, and invasive breast carcinoma[12]	
Fingolimod (Gilenya®)	• FREEDOMS: Malignancy diagnosed in eight patients on fingolimod (*n*=854), including five cases of basal cell carcinoma, one malignant melanoma, one Bowen's disease, and one breast cancer[13] • FREEDOMS II: Twenty-seven neoplasms in the fingolimod-treated group (*N*=728), including 16 basal cell carcinoma, four squamous-cell carcinoma, one uterine leiomyoma, and one thyroid cancer[14] • TRANSFORMS: In the fingolimod group (*n*=849), there were five basal cell carcinomas, three melanomas, and four breast cancers[15]	• Possible borderline significant increase in invasive cancer risk (not possible to attribute to specific cancer type) compared to the general population in a Swedish nationwide register-based cohort study[8] • Signal for increased risk of skin cancer including basal cell carcinoma, squamous cell carcinoma, and melanoma compared to other DMTs in a 17-year review of the United States (US) Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) data[16]
Siponimod (Mayzent®)	EXPAND: 14 skin neoplasms (malignant and unspecified) in the siponimod arm (*n*=1105), similar to placebo[17]	Signal for increased risk of basal cell carcinoma compared to other DMTs in a 17-year review of the FAERS data[16]
Ozanimod (Zeposia®)	• SUNBEAM: Three cancers were diagnosed in the ozanimod group (*n*=898) including testicular sarcoma, invasive breast cancer, and basal cell carcinoma and none in the interferon beta-1a group (*n*=448)[18] • RADIANCE: Five new malignancies in the ozanimod group (*n*=873), including two breast cancers and basal cell carcinomas, and one of keratacanthoma[19]	DAYBREAK open-label extension study: In the five-year extension study, the IR of basal cell carcinoma in the parent trials plus DAYBREAK was within that expected of European and US populations. There were nine cases of breast cancer in the ozanimod groups compared to the expected incidence of seven cases based on applying the cancer incidence rate in an age-matched female population[20]
Cladribine (Mavenclad®)	• CLARITY: Five cancers were diagnosed in patients on cladribine (*n*=884), including metastatic pancreatic carcinoma, malignant melanoma, ovarian cancer, choriocarcinoma and cervical carcinoma in situ (excluding benign uterine leiomyomas)[21] • ORACLE-MS: Malignancies in cladribine arms (*n*=410) included one papillary thyroid cancer and one squamous-cell carcinoma of the skin[22]	• No increased risk of malignancy relative to matched GLOBOCAN reference population[23] • No increased risk of malignancy compared to patients on other DMTs in a meta-analysis of phase III trials in RRMS[24]
Dimethyl fumarate (Tecfidera®)	• CONFIRM: No malignant neoplasms were reported in the dimethyl fumarate groups (*n*=703)[25] • DEFINE: Four malignancies in the dimethyl fumarate groups (*n*=826)	ENDORSE extension study: In a 13-year interim analysis, there was no increased risk of malignancy among patients treated with dimethyl fumarate compared to IR in the general US population[27]

	including basal cell carcinoma, breast cancer, cervical carcinoma, and transitional cell carcinoma[26]	
Teriflunomide	• TEMSO: One patient on teriflunomide (*n*=723) was diagnosed with cervical carcinoma in situ[28] • TOPIC: There were no malignancies in those on teriflunomide (safety data for *n*=423)[29] • TOWER: On thyroid tumour was diagnosed in teriflunomide-treated patients (*n*=777)[30]	TEMSO extension study: In the 9-year study, there was no clustering of malignancies in those on teriflunomide and the overall malignancy IR was comparable to the general MS population in Sweden[31]
Interferon β-1b (Betaferon®)	IFNB Multiple Sclerosis Study Group trial: No cancers reported under adverse events (*n*=249)[32]	• No increased cancer risk over a 12-year period compared to MS controls[33] • Analysis of pooled safety data from 12 clinical trials did not demonstrate an increased risk of malignancy in patients on subcutaneous interferon β-1a compared to the general population[34]
Glatiramer acetate (Copaxone®)	Copolymer 1 Multiple Sclerosis Study Group trial: No cancers reported under adverse events in those on glatiramer (*n*=125)[35]	There was no evidence of an increased risk of malignancy in patients treated with glatiramer in the French EDMUS database compared to the reference population[36]

Table 4. Commonly prescribed symptomatic treatments

Symptom	Medications	Route of administration	Mechanism of action	Adverse effects (see full PI)	TGA pregnancy category	Subsidised in AU and/or NZ	Other considerations
Fatigue	Methylphenidate	PO	CNS stimulant that blocks neuronal reuptake of dopamine and noradrenaline	Headache, drowsiness, dizziness, anorexia, nausea, dry mouth, nasopharyngitis, cough, insomnia, agitation, anxiety, depression, psychosis, suicidality, tics, serotonin syndrome, tremor, dyskinesia, rash, hair loss, hyperhidrosis, tachycardia, palpitations, hypertension, stroke, myocardial infarction, peripheral vasculopathy, priapism, increased intraocular pressure, reduced seizure threshold, sudden death (those with pre-existing structural cardiac abnormalities or other serious cardiac problems must be assessed by a cardiologist prior to commencement)[37]	D	No	• Not superior to placebo[38] • Potential drug of dependence
	Modafinil	PO	CNS stimulant that promotes wakefulness; exact mechanism not known	Headache, dizziness, nausea, dyspepsia, diarrhoea, rhinitis, insomnia, agitation, anxiety, depression, psychosis, suicidality, hypertension, tachycardia, palpitations, vasodilation, paraesthesia, pain	D	No	• Not superior to placebo[38] • Potential drug of dependence
	Amantadine	PO	Dopaminergic and antiviral medication; unknown mechanism in fatigue	Livedo reticularis, peripheral oedema, headache, dizziness, blurred vision, nausea, anorexia, dry mouth, dyspepsia, lethargy, insomnia, agitation, depression, anxiety, hallucinations, ataxia, dysarthria, palpitations, orthostatic hypotension, impulse control disorders (gambling, hypersexuality)	B3	NZ only	• Not superior to placebo[38]
Spasticity	Baclofen	PO	GABA analogue that activates $GABA_B$ receptors and acts as a	Nausea, sedation, somnolence, weakness, dizziness, confusion, headache, diarrhoea, dysuria, depression, suicidality, euphoria, insomnia, hallucinations, hypotension, reduced cardiac output,	B3	AU, NZ	

		central muscle relaxant	rash, hyperhidrosis, ataxia, tremor, tinnitus, nystagmus, visual disturbance, reduced seizure threshold			
Gabapentin	PO	GABA analogue that acts on voltage-dependent calcium channels (α2δ subunit) to inhibit excitatory neurotransmitter release	Fatigue, somnolence, confusion, headache, dizziness, ataxia, tremor, agitation, anxiety, depression, suicidality, nausea, dyspepsia, dry mouth, rhinitis, visual blurring, diplopia, nystagmus, dysarthria, amnesia, increased appetite, weight gain, pain, pruritis, peripheral oedema, vasodilation, respiratory depression	B3	NZ only	• Potential drug of dependence
Pregabalin	PO	GABA analogue that acts on voltage-dependent calcium channels (α2δ subunit) to inhibit excitatory neurotransmitter release	Dizziness, somnolence, confusion, depression, headache, ataxia, tremor, agitation, euphoria, suicidality, nasopharyngitis, blurred vision, diplopia, nausea, constipation, dry mouth, weight gain, peripheral oedema, congestive cardiac failure, respiratory depression	D	NZ only	• Potential drug of dependence
Diazepam	PO	Benzodiazepine that acts on central $GABA_A$ receptors to enhance the inhibitory action of GABA	Sedation, fatigue, somnolence, confusion, dizziness, ataxia, weakness, dysarthria, headache, tremor, amnesia, agitation, anxiety, hallucinations, nausea, blurred vision, diplopia, urinary retention, incontinence, rash, hypotension, cardiac failure, respiratory depression	C	AU, NZ	• Potential drug of dependence
Botulinum toxin A	IM	Inhibits the release of ACh into the neuromuscular junction causing muscle relaxation	Local pain, bleeding, infection, sensory change, paraesthesia, muscle weakness	B3	AU for moderate-severe spasticity of the upper or lower limb following an acute event; NZ	
Nabiximols	Oromucosal spray	Cannabinoid containing THC and CBD that acts as a partial agonist at CB_1 and CB_2	Fatigue, somnolence, dizziness, mood disturbance, headache, glossodynia, myalgia, nausea, dry mouth, anorexia, diarrhoea, constipation, blurred vision, depression, euphoria, tachycardia,	B2	No	

			cannabinoid receptors leading to muscle relaxation	hypertension			
	Cannabidiol	PO drops	Acts at CB_1 and CB_2 cannabinoid receptors and ion channels to modulate pain pathways	Drowsiness, somnolence, dizziness, nausea, vomiting, change in appetite, diarrhoea, constipation, headache, dry mouth, agitation, insomnia, tremor, pyrexia, rash, infection, weight loss	B2	No	
Hyperactive bladder symptoms (e.g., urinary urgency)	Oxybutynin	PO	Anticholinergic that relaxes bladder smooth muscle	Drowsiness, blurred vision, flushing, dry mouth, dry eyes, dry skin, urinary hesitancy, UTI, urinary retention, nausea, diarrhoea, constipation, intestinal obstruction, dizziness, headache, confusion, agitation, hallucinations, weakness	B1	AU for detrusor overactivity; NZ	
	Solifenacin	PO		Dry mouth, nausea, fatigue, blurred vision, dyspepsia, cough, constipation, intestinal obstruction, pain, hypertension, QT prolongation, UTI, urinary retention	B3	NZ only	
	Mirabegron	PO	Selective β_3 adrenoreceptor agonist that relaxes bladder smooth muscle	Hypertension, nasopharyngitis, UTI, urinary retention, headache, blurred vision, dizziness, constipation, diarrhoea, pain, tachycardia	B3	No	
	Botulinum toxin A	IM	See above	Urinary retention	B3	AU for urinary incontinence due to neurogenic detrusor overactivity; NZ	
Gait dysfunction	Fampridine	PO	Inhibits potassium channels leading to improved conduction in damaged nerves	UTI, nasopharyngitis, sore throat, headache, dizziness, unsteadiness, tremor, paraesthesia, anxiety, insomnia, nausea, constipation, diarrhoea, dyspepsia, dyspnoea, weakness, pain, seizures	C	No	• Heterogeneous studies demonstrating small benefits to ability to walk

							short distances and perceived walking ability[39]
Neuropathic pain	Amitriptyline	PO	Tricyclic antidepressant	Worsening of depression, suicidality, aggression, agitation, constipation, orthostatic hypotension, tachycardia, palpitations, somnolence, confusion, tremor, dizziness, headache, dysarthria, ataxia, paraesthesia, hyperhidrosis, dry mouth, nasal congestion, nausea, weight gain, visual disturbance, mydriasis, urinary and sexual dysfunction, oedema, hyponatraemia, cardiac conduction abnormalities, serotonin syndrome	C	AU, NZ	
	Carbamazepine	PO	Sodium channel blocker	Fatigue, somnolence, dizziness, confusion, ataxia, agitation, depression, suicidality, nausea, vomiting, dry mouth, headache, blurred vision, oedema, hyponatraemia, hypothyroidism, leukopaenia, thrombocytopaenia, eosinophilia, urticaria, increased risk of SJS/TEN/DRESS (especially Han Chinese and Thai populations with the HLA-B*1502 allele and Japanese and Northern European populations with HLA-A*3101 allele)[40]	D	AU, NZ	• First-line for trigeminal neuralgia • Consider HLA-B*1502 and HLA-A*3101 prior to commencement in relevant populations[40] • Periodic monitoring of FBE, UEC, LFTs
	Gabapentin	See above				AU Repatriation PBS only for refractory neuropathic pain; NZ	
	Pregabalin	See above				AU for refractory neuropathic pain; NZ	

	Duloxetine	PO	Serotonin noradrenaline reuptake inhibitor	Nausea, vomiting, dry mouth, dizziness, fatigue, somnolence, anorexia, insomnia, anxiety, agitation, suicidality, headache, diarrhoea, constipation, nasopharyngitis, cough, hyperhidrosis, palpitations, hypertension, orthostatic hypotension, syncope, tremor, paraesthesia, mydriasis, hot flushes, weight loss, sexual dysfunction, polyuria	B3	No
	Cannabidiol	See above				No

ACh: acetylcholine; AU: Australia; CBD: cannabidiol; DRESS: drug rash with eosinophilia and systemic symptoms; CNS: central nervous system; FBE: full blood count; GABA: gamma-aminobutyric acid; HLA: human leukocyte antigen; IM: intramuscular; LFTs: liver function tests; NZ: New Zealand; PI: product information; PO: per oral; SJS: Stevens-Johnson Syndrome; TEN: toxic epidermal necrolysis; TGA: Therapeutic Goods Administration; THC: delta-9-tetrahydrocannabinol; UEC: urea, electrolytes and creatinine; UTI: urinary tract infection

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