

## Appendix A: Summary of evidence from surveillance

### 2018 surveillance of Multiple sclerosis in adults: management (2014) NICE guideline CG186

#### Summary of evidence from surveillance

Studies identified in searches are summarised from the information presented in their abstracts.

Feedback from topic experts who advised us on the approach to this surveillance review, was considered alongside the evidence to reach a final decision on the need to update each section of the guideline.

#### 1.1 Diagnosing MS

##### Recommendations in this section of the guideline

- 1.1.1 Be aware that clinical presentations in multiple sclerosis (MS) include:
- loss or reduction of vision in 1 eye with painful eye movements
  - double vision
  - ascending sensory disturbance and/or weakness
  - problems with balance, unsteadiness or clumsiness
  - altered sensation travelling down the back and sometimes into the limbs when bending the neck forwards (Lhermitte's symptom).
- 1.1.2 Be aware that usually people with MS present with neurological symptoms or signs as described in recommendation 1.1.1, and:
- are often aged under 50 **and**
  - may have a history of previous neurological symptoms **and**
  - have symptoms that have evolved over more than 24 hours **and**
  - have symptoms that may persist over several days or weeks and then improve.

- 1.1.3 Do not routinely suspect MS if a person's main symptoms are fatigue, depression or dizziness unless they have a history or evidence of focal neurological symptoms or signs.
- 1.1.4 Before referring a person suspected of having MS to a neurologist, exclude alternative diagnoses by performing blood tests including:
- full blood count
  - inflammatory markers for example erythrocyte sedimentation rate, C-reactive protein
  - liver function tests
  - renal function tests
  - calcium
  - glucose
  - thyroid function tests
  - vitamin B<sub>12</sub>
  - HIV serology.
- 1.1.5 Do not diagnose MS on the basis of MRI findings alone.
- 1.1.6 Refer people suspected of having MS to a consultant neurologist. Speak to the consultant neurologist if you think a person needs to be seen urgently.
- 1.1.7 Only a consultant neurologist should make the diagnosis of MS on the basis of established up-to-date criteria, such as the revised 2010 McDonald criteria\*, after:
- assessing that episodes are consistent with an inflammatory process
  - excluding alternative diagnoses
  - establishing that lesions have developed at different times and are in different anatomical locations for a diagnosis of relapsing–remitting MS
  - establishing progressive neurological deterioration over 1 year or more for a diagnosis of primary progressive MS.
- 1.1.8 If a person is suspected\* of having MS but does not fulfil the diagnostic criteria, plan a review. Discuss the timing of the review with the person and ensure they know who to contact for advice if they develop further neurological symptoms or if current symptoms worsen.
- 1.1.9 Offer people suspected of having MS, information about support groups and national charities.

\* Polman CH, Reingold SC, Banwell B et al. (2011) Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Annals of Neurology* 69: 292–302.

## Surveillance decision

This recommendation should be updated.

## Editorial amendments

Recommendation 1.1.7 references 'the revised 2010 McDonald criteria', this was revised again in 2017, date should be changed in the recommendation to 2017; and the reference in footnote 2 should be changed to Thompson AJ, Banwell BL, Barkhof F, et al (2018) Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurology* 17(2):162-173.

## 2018 surveillance summary

### Diagnosing MS

No evidence was identified.

#### Diagnosing optic neuritis and neuromyelitis optica

A systematic review and meta-analysis included 30 case control and consecutive enrolment studies (n=not reported in abstract (NR)) evaluating the overall diagnostic accuracy of tests for detecting AQP4-Ab antibodies for diagnosing neuromyelitis optica (NMO). Three different immunoassays were included: cell based assay (CBA; sensitivity: 0.76, 95% CI 0.67-0.82), tissue-based assay (TBA; sensitivity: 0.59, 95% CI 0.50-0.67) and ELISA test (sensitivity: 0.65, 95% CI 0.53-0.75). The mean specificity of the CBA: 0.99 (95% CI 0.97-0.99), TBA: 0.98 (95% CI 0.97-0.99) and ELISA: 0.97(95% CI 0.96-0.99). [1]

A systematic review included 7 studies (n=162) assessing the diagnostic accuracy of ultrasonography of optic nerve diameter (OND) for assessment of acute optic neuritis (ON). Results indicated that OND is significantly thicker in the affected eye versus the unaffected eye or controls (statistics were not reported in the

abstract); and an increased OND was found in 78-100% of patients. [2]

A meta-analysis of 42 studies (n=NR) compared ganglion cell layer (GCL) thickness in multiple sclerosis (MS) patients with and without prior ON to healthy controls. It was reported that in acute ON there was significant thinning of the GCL within the first 5 weeks, which was earlier than retinal nerve fiber layer (RNFL) thinning; GCL thinning at 1-2 months after acute ON was described as predicting visual function at 6 months; and that the thickness of the GCL was significantly reduced in MS patients with and without previous ON compared with healthy controls. It was also reported that GCL thinning was associated with visual function in 'most studies' and with expanded disability status scale (EDSS) scores. No data or statistics were reported in the abstract. [3]

A systematic review included 110 cross-sectional and longitudinal studies investigating the use of spectral domain optical coherence tomography (SD-OCT) to recognise and monitor inflammation and neurodegeneration in people with MS with optic neuritis (MSON) or without optic neuritis (MSNON). 40 studies met the quality criteria (published OCT quality

control criteria) for inclusion in a meta-analysis (n=1,667 MSON eyes, 4,109 MSNON and 1,697 eyes from healthy controls). The peripapillary and macula RNFL showed significant thinning in MSON and MSNON eyes compared with controls. Atrophy of the macular GCL and inner plexiform layer was significantly greater in MSON and MSNON eyes compared with controls. There was a small, but significant difference in inner nuclear layer thickening in MSON eyes compared with controls. While there was no significant difference in the thickness of the combined outer nuclear layer and outer plexiform layer in MSON or MSNON eyes compared with control eyes, there was a small significant difference in thickness of the combined layer in MSON eyes compared with MSNON eyes. [4]

A systematic review and meta-analysis included 24 studies (n=NR) evaluating whether OCT can differentially diagnose between NMO and MS. The meta-analysis indicated that RNFL was more severe in NMO than in MS, and that the inter-eye RNFL difference between eyes with or without ON was much larger in people with NMO than those with MS (no statistics reported in the abstract). [5]

## Intelligence gathering

Intelligence identified [Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria](#). This updates the 2010 McDonald criteria with the following changes: 'in patients with a typical clinically isolated syndrome and clinical or MRI demonstration of dissemination in space, the presence of CSF-specific oligoclonal bands allows a diagnosis of multiple sclerosis; symptomatic lesions can be used to demonstrate dissemination in

space or time in patients with supratentorial, infratentorial, or spinal cord syndrome; and cortical lesions can be used to demonstrate dissemination in space' and 'at the time of diagnosis, a provisional disease course should be specified (relapsing-remitting, primary progressive, or secondary progressive) and whether the course is active or not, and progressive or not based on the previous year's history. The phenotype should be periodically re-evaluated based on accumulated information'.

## Impact statement

The updated diagnostic criteria may have an impact on the recommendations concerning the diagnosis of MS, the information and support people with MS receive at diagnosis and when their condition is reviewed.

There were several systematic reviews identified concerning the diagnosis of optic neuritis and neuromyelitis optica. The evidence indicates that AQP4 detection in serum with immunoassay may be useful in differentiating NMO from MS; and retinal nerve fiber layer loss measured by optical coherence tomography may be useful in differentiating NMO or ON from MS. For ON, ultrasonography of optic nerve diameter may be used for the diagnosis of acute ON, ganglion cell layer thinning may be an indicator of neurodegeneration in ON and MS. The current recommendations 1.1.10 and 1.1.11 do not provide this level of detail, but highlight the need to refer to specialists who will use established up-to-date criteria for diagnoses.

**New evidence identified that may change current recommendations.**

## 1.2 Providing information and support

### **Recommendations in this section of the guideline**

- 1.2.1 NICE has produced guidance on the components of good patient experience in adult NHS services. This includes recommendations on communication, information and coordination of care. Follow the recommendations in [Patient experience in adult NHS services](#) (NICE clinical guideline 138).

#### **Information at the time of diagnosis**

- 1.2.2 The consultant neurologist should ensure that people with MS and, with their agreement their family members or carers, are offered oral and written information at the time of diagnosis. This should include, but not be limited to, information about:
- what MS is
  - treatments, including disease-modifying therapies
  - symptom management
  - how support groups, local services, social services and national charities are organised and how to get in touch with them
  - legal requirements such as notifying the [Driver and Vehicle Licensing Agency \(DVLA\)](#) and legal rights including social care, employment rights and benefits.
- 1.2.3 Discuss with the person with MS and their family members or carers whether they have social care needs and if so refer them to social services for assessment. Ensure the needs of children of people with MS are addressed.
- 1.2.4 Offer the person with MS a face-to-face follow-up appointment with a healthcare professional with expertise in MS to take place within 6 weeks of diagnosis.

#### **Ongoing information and support**

- 1.2.5 Review information, support and social care needs regularly. Continue to offer information and support to people with MS or their family members or carers even if this has been declined previously.
- 1.2.6 Ensure people with MS and their family members or carers have a management plan that includes who to contact if their symptoms change significantly.
- 1.2.7 Explain to people with MS that the possible causes of symptom changes include:
- another illness such as an infection
  - further relapse
  - change of disease status (for example progression).
- 1.2.8 Talk to people with MS and their family members or carers about the possibility that the condition might lead to cognitive problems.

- 1.2.9 When appropriate, explain to the person with MS (and their family members or carers if the person wishes) about advance care planning and power of attorney.

## Surveillance decision

This recommendation should be updated.

## Editorial amendments

None

## 2018 surveillance summary

### Providing information and support

No directly relevant evidence was identified, but indirectly relevant evidence was identified and is described in the summary for recommendation 1.3.

### Intelligence gathering

Initial intelligence gathering identified the following reports on patients' experiences of living with MS:

[Anthony: Multiple Sclerosis and Mental Health](#) describes the experiences of mental health for a person with MS, and how he feels it isn't understood by the public or medical profession and that he isn't listened to.

[Not NICE Enough, A qualitative study of MND, MS and Parkinsons Pathways in accordance with the National Institute of Health and Care Excellence \(NICE\) Guidance](#) reports on a survey that aimed to understand the experiences of patients with neurological conditions (including MS) in Staffordshire and Stoke-on-Trent in order to identify gaps in the services; and follow on qualitative research designed to understand the experience of people with MS, motor neurone disease and Parkinson's against NICE guidelines to identify gaps and barriers in the pathways.

The authors reported that in MS care 'there was a lack of provision of support during diagnosis' and a lack of 'consistent follow-up after diagnosis'. Results included 13 respondents (54.17%) reporting that 'they were not given support at the time of diagnosis to manage and understand the condition by the consultant neurologist making the diagnosis', which was highlighted across all of the 6 clinical commissioning group (CCG) areas; and 'all the respondents in East Staffordshire, Cannock Chase and Warwickshire North CCG had reported the lack of follow-up after diagnosis.'

[Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria](#) includes the recommendation that 'at the time of diagnosis, a provisional disease course should be specified (relapsing-remitting, primary progressive, or secondary progressive) and whether the course is active or not, and progressive or not based on the previous year's history. The phenotype should be periodically re-evaluated based on accumulated information'.

A topic expert highlighted that there are 4 main types of MS, which have differing outcomes and there can be a range of interventions for each type, which people with MS should be made aware of.

## Impact statement

Evidence was identified concerning the patient experience which indicates that there is a problem with the implementation of person-centred care, rather than an issue with existing recommendations as recommendation 1.2.1 highlights [Patient experience in adult NHS services](#) (NICE clinical guideline 138) and the importance of providing information and support at the time of diagnosis.

The new diagnostic criteria, which includes recommendations concerning determining the disease course, along with views that patients should have further information concerning the type of MS they have, indicate that this recommendation may require updating.

**New evidence identified that may change current recommendations.**

## 1.3 Coordination of care

### Recommendations in this section of the guideline

- 1.3.1 Care for people with MS using a coordinated multidisciplinary approach. Involve professionals who can best meet the needs of the person with MS and who have expertise in managing MS including:
- consultant neurologists
  - MS nurses
  - physiotherapists and occupational therapists
  - speech and language therapists, psychologists, dietitians, social care and continence specialists
  - GPs.
- 1.3.2 Offer the person with MS an appropriate single point of contact to coordinate care and help them access services.

### Surveillance decision

This recommendation should not be updated.

### Editorial amendments

None

### 2018 surveillance summary

### Co-ordination of care

A systematic review included 8 studies evaluating the barriers to accessing and using health care services that people with MS face. The authors reported that, looking at the continuum of health care delivery, in the before-visit phase transportation was a common barrier. During the healthcare visit quality of communication was the major concern. After the visit, the major barrier was discontinued referral. [6]

A systematic narrative review of 5 qualitative studies was undertaken to evaluate people with MS' experiences of UK health care services. It was reported that studies mostly investigated diagnosis or palliative care, with the following themes identified as important: the emotional experience of health care, continuity of care and access to services, and support from health care professionals. Studies were assessed using CASP and found to be mainly of poor quality and focussed on a homogenous sample. [7]

A systematic review of 17 qualitative studies explored the conceptual understanding of the experiences of carers of people with MS to identify factors that affect carers' quality of life (QoL). A meta-synthesis resulted in 9 themes: 'changes and losses, challenges revolving around MS, caregiving demands, burden of care, future concerns, external stressors, experiences of support, strategies used in managing the caregiving role, and motivating factors'. [8]

A qualitative study explored the perspectives and experiences of healthcare professionals and people with

MS in UK healthcare services for MS. Semi-structured interviews were undertaken with people with MS (n=24), practice nurses (n=13), GPs (n=12) and MS specialist nurses (n=9). A thematic analysis mapped themes onto NICE guideline CG186. Continuity of care and patient-centred responsive care were of key importance for people with MS and professionals; but people with MS reported poor experiences of care that included: poor access to services, poor continuity of care, and poor interpersonal interactions. [9]

A systematic review included 26 studies evaluating the costs and benefits of integrated care models for patients with chronic diseases including MS (2 studies). The incremental cost for integrated care models in treating people with MS ranged from - €822 to + €339.43. One of the 2 studies reported a positive economic impact of integrated care models. [10]

### Intelligence gathering

Initial intelligence gathering identified [MS treatment in England: is access still a lottery?](#) which reports on the findings of a survey on the treatment, health and care of people with MS in the UK (n=11,024; carried out between February and April 2016). Key findings include:

- 'In England, 56% of those who could potentially benefit from taking a disease modifying therapy (DMT) are doing so (an increase from 40% in 2013).
- Only a small number of respondents in England are taking symptom management treatments specifically licensed for MS ...

- Access to health professionals and the right information are key to access to a DMT – 81% of people who have access to MS specialists and the right information are taking a DMT but just 10% of people who could benefit from these treatments and did not access any of these services, are taking one.
- 86% of respondents had their need for access to a neurologist met (increase from 83% in 2013). 83% of respondents had not been offered a care plan or a care plan review for their health care.
- 17% of survey respondents answered “not at all” when asked if they felt that the professionals who help plan their care worked well together.
- The most common key contact for health care and support in relation to MS was a specialist nurse (45%). One in five identified their GP as their key contact for health care and support in relation to their MS.
- A quarter of respondents (26%) required support to remain physically

active in the past 12 months but had not received any.

- One in five of respondents required emotional support but had not received this.’

A topic expert noted that there is on-going research looking at the added value of MS nurses (no reference given).

### Impact statement

The qualitative evidence highlights the barriers faced by people with MS in accessing services and in receiving healthcare that meets their needs. A specific literature search for research exploring the impact of MS nurses on delivering healthcare to people with MS did not yield any publicly available peer-reviewed research. While there appear to be issues with the implementation of recommendation 1.3 (and recommendation 1.2), the evidence does not indicate that the recommendations require updating.

New evidence is unlikely to change guideline recommendations.

## 1.4 Modifiable risk factors for relapse or progression of MS

### Recommendations in this section of the guideline

#### Exercise

- 1.4.1 Encourage people with MS to exercise. Advise them that regular exercise may have beneficial effects on their MS and does not have any harmful effects on their MS.

#### Vaccinations

- 1.4.2 Be aware that live vaccinations may be contraindicated in people with MS who are being treated with disease-modifying therapies.
- 1.4.3 Discuss with the person with MS:
- the possible benefits of flu vaccination **and**

- the possible risk of relapse after flu vaccination if they have relapsing–remitting MS.

1.4.4 Offer flu vaccinations to people with MS in accordance with national guidelines, which recommend an individualised approach according to the person's needs\*.

### Pregnancy

1.4.5 Explain to women of childbearing age with MS that:

- relapse rates may reduce during pregnancy and may increase 3–6 months after childbirth before returning to pre-pregnancy rates
- pregnancy does not increase the risk of progression of disease.

1.4.6 If a person with MS is thinking about pregnancy, give them the opportunity to talk with a healthcare professional with knowledge of MS about:

- fertility
- the risk of the child developing MS
- use of vitamin D before conception and during pregnancy
- medication use in pregnancy
- pain relief during delivery (including epidurals)
- care of the child
- breastfeeding.

### Smoking

1.4.7 Advise people with MS not to smoke and explain that it may increase the progression of disability. (See [Smoking cessation services](#) NICE public health guideline 10.)

\* 'Chronic neurological disease: conditions in which respiratory function may be compromised, due to neurological disease (e.g. polio syndrome sufferers). Clinicians should consider on an individual basis the clinical needs of patients including individuals with cerebral palsy, multiple sclerosis and related or other similar conditions; or hereditary and degenerative disease of the nervous system of muscles; or severe disability.' (Department of Health 2013)

### Surveillance decision

No new information was identified at the surveillance review.

### Editorial amendments

Recommendation 1.4.7 references [Smoking cessation services](#) NICE public health guideline 10, this guideline no longer exists, it has been replaced by [Stop smoking interventions and services](#) NICE guideline NG92. The recommendation should be updated with the new guideline information.

### 2018 surveillance summary

### Modifiable risk factors for relapse or progression of MS

No relevant evidence was identified.

### Impact statement

No new evidence. Recommendations are unlikely to change.

### Intelligence gathering

No relevant evidence was identified.

## 1.5 MS symptom management and rehabilitation

### Recommendations in this section of the guideline

The guideline does not make recommendations for all symptoms that occur in people with MS. Some symptoms are addressed in other NICE guidelines and these are referenced where appropriate.

- 1.5.1 Determine how often the person with MS will need to be seen based on:
- their needs, and those of their family and carers **and**
  - the frequency of visits needed for different types of treatment (such as review of disease-modifying therapies, rehabilitation and symptom management).

#### Fatigue

- 1.5.2 Assess and offer treatment to people with MS who have fatigue for anxiety, depression, difficulty in sleeping, and any potential medical problems such as anaemia or thyroid disease.
- 1.5.3 Explain that MS-related fatigue may be precipitated by heat, overexertion and stress or may be related to the time of day.
- 1.5.4 Offer amantadine\* to treat fatigue in people with MS.
- 1.5.5 Consider mindfulness-based training, cognitive behavioural therapy or fatigue management for treating MS-related fatigue.
- 1.5.6 Advise people that aerobic, balance and stretching exercises including yoga may be helpful in treating MS-related fatigue.
- 1.5.7 Do not use vitamin B<sub>12</sub> injections to treat fatigue in people with MS.
- 1.5.8 Consider a comprehensive programme of aerobic and moderate progressive resistance activity combined with cognitive behavioural techniques for fatigue in people with MS with moderately impaired mobility (an EDSS\*\* score of greater than or equal to 4).

#### Mobility

- 1.5.9 Ensure people with MS and mobility problems have access to an assessment to establish individual goals and discuss ways in which to achieve them. This would

usually involve rehabilitation specialists and physiotherapists with expertise in MS.

- 1.5.10 Do not use fampridine to treat lack of mobility in people with MS because it is not a cost effective treatment†.

### **Mobility or fatigue**

- 1.5.11 Consider supervised exercise programmes involving moderate progressive resistance training and aerobic exercise to treat people with MS who have mobility problems and/or fatigue.

### **Mobility and/or fatigue with balance problems**

- 1.5.12 Consider vestibular rehabilitation for people with MS who have fatigue or mobility problems associated with limited standing balance.

### **Treatment programmes for mobility and/or fatigue**

- 1.5.13 Encourage people with MS to keep exercising after treatment programmes end for longer term benefits (see [Behaviour change: individual approaches](#) NICE public health guideline 49).
- 1.5.14 Help the person with MS continue to exercise, for example by referring them to exercise referral schemes.
- 1.5.15 If more than one of the interventions recommended for mobility or fatigue are suitable, offer treatment based on which the person prefers and whether they can continue the activity after the treatment programme ends.

### **Spasticity**

- 1.5.16 In people with MS assess and offer treatment for factors that may aggravate spasticity such as constipation, urinary tract or other infections, inappropriately fitted mobility aids, pressure ulcers, posture and pain.
- 1.5.17 Encourage people with MS to manage their own spasticity symptoms by explaining how doses of drugs can be adjusted within agreed limits.
- 1.5.18 Ensure that the person with MS:
- has tried the drug at an optimal dose, or the maximum dose they can tolerate
  - stops the drug if there is no benefit at the maximum tolerated dose
  - has their drug treatment reviewed at least annually once the optimal dose has been reached.
- 1.5.19 Consider baclofen or gabapentin†† as a first-line drug to treat spasticity in MS depending on contraindications and the person's comorbidities and preferences. If the person with MS cannot tolerate one of these drugs consider switching to the other.
- 1.5.20 Consider a combination of baclofen and gabapentin††,‡ for people with MS if:
- individual drugs do not provide adequate relief **or**
  - side effects from individual drugs prevent the dose being increased.

- 1.5.21 Consider tizanidine or dantrolene as a second-line option to treat spasticity in people with MS.
- 1.5.22 Consider benzodiazepines as a third-line option to treat spasticity in MS and be aware of their potential benefit in treating nocturnal spasms.
- 1.5.23 Do not offer Sativex to treat spasticity in people with MS because it is not a cost effective treatment††.
- 1.5.24 If spasticity cannot be managed with any of the above pharmacological treatments, refer the person to specialist spasticity services.

#### **Oscillopsia#**

- 1.5.25 Consider gabapentin†† as a first-line drug to treat oscillopsia in people with MS.
- 1.5.26 Consider memantine⊥ as the second-line treatment for oscillopsia in people with MS.
- 1.5.27 Refer the person with MS for specialist advice if there is no improvement of oscillopsia after treatment with gabapentin and memantine or side effects prevent continued use.

#### **Emotional lability◇**

- 1.5.28 Consider amitriptyline◆ to treat emotional lability in people with MS.

#### **Pain**

- 1.5.29 Treat neuropathic pain in people with MS according to [Neuropathic pain – pharmacological management](#) (NICE clinical guideline 173) and refer to pain services if appropriate.
- 1.5.30 Be aware that musculoskeletal pain is common in people with MS and is usually secondary to problems with mobility and posture. Assess musculoskeletal pain, offer treatment to the person and refer them as appropriate.

#### **Cognition including memory**

- 1.5.31 Be aware that the symptoms of MS can include cognitive problems, including memory problems that the person may not immediately recognise or associate with their MS.
- 1.5.32 Be aware that anxiety, depression, difficulty in sleeping and fatigue can impact on cognitive problems. If a person with MS experiences these symptoms and has problems with memory and cognition, offer them an assessment and treatment.
- 1.5.33 Consider referring people with MS and persisting memory or cognitive problems to both an occupational therapist and a neuropsychologist to assess and manage these symptoms.

\* At the time of publication (October 2014), amantadine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing medicines – guidance for doctors](#) for further information.

\*\* Expanded Disability Status Scale.

† This recommendation does not apply to people who have already started treatment with fampridine in the NHS who should be able to continue treatment until they and their NHS clinician think it appropriate to stop.

†† At the time of publication (October 2014), gabapentin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing medicines – guidance for doctors](#) for further information.

‡ Use caution when using gabapentin and baclofen in combination. For more information on cautions for these drugs see the summary of product characteristics for [gabapentin](#) and [baclofen](#) and the [British National Formulary](#).

‡‡ This recommendation does not apply to people who have already started treatment with Sativex in the NHS who should be able to continue treatment until they and their NHS clinician think it appropriate to stop.

# The subjective sensation of horizontal and/or vertical movement of the visual field that is unexplained by movement of the observer or environment.

⊥ At the time of publication (October 2014), memantine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing medicines – guidance for doctors](#) for further information.

◇ Involuntary laughing and crying related to a frontal lobe lesion.

◆ At the time of publication (October 2014), amitriptyline did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing medicines – guidance for doctors](#) for further information.

## Surveillance decision

This recommendation should be updated.

## Editorial amendments

Recommendation 1.5.18 should be amended with information that would cover concerns about stopping drug use, including abrupt withdrawal of baclofen. The recommendation should be edited to read as:

- 1.5.18 Ensure that the person with MS:
- has tried the drug at an optimal dose, or the maximum dose they can tolerate
  - stops the drug if there is no benefit at the maximum tolerated dose; but note any special precautions required when stopping specific drugs.
  - has their drug treatment reviewed at least annually once the optimal dose has been reached.

Recommendation 1.5.32 should reference [Depression in adults with chronic physical health problems](#) NICE clinical guideline 91. The recommendation should be edited to read as:

- 1.5.32 Be aware that anxiety, depression (see [Depression in adults with chronic physical health problems](#) NICE clinical guideline 91), difficulty in sleeping and fatigue can impact on cognitive problems. If a person with MS experiences these symptoms and has problems with memory and cognition, offer them an assessment and treatment.

Footnote hyperlinks for the summary of product characteristics for gabapentin and baclofen are broken; these should be:

<http://www.mhra.gov.uk/spc-pil/?subsName=GABAPENTIN&pageID=SecondLevel> for gabapentin and

<http://www.mhra.gov.uk/spc-pil/?subsName=BACLOFEN&pageID=SecondLevel> for baclofen.

## 2018 surveillance summary

### Fatigue

A systematic review of reviews investigated the effectiveness of pharmacological and non-pharmacological interventions for treating MS-related fatigue. Seventeen non-pharmacological, 5 pharmacological and 2 reviews combining non-pharmacological and pharmacological interventions were identified (covering 339 studies in total). The authors reported that there was no strong evidence supporting the use of pharmacological interventions in treating MS-related fatigue. For amantadine, there was limited/conflicting evidence of effectiveness. The only pharmacological treatment with potential benefits identified was modafinil [currently out of scope for NICE guideline CG186; see impact statement for further details]. For non-pharmacological treatments, there was strong evidence in favour of yoga and education (energy conservation/fatigue management programs) in treating MS-related fatigue. There was also evidence that exercise was effective in reducing fatigue, but this constituted a broad category of different types of exercise.

The authors also reported that there was evidence from a single intervention that a combination of physical and cognitive strategies showed 'promising results'. [11]

### Amantadine

A randomised control trial (RCT) (n=60 randomised, 59 treated) assessed whether amantadine (extended release capsules, 274 mg/day) compared with placebo was effective in improving walking ability in walking impaired people with MS when given over 4 weeks. A significant improvement in walking speed was observed (as measured by the Timed 25-Foot Walk test (T25FW)) and there was also a 10% placebo-adjusted improvement in timed up and go (TUG) test (stats=NR). There were no changes between groups in fatigue, depression, or cognition. The most frequently reported adverse events were dry mouth, constipation, and insomnia; 5 participants in the intervention group discontinued treatment due to adverse events, with 1 having a serious event (suspected serotonin syndrome). [12]

### Mindfulness, cognitive behavioural therapy (CBT) and fatigue management

A systematic review included 20 studies (n=1,249) in order to evaluate the effectiveness of psychological interventions in managing fatigue in people with MS. A meta-analysis was undertaken based on RCTs that reported sufficient data (n=NR). This revealed that levels of fatigue were significantly reduced in CBT compared with non-active and active controls (relaxation or psychotherapy); and in relaxation and mindfulness-based interventions compared with non-active controls. Heterogeneity in the 4 meta-analyses was described as varying from none to moderate. [13]

A systematic review included 16 wellness-based interventions (reported in 21 articles) undertaken with people with progressive MS. Level of evidence was evaluated using the American Academy of Neurology criteria (no data or statistics were reported in the abstract). The authors reported that there were 3 trials involving mindfulness-based training and reported that it is probably effective (level B evidence) on psychological distress, depression, anxiety, pain, and QoL in people with progressive MS (fatigue was not specifically reported on). [14]

A systematic review included 10 RCTs (n=1,021) that evaluated the effectiveness of patient education programs on fatigue in people with MS. Meta-analysis revealed that these programs have a significant positive effect on fatigue severity, but not on depression; and that patient education programs based on CBT have a greater effect on fatigue than other interventions that were categorised as teaching patients

ways of managing daily fatigue. In addition, interventions employing an individual approach led to a significant reduction in fatigue, while group-based approaches did not. [15]

A systematic review and meta-analysis included 4 RCTs (n=403) evaluating the effects of CBT for the treatment of MS-related fatigue. CBT was found to have a significant positive short-term effect on fatigue; and data from 3 RCTs indicated that CBT had a significant long-term effect on fatigue. The authors reported that the effect of CBT on fatigue decreases with cessation of treatment. [16]

A systematic review included 13 RCTs (n=1,617) evaluating the impact of psychosocial therapies for people with MS on depressive symptoms, anxiety, pain, fatigue, or health-related QoL. The authors reported that due to a lack of data, a meta-analysis was not possible to assess pain outcomes. But meta-analysis indicated that psychosocial therapies have a small but significant beneficial effect on depressive symptoms, anxiety, fatigue, mental and total health-related QoL. Interventions were found to be more effective for health-related QoL in patients with relapsing-remitting MS and when treatment doses were larger. CBT was reported to be ineffective when considered on its own, but the authors noted that this may be 'due to smaller treatment doses in CBT studies'. [17]

A systematic review included 11 RCTs (n=1,104) evaluating the effectiveness of telephone psychotherapy on psychological outcomes in people with MS. A meta-analysis revealed that compared with controls and other interventions, telephone psychotherapy resulted in a

moderate effect on depression, and small to moderate short-term effects on fatigue, QoL, MS symptoms, physical activity, and medication adherence. The authors assessed methodological quality using a 'standardised list of methodological criteria' and reported that all studies had at least 1 high or unclear risk of bias. [18]

A systematic review of 39 reviews evaluated the effectiveness of rehabilitation for improving function and participation in people with MS; quality of evidence was assessed using GRADE. The authors reported that there was 'strong' evidence that physical therapy improves activity and participation and that exercise-based educational programs reduce patient-reported fatigue. There was 'moderate' evidence that multidisciplinary rehabilitation leads to longer-term gains in activity and participation, that CBT improves depression and that information-provision interventions improves patient knowledge. Authors stated that there was 'limited' evidence of better patient outcomes from psychological and symptom management programs (fatigue, spasticity). The evidence was inconclusive for other rehabilitation interventions because of limited methodologically robust studies. [19]

#### Aerobic, balance and stretching exercises

A Cochrane review included 36 clinical trials in adults with MS (n=1,603) comparing exercise with no exercise or with other treatments. A meta-analysis of pooled data from 26 trials revealed that exercise therapy compared with non-exercise control had a significant effect on reducing fatigue; this applied to endurance training, mixed training (muscle power

training mixed with endurance training) and 'other' training (e.g. yoga, tai-chi). No side-effects/safety issues were associated with exercise therapy. [20]

A systematic review included 20 studies (14 RCTs and 6 non-RCTs; n=NR) evaluating the effect of strength training (using free weights, machine exercises and eccentric cycling) in adults with Parkinson disease or MS. Results of pooled data from people with MS reported that strength training significantly improved muscle strength, fatigue, functional capacity, QoL, power and electromyography activity. [21]

A systematic review including 10 RCTs with people with chronic conditions or age-related fatigue (n=689) evaluated the effectiveness of tai-chi in reducing fatigue. While a meta-analysis revealed that compared with 'conventional therapy' tai-chi significantly improves fatigue across populations, when studies with people with MS only were included (n=NR), no significant effects on fatigue were found. Studies were reported to be at high risk of bias due to lack of blinding (Cochrane Risk of Bias tool). [22]

A systematic review included 7 RCTs (n=670) evaluating the efficacy and safety of yoga in people with MS. Compared with usual care, yoga was associated with a significant improvement in fatigue and mood in the short-term effects, however the findings were described as 'not robust against bias'. There were no effects of yoga on health-related QoL, muscle function, or cognitive function. Yoga was not associated with any serious adverse events. [23]

#### Vitamin B12 injections

No evidence was identified.

## Other pharmacological treatments

An RCT (n=32) investigated the effects of prolonged-release fampridine on cognitive functioning, fatigue and depression in people with MS (off-label use of fampridine as it is only licensed for use in treating mobility in people with MS). Open-label treatment with prolonged-release-fampridine resulted in significant improvements in cognitive measures of alertness, psychomotor speed and verbal fluency; and significant improvements in patients' perception of reduced fatigue. In the second year there was a randomised, double-blind, placebo-controlled assessment which also reported significant improvements in the treatment compared with placebo group in 'phasic alertness' and measures of fatigue; and reported significant improvements in depressive symptoms. [24]

## Mobility

### Fampridine

A systematic review included 10 studies (RCTs, systematic reviews, and meta-analyses; n=NR) comparing the effects of dalfampridine versus task-specific gait training interventions in people with MS. There were no significant differences in gait speed between the interventions. [25]

A systematic review included 13 RCTs (n=NR) evaluating the efficacy and safety of various pharmacological treatments on gait outcomes in people with MS. In the 9 RCTs evaluating fampridine only 39% (pooled mean) of participants responded to the medication, in those people fampridine significantly increase gait speed. Fampridine 10 mg twice daily significantly improved gait endurance. [26]

An RCT (n=53) investigated the long-term efficacy of prolonged-release fampridine in people with MS. Participants were assessed regularly over 2 years with validated tools assessing gait (Timed 25-Foot Walk, 6-Minute Walk Test (6MWT), and 12-item MS Walking Scale): there were significant improvements in walking speed, endurance, and self-perceived ambulatory function during open-label and double-blind controlled treatment with fampridine. The authors reported that 'several patients showed changes in drug responsiveness over time, resulting in an increased proportion of patients exceeding 10% or 20% improvements in walking measures after long-term treatment'. [27]

A cross-over RCT (n=25) assessed the effectiveness of fampridine on gait in people with MS. There was a 17 meter improvement in the 6MWT in the treatment arm (p=0.08), which was considered significant by the authors. [28]

A 14 week pilot RCT (n=41) assessed the impact of prolonged-release fampridine 10mg versus placebo when added to a 6 week enabling active motor training intervention in people with MS. Participants were assessed for gait using the 6MWT and the five-times-sit-to-stand test at -4, 0, 6 and 14 weeks. There were no differences between groups, with gait measures remaining stable between -4 and 0 weeks and showing significant improvements at weeks 6 and 14. The authors reported that the fampridine group achieved a greater mean percentage improvement and had a higher number of responders in tasks, but noted that the study was underpowered to reach statistical significance. [29]

## Exercises

### General exercise/physical activity

A systematic review of 13 RCTs (n=NR) investigated the impact of exercise training on walking ability in people with MS. A meta-analysis found that there were significant improvements in walking speed when measured by the 10-m walk test, but not in the T25FW for exercise training; and there were significant improvements in endurance (increased walking distance measured by the 6-minute and 2-minute walk tests) for people with MS who exercised. There were no improvements in mobility (measured by the TUG test). [30]

A systematic review included 14 RCTs (n=NR) of interventions that aimed to change physical activity behaviour in people with MS. A meta-analysis indicated that there was a significant short-term increase in self-reported physical activity in studies with non-active control groups, but no change in objectively measured physical activity, nor in the long-term. [31]

A systematic review included 26 RCTs (n=1,295) evaluating the risks of relapse and other adverse events associated with exercise training in people with MS. The relative risk of relapse from exercise training compared with controls was 0.73; and while the relative risk of adverse events for exercise training compared with controls was 1.67, this risk was described as no higher than in healthy populations. [32]

A systematic review included 20 RCTs (n=NR) evaluating the effect of exercise training on muscular and cardiorespiratory fitness in people with MS. A meta-analysis indicated that exercise training is associated with significant changes in

muscular (small effect size) and cardiorespiratory (moderate effect size) fitness outcomes in people with MS. [33]

Note that a systematic review of 37 RCTs (n=NR) which evaluated interventions targeting risk factors for MS progressions reported no significant difference in EDSS scores after exercise interventions compared with untreated controls (data from 7 RCTs; described by authors as very low quality evidence). [34]

### Progressive resistance training

A systematic review evaluating the impairments of muscle mechanical function in people with MS included 10 studies that assessed the effects of progressive resistance training on muscle mechanical function. The results showed that progressive resistance training has a significant, small effect on muscle mechanical function in people with MS. [35]

### Gait training

A systematic review included 7 RCTs (n=205) comparing robot-assisted gait training (RAGT) with conventional walking rehabilitation treatment (CWT) in patients with MS. The results of a meta-analysis indicated that RAGT compared with CWT led to a significant improvement in 6MWT, but no significant differences in the Berg Balance Scale, 10-meter walk test, TUG test or stride length. [36]

### Whole body vibration (WBV) training

A systematic review included 7 RCT (n=250) evaluating the feasibility and efficacy of long-term WBV training in improving mobility of people with MS. A meta-analysis (n=201 as 41 patients withdrew from the studies) reported a

small significant improvement in 2-6 minute walking endurance from WBV, but no benefits in measures of short-distance walking speed or balance for people with MS. The methodological quality of studies was described as poor. [37] Another study reported on the meta-analysis (n=201) findings concerning the impact of WBV on functional mobility of people with MS: there was a significance improvement in knee extensor strength from WBV; but no differences in knee flexor strength, TUG test nor walking speed between controls and those in the WBV intervention. [38]

### **Remotely delivered interventions**

A systematic review included 9 studies evaluating the effectiveness and user experience of web-based interventions in increasing physical activity in people with MS. A meta-analysis of data from 4 studies found a significant improvement in self-reported physical activity in web-based interventions; and a narrative review of accelerometry data from 3 studies indicated increases in objective measures of physical activity. [39]

A systematic review of 11 RCTs (n=NR) investigated the effectiveness of technology-based distance physical rehabilitation interventions (via the internet, telephone, exergaming, and pedometers) in people with MS. The results of a meta-analysis indicate that there was a medium size, significant increase in physical activity in the technology-based intervention group when compared with control group (usual care, minimal treatment, and no treatment) in people with MS. Quality of the studies was described as good (details of quality appraisal tool not given in abstract). [40]

A systematic review of 11 studies (n=466) evaluated the effectiveness of virtual reality interventions on balance and gait in people with MS. A meta-analysis of the pooled data indicated that virtual reality balance training is more effective than no intervention for postural control improvement, but not when compared with conventional training. The results for virtual gait rehabilitation were described as inconclusive. [41]

### **Mobility and/or fatigue with balance problems**

A systematic review included 15 randomised/quasi-randomised studies (n=1,295) evaluating the effectiveness of falls management/balance rehabilitation interventions in people with MS compared with usual care or placebo. A meta-analysis indicated that there was a non-significant decrease in falls and a significant increase in balance in intervention groups, with gait, balance, and functional training interventions showing the largest effect sizes. [42]

A systematic review included 5 RCTs (n=NR) evaluating the effectiveness of commercial video games on postural balance in people with MS. A meta-analysis of data from 4 of the RCTs revealed that, compared with controls, video game therapy did not have an impact on balance when measured by the Four Step Square Test or T25FW scores. While there was a significant positive effect of intervention on balance when measured by the Berg Balance Scale, the authors reported that the effect was 'not greater than the minimum detectable change reported in the literature'. [43]

A systematic review included 8 RCTs/quasi-experimental trials evaluating

the impact of aquatic exercises on balance in people with multiple sclerosis, Parkinson's disease and hemiplegia. Aquatic exercise was reported to significantly improve static and dynamic balance and gait ability in patients with multiple sclerosis. The studies were described as having fair to good methodological quality, as assessed using the Downs and Black checklist. [44]

A systematic review and meta-analysis including 42 studies (n=1,480) evaluated the effects of dual-tasks and dual-task training on postural stability. The meta-analysis including only those studies involving people with MS (n=NR) found a non-significant adverse effect of dual-tasks on postural stability. [45]

A systematic review included 6 studies evaluating the effect of textured or other types of stimulating insoles on gait characteristics and balance/postural control in people with multiple sclerosis and Parkinson's disease. Five studies had low methodological quality and only 1 was of moderate quality (measured using CONSORT statement). There was no significant effect of these insoles on balance or gait impairment in people with MS. [46]

### **Treatment programmes for mobility and/or fatigue**

A systematic review included RCTs and other controlled trials (n=19) evaluating the impact of behaviour change interventions on physical activity in people with MS. Trials without a risk of bias were identified and meta-analysis of these trials reported that behaviour change interventions of 8-12 weeks duration significantly increased physical activity participation but did not significantly

impact on the physical components of QoL or fatigue. [47]

A systematic review assessed the effectiveness of rehabilitation treatments in people with MS (number of studies and study design inclusion criteria=NR). Level of evidence was evaluated using the American Academy of Neurology criteria (no data or statistics were reported in the abstract). The authors reported that: weekly home/outpatient physical therapy over 8 weeks is probably effective in improving balance, disability, and gait, but is probably ineffective for improving upper extremity dexterity; 3 weeks of inpatient exercises followed by 15 weeks of home exercises and 6 weeks of multidisciplinary outpatient rehabilitation were described as possibly effective in improving disability and/or function; Motor and sensory balance training or motor balance training over 3 weeks is possibly effective for improving balance; Breathing-enhanced upper extremity exercises over 6 weeks are possibly effective for improving gait but possibly ineffective for improving disability; and inspiratory muscle training for 10 weeks possibly improves maximal inspiratory pressure. The authors noted that there was a lack of well-designed studies in this area. [48, 49]

A systematic review of 9 qualitative studies reported on a meta-synthesis that aimed to identify factors influencing intention to exercise and the execution of exercise in people with MS. This reported that social support, professional support and outcome expectations influence intention to exercise and execution of exercise. [50]

A systematic review included 19 qualitative studies on the perceived

determinants and consequences of physical activity and exercise in people with MS. An inductive analysis guided by the Physical Activity for people with Disabilities framework and Social Cognitive Theory was undertaken. Identified perceived barriers to physical activity were environmental: 'minimal or no disabled facilities, and minimal or conflicting advice from healthcare professionals' and personal: fatigue, fear, apprehension. Perceived facilitators related to the environment: 'type of exercise modality and peer support' and personal facilitators: 'appropriate exercise and feelings of accomplishment'. Perceived benefits of physical activity/exercise: maintaining physical functions, increased social participation, feelings of self-management and control. Perceived adverse consequences: increased fatigue, feelings of frustration and lost control. [51]

## **Spasticity**

### **Pharmacological management of spasticity**

A systematic review included 23 RCTs (n=2,720) evaluating the efficacy and safety of pharmacological treatments for spasticity in people with MS. Results indicated that compared with placebo, cannabinoids and botulinum toxin led to a significant improvement in spasticity; botulinum toxin also resulted in significant improvements in spasticity when compared with tizanidine and baclofen. Significantly more 'mild' adverse effects were reported in people using cannabinoids, tizanidine and diazepam compared with placebo. The authors reported that botulinum toxin was the optimal treatment, and the surface under the cumulative ranking curves indicated that cannabinoids and transcutaneous

electrical nerve stimulation (TENS) could also be considered for treatment of spasticity if safety is verified. [52]

A systematic review included 13 RCTs (n=NR) evaluating the efficacy and safety of pharmacological treatments on gait outcomes in people with MS. Only 1 RCT was available on baclofen, which found it had no significant impact on gait. There were conflicting findings across 3 RCTs on the efficacy of cannabinoid on gait outcomes. [26]

A systematic review including RCTs and observational studies (n=NR) evaluated the effectiveness of pharmacological treatments of spasticity in people with MS. Results 'supported' the use of baclofen, tizanidine and gabapentin as first-line options, with diazepam or dantrolene as second-line options. Nabiximols (Sativex) was described as having a positive effect as an add-on therapy in patients with poor response and/or tolerance to first-line treatments. No statistics were reported in the abstract. [53]

A systematic review included 16 RCTs (n=2,597) evaluating the effectiveness of cannabinoids on spasticity and spasm frequency in people with MS. Compared with usual care or placebo cannabinoids did not significantly decrease spasticity or spasm frequency. Evidence was described as having 'moderate-certainty' (quality evaluation not described). Use of cannabinoids compared with placebo was associated with a significant increase in dizziness, somnolence and nausea. [54]

A two-phase pragmatic RCT (n=106) investigated the effects of Sativex as an add-on therapy to optimised standard anti-spasticity treatment in patients with moderate to severe MS-related spasticity.

In the 1st phase participants (n=191) received add-on Sativex for 4 weeks to identify initial responders (at least a 20% improvement from baseline in spasticity numerical rating scale (NRS) score). Following washout, initial responders (n=106) were then randomised to receive add-on Sativex or placebo for 12 weeks (double-blinded). In both phases anti-spasticity medications could be adapted in order to ensure patients received the optimal therapy. After 12 weeks of phase 2 there were significantly more people in the Sativex group that had a clinically relevant improvement in spasticity (at least a 30% improvement from baseline in NRS score) compared with placebo group; and there was a significant improvement in spasticity NRS, pain NRS and modified Ashworth's scale from baseline in phase 2 to week 12 in the Sativex group. [55]

### Cost-effectiveness

A systematic review included 10 studies assessing the economic costs and benefits of prescribed cannabis-based medicines for the management of MS. The results reported that 4 of 5 industry-sponsored cost-utility analyses for the use of nabiximols to treat spasticity in MS found that nabiximols was cost-effective from a European health system perspective, with 1 study from the UK indicating that it was not cost-effective: Incremental cost-effectiveness ratios per QALY gained were £49,257 (UK), £10,891 (Wales), €11,214 (Germany), €4968 (Italy) and dominant (Spain). No improvements in EQ-5D scores were found for nabiximols versus standard care for the management of MS spasticity. Study quality was reported as moderate overall, with limited inclusion of relevant societal costs and discussions of potential bias. [56]

A UK study assessed the cost-effectiveness of tetrahydrocannabinol/cannabidiol (THC/CBD) oromucosal spray in the treatment of moderate-severe spasticity in people with MS. A Markov model was developed to compare THC/CBD plus standard care (SC) treatments with SC alone. THC/CBD was found to be cost-effective and dominant if home care costs were included: at 30 years, total incremental cost for THC/CBD plus SC treatment was estimated at £3,836/patient; incremental cost-effectiveness ratio (ICER): £10,891/QALY. Hospital admission costs had the greatest effect on the base case ICER. Inclusion of carer cost led to incremental cost of -£33,609/patient (ICER: -£95,423/QALY). [57]

A study on the cost-effectiveness of Sativex adapted a previously published Markov model-based analysis for the Italian setting. Year of costing was 2013. The base case ICER for Sativex use in Italy over a 5-year period was estimated as €4,968 per QALY gained. ICER for Sativex remained below €30,000 per QALY gained when deterministic and probabilistic sensitivity analyses were conducted. [58]

### Botulinum toxin

A systematic review was undertaken to investigate the impact of botulinum neurotoxin on various outcomes in people with MS. Included study designs and number of studies included was not clearly described in the abstract. Level of efficacy was determined using assessment's criteria set forth by the Subcommittee on Guideline Development of the American Academy of Neurology. In relation to spasticity, the authors reported that there

was level B evidence (i.e. probably effective based on RCTs) supporting the use of intramuscular botulinum neurotoxin injections for spasticity in MS. [59]

### **Oscillopsia**

No evidence was identified.

### **Emotional lability**

No evidence was identified.

### **Pain**

A systematic review and meta-analysis included 4 RCTs (n=NR) evaluating the efficacy of TENS for chronic pain in people with MS. TENS was reported to have a significant, medium effect size, effect on pain. [60]

A systematic review included 13 'experimental studies' (n=NR) evaluating non-pharmacological strategies for managing pain in people with MS. Interventions included education, electrical stimulation, and physical therapies. Meta-analysis was not possible due to lack of data per intervention type. Results for education and physical therapies were reported as inconclusive; while results from 2 trials of TENS indicated that it may be effective in reducing central neuropathic pain in MS. [61]

### **Cognition including memory**

#### **Exercise**

A systematic review of 26 studies (including 6 RCTs) assessed the impact of exercise and physical activity on cognition in people with MS. The authors reported that the evidence for the effects of exercise on cognition in MS is conflicting but that there is 'overall positive, but not definitive evidence for the effects of physical activity and physical fitness' on

cognition in people with MS (no data or statistics were reported in the abstract). It was reported that 'there is insufficient well-designed research to definitively conclude that exercise, physical activity, and physical fitness are effective for improving cognition in MS' because of methodological issues of included studies (measured according to American Academy of Neurology criteria), poorly-developed exercise interventions, and a lack of studies including cognitively-impaired people with MS. [62]

A systematic review included 19 studies (study designs=NR) investigating the relationship between physical activity and cognitive performance in people with MS. The authors reported that 10 studies were on physical activity interventions; these reported mixed results on the effectiveness of physical activity in improving cognitive function in people with MS (no data or statistics were reported in the abstract). [63]

A systematic review included 13 RCTs on the effects of exercise therapy on the QoL of people with MS in Iran. A meta-analysis of the pooled data revealed significant, large effect sizes for exercise therapy on the mental, physical, and overall QoL for Iranian people with MS. Due to the heterogeneous nature of the interventions in the included studies, it is however not clear what the content of an effective exercise therapy program should be. [64]

#### **Rehabilitation**

A Cochrane review included 20 RCTs and quasi-randomised trials (n=966 MS participants and 20 healthy controls) that assessed the effects of cognitive training and neuropsychological rehabilitation on health-related factors in people with MS. A

meta-analyses of pooled data on cognitive training interventions revealed that these interventions significantly improved memory span and working memory. A meta-analyses of pooled data on cognitive training combined with other neuropsychological rehabilitation methods revealed that these interventions significantly improved attention, immediate verbal memory and delayed memory. The overall quality and comparability of studies was described by the authors as low due to methodological limitations and heterogeneity of interventions and outcome measures. [65]

A Cochrane review included 15 RCTs or quasi-randomised trials (n=989) that evaluated memory rehabilitation interventions for people with MS. Interventions included memory retraining techniques (e.g. computerised programmes and training on internal and external memory aids). Control conditions varied, and included assessment-only groups, discussion and games, non-specific cognitive retraining, and attention or visuospatial training. While there was evidence that memory rehabilitation interventions led to significant improvements in objective assessments of memory in the immediate and long-term, and in QoL in the immediate follow-up, this was mainly due to lower quality studies inflating the results. It was reported that, compared with control groups, intervention groups had significantly more difficulties in completing activities of daily living in long-term follow-up, but no differences on immediate follow-up. There were no significant immediate or long-term effects on subjective reports of memory problems or mood; and no significant long-term

effects on QoL. The risk of bias of the included studies was described as generally low, but 8 studies had high risk of bias. [66]

A systematic review of reviews (n=39) evaluated the effectiveness of rehabilitation for improving function and participation in people with MS. GRADE was used to assess quality of evidence. The authors reported that there was 'moderate' evidence that multidisciplinary rehabilitation leads to longer-term gains in activity and participation, that CBT improves depression and that information-provision interventions improves patient knowledge. [19]

A meta-analysis of 9 studies (RCTs and non-RCTs; n=NR) investigated the effectiveness of computer-based cognitive rehabilitation on the neuropsychological performance of patients with MS. Computer-based cognitive training interventions were reported to have a significant effect on the performance of the memory domain of patients with MS, in particular in Selective Reminding Test, delayed recall. [67]

A systematic review of 7 qualitative studies (n=195) reported on a meta-synthesis of people with MS' perspectives of cognitive rehabilitation for memory, attention, and executive function problems. A thematic synthesis approach identified that people with MS who have cognitive deficits benefit from cognitive rehabilitation programmes: they benefited from a rehabilitation group environment, it enabled reflection and awareness of their cognitive deficits, was associated with increased knowledge and understanding of their illness; 'increased strategy use was reported and associated with

improvements in cognitive functioning and greater confidence and perseverance; participants reported emotional and social improvements, and felt more optimistic'. [68]

### Assessment

A systematic review reported on 48 studies (n=1,483) investigating the feasibility and safety of cardiopulmonary exercise testing (CPET) in people with MS. Test abnormalities, reported in 10% of tests, were mainly due to being unable to maintain pedalling at a specific resistance, this was interpreted as indicating that the CPET is feasible as long as it is 'tailored to the physical abilities of the patient'. All adverse events were temporary and only occurred in 2.1% of tests. [69]

A systematic review included 40 studies (n=165 controls and 1,137 with MS) assessing the psychometric properties of the VO<sub>2</sub> max test of aerobic capacity in people with MS, reporting the aerobic capacity in people with MS compared with healthy people, or evaluating the effects of exercise on VO<sub>2</sub> max in people with MS. Results were reported as indicating that VO<sub>2</sub>max testing is a valid measure of aerobic capacity in people with MS who have low-to-mild disability, and an (approximately) 10% change between 2 tests performed on separate days is considered the smallest reliable change (with 95% certainty) in VO<sub>2</sub>max in this population. A meta-analysis of longitudinal exercise studies found that aerobic training improves VO<sub>2</sub> max in people with MS 'to a degree that is associated with secondary health benefits' (statistical significance not reported in abstract). [70]

A systematic review of 33 studies (19 cross-sectional, 5 RCTs, 9 with prospective

study designs; n=3,901) assessed the ability of measures of balance to identifying risk of falling in people with MS. A meta-analysis revealed that people with MS who are 'fallers' performed significantly worse than non-fallers on all balance measures analysed except the TUG (Cognitive) test. The measures were however described as having poor predictive ability for falls risk in people with MS. [71]

A systematic review included 120 studies (n=NR) assessing the psychometric properties (validity, reliability, sensitivity of change) of the EDSS and Multiple Sclerosis Functional Composite (MSFC). The authors reported that the EDSS has some 'weaknesses' in reliability and sensitivity to change, while the MSFC is limited by learning effects and the z-scores method used to calculate the total score (no data or statistics were reported in the abstract); but concluded that both instruments are 'suitable to detect the effectiveness of clinical interventions and to monitor disease progression'. [72]

A systematic review and meta-analysis assessed the psychometric properties of generic utility measures in MS. The following measures were included: the EQ-5D (n = 9 studies), EQ-5D-5 Level (n = 1), the Health Utilities Index Mark 3/2 (HUI2/HUI3) (n = 3), the SF-6D (n = 2), the Assessment of Quality of Life (AQOL) (n = 2), and the Quality of Well-Being (QWB) scale (n = 1). The HUI3 demonstrated the strongest psychometric properties when compared with other utility measures (reliability and discriminative ability for levels of disability), but it only measures impairment and excludes important components of HRQL (e.g. participation restrictions). While the EQ-5D, SF-6D and

QWB scale include items on participation, they demonstrated a lack of content validity in MS by missing certain domains that were important to the disease, as well as difficulty in differentiating between different levels of disability in MS (mild/moderate/severe). [73]

A systematic review included 4 studies (n=NR) assessing the psychometric properties of anxiety screening tools for measuring anxiety in people with MS. The following tools were assessed: the Hospital Anxiety and Depression Scale-Anxiety (HADS-A), Beck Anxiety Inventory (BAI), and 7-item Generalized Anxiety Disorder Scale (GAD-7). All tools were validated against reference standards; the authors reported that HADS-A had higher measures of sensitivity and specificity than BAI and the GAD-7 (no data or statistics reported). [74]

## Intelligence gathering

It was noted that the [British National Formulary](#) advises that baclofen is not withdrawn abruptly, as this is associated with a risk of hyperactive state, may exacerbate spasticity, and precipitate autonomic dysfunction including hyperthermia, psychiatric reactions and convulsions; to minimise risk. It advises discontinuing baclofen treatment by gradual dose reduction over at least 1–2 weeks (longer if symptoms occur).

The following on-going research was identified:

A Cochrane review on [Interventions for preventing falls in people with multiple sclerosis](#)

[Changing physical activity behaviour in people with MS: the iStep-MS trial](#)

A Cochrane review on [Non-pharmacological interventions for chronic pain in multiple sclerosis](#)

A Cochrane review on [Rehabilitation for people with multiple sclerosis: an overview of Cochrane systematic reviews](#)

[Cognitive Rehabilitation for Attention and Memory in people with Multiple Sclerosis \(MS\)](#)

[An evaluation of an online mindfulness programme for people with multiple sclerosis](#)

A topic expert expressed concern that the current recommendations function as a list for managing symptoms rather than reflecting a rehabilitation approach, for example, considering how people with MS can balance the use of one drug/intervention against another when looking at function.

## Impact statement

The recommendations on symptom management and rehabilitation have been structured in relation to symptoms and interventions that may address each symptom, but have not considered how different interventions may address multiple symptoms, or the possible interactive effects of prescribing multiple pharmacotherapies for different symptoms. It is recommended that a rehabilitation approach is considered when this recommendation is updated with details highlighted below.

### Fatigue

Recommendation 1.5.4 recommends offering amantadine to treat fatigue in people with MS, however new evidence from a systematic review of reviews and an RCT indicates that amantadine may not

be an effective treatment. It should be noted that the systematic review of reviews did not provide a meta-analysis of the data that contributed to reviews in order to support these conclusions. The authors of the systematic review also reported that modafinil was the only pharmacological treatment with potential benefits on fatigue. Modafinil was not included for consideration in NICE guideline CG186 because of a [European Medicines Agency directive](#) which states that there are significant harms associated with the drug and concluded that 'the benefits of modafinil-containing medicines continue to outweigh their risks only in the treatment of narcolepsy'. Modafinil is not licensed for treating fatigue in MS. There is a [NICE evidence summary](#) published in April 2013 on the use of modafinil for MS-related fatigue which concluded that 'RCTs do not provide any evidence of the longer-term safety and efficacy of modafinil for treating fatigue in MS', however this conclusion was based on 2 small RCTs. Due to the mixed findings concerning the effectiveness of amantadine on fatigue, the pharmacological treatment of fatigue should be considered for an update.

The new evidence indicates that offering mindfulness-based training, CBT or fatigue management is effective for treating MS-related fatigue, as recommendation 1.5.5 currently only recommends that these interventions are 'considered', this evidence could be reviewed to assess whether the strength of the recommendation could be changed. The new evidence supports the current recommendation 1.5.6 to advise people that aerobic, balance and stretching exercises including yoga may be helpful in treating MS-related fatigue.

As no evidence was identified concerning the use of vitamin B<sub>12</sub> injections to treat fatigue, there is no indication that recommendation 1.5.7 requires updating.

### Mobility

There was mixed evidence concerning the effectiveness of fampridine on mobility (measured by gait speed or endurance), in people with MS. While most studies reported that fampridine significantly improved mobility when compared with placebo, it did not seem to improve mobility when compared with gait training interventions. No cost-effectiveness studies were identified. Given the new evidence on effectiveness, it is recommended that assessment of the cost-effectiveness of fampridine for treating mobility in people with MS is considered for update.

New evidence was identified that indicated exercise training leads to an improvement in physical activity. Only 1 systematic review was identified that looked at resistance training, results of which support recommendation 1.5.11 to provide resistance training to improve mobility in people with MS. No specific evidence was identified concerning the impact of aerobic activity *per se* on mobility. There was new evidence that indicates that exercise training delivered remotely can lead to increases in physical activity and possibly mobility. The new studies provide evidence that addresses [research recommendation 2.3](#) on determining the optimal frequency, intensity and form of rehabilitation for mobility problems in people with MS.

### Mobility and/or fatigue with balance problems

No evidence was identified concerning the effectiveness of vestibular rehabilitation on balance (recommendation 1.5.12); but new evidence was identified indicating that falls management/balance rehabilitation and aquatic exercises can lead to improvements in balance for people with MS. Evidence on falls management/balance rehabilitation and aquatic exercises on balance should be considered in an update.

### Treatment programmes for mobility and/or fatigue

The new evidence is in line with current recommendations to support people in continuing to engage in physical activity by considering the principles of behaviour change and patient choice.

### Spasticity

Evidence was mixed concerning the effectiveness of baclofen as a first-line treatment for spasticity in people with MS. It was also noted that there is a safety warning concerning the withdrawal of baclofen treatment that should be highlighted within recommendation 1.5.18 following information on discontinuation of treatment (see [editorial amendments](#)).

Evidence supported recommendations to prescribe gabapentin, tizanidine, dantrolene and benzodiazepines for spasticity in people with MS. There was also evidence supporting the use of botulinum toxin (not currently recommended, but within scope) and Sativex in treating spasticity. While Sativex is not currently recommended for use in treating spasticity as it was found to be not cost-effective (recommendation

1.5.23), more recent cost-effectiveness studies indicate that it may be cost-effective. Evidence concerning the effectiveness of botulinum toxin and cost-effectiveness of Sativex for treating spasticity in people with MS should be considered in an update of NICE guideline CG186.

### Pain

There are currently no recommendations concerning non-pharmacological management of pain; however there is a small body of evidence that indicates that TENS is effective in relieving pain in people with MS. There is also an on-going Cochrane review on non-pharmacological interventions for chronic pain in MS that could inform an update in this area, once published.

### Cognition including memory

Recommendations 1.5.31-33 highlight the need to assess and treat cognitive problems; but there are no details provided of interventions that may be beneficial for people with MS that experience cognitive problems.

The new evidence reports mixed results concerning the effectiveness of exercise on improving cognition in people with MS, although it may improve QoL overall.

While methodological quality of studies is reported as low overall, and intervention and control content varies in RCTs assessing cognitive rehabilitation programmes, Cochrane and systematic review level evidence indicates that rehabilitation programmes can lead to improvements in memory in people with MS. The current recommendations 1.5.31-33 should be updated with additional details concerning the content of effective

cognitive rehabilitation programmes for improving memory in people with MS. There is also an on-going Cochrane review on cognitive rehabilitation for people with MS that could inform an update in this area, once published.

### Assessment

There is systematic review level evidence that indicates that there are suitable tools for assessing functional ability in people

with MS. The EDSS tool for MS, is mentioned within the recommendations, but it is beyond the remit of the guideline to recommend specific tools that should be used to assess function in people with MS.

**New evidence identified that may change current recommendations.**

## 1.6 Comprehensive review

### Recommendations in this section of the guideline

- 1.6.1 Ensure all people with MS have a comprehensive review of all aspects of their care at least once a year.
- 1.6.2 Ensure the comprehensive review is carried out by healthcare professionals with expertise in MS and its complications. Involve different healthcare professionals with expertise in specific areas of the review if needed.
- 1.6.3 Tailor the comprehensive review to the needs of the person with MS assessing:
  - MS symptoms:
    - mobility and balance including falls
    - need for mobility aids including wheelchair assessment
    - use of arms and hands
    - muscle spasms and stiffness
    - tremor
    - bladder (see [Urinary incontinence in neurological disease](#) NICE clinical guideline 148), bowel (see [Faecal incontinence](#) NICE clinical guideline 49) and sexual function
    - sensory symptoms and pain
    - speech and swallowing (see [Nutrition support in adults](#) NICE clinical guideline 32)
    - vision
    - cognitive symptoms
    - fatigue

- depression (see [Depression in adults with chronic physical health problems](#) NICE clinical guideline 91) and anxiety (see [Generalised anxiety disorder and panic disorder](#) NICE clinical guideline 113)
- sleep
- respiratory function.
- MS disease course:
  - relapses in last year.
- General health:
  - weight
  - smoking, alcohol and recreational drugs
  - exercise
  - access to routine health screening and contraception
  - care of other chronic conditions.
- Social activity and participation:
  - family and social circumstances
  - driving and access to transport
  - employment
  - access to daily activities and leisure.
- Care and carers:
  - personal care needs
  - social care needs
  - access to adaptations and equipment at home.

- 1.6.4 Refer any issues identified during the comprehensive review of the person with MS to members of the MS multidisciplinary team and other appropriate teams so that they can be managed.
- 1.6.5 Ensure people with MS are offered a medication review in line with [Medicines adherence](#) (NICE clinical guideline 76).
- 1.6.6 Ensure people with MS have their bone health regularly assessed and reviewed in line with [Osteoporosis: assessing the risk of fragility fracture](#) (NICE clinical guideline 146).
- 1.6.7 Ensure people with MS and severely reduced mobility are regularly assessed and reviewed for risk of contractures.\*

- 1.6.8 Check people with MS and severely reduced mobility at every contact for areas at risk of pressure ulcers (see [Pressure ulcers](#) NICE clinical guideline 179).
- 1.6.9 Discuss the care provided by carers and care workers as part of the person's care plan. Ensure carers know about their right to a local authority carer's assessment and how to apply for one.
- 1.6.10 Refer people with MS to palliative care services for symptom control and for end of life care when appropriate.

\* A contracture is a shortening in the soft tissues (that is, tendons, muscles or ligaments) around a joint that limits the passive (and active) range of movement at that joint.

## Surveillance decision

This recommendation should not be updated.

## Editorial amendments

Recommendation 1.6.5 should be amended with reference to Medicines optimisation (NICE guideline NG5). The recommendation should be edited to read as:

1.6.5 Ensure people with MS are offered a medication review in line with [Medicines adherence](#) (NICE clinical guideline 76) and [Medicines optimisation](#) (NICE guideline NG5).

## 2018 surveillance summary

### Comprehensive review

No relevant evidence was identified.

### Intelligence gathering

Initial intelligence gathering identified the following reports on patients' experiences of living with MS: [Not NICE Enough, A qualitative study of MND, MS and Parkinsons Pathways in accordance with the National Institute of Health and Care Excellence \(NICE\) Guidance](#) which reports that 'MS care and treatment is reported to be positive in areas such as comprehensive review of the condition and in managing relapses'. The authors reported that 'patients with MS were mostly treated in accordance with the NICE guidelines across Staffordshire and Stoke-on-Trent region. All of the quality statements, except one, were on average in line with

the expectations of the NICE guidelines' and that '19 respondents (79.17%) reported that they were offered a comprehensive review by their relevant healthcare professional. This was consistently positive across the different CCG areas in the region'.

Related NICE guidance on [Medicines optimisation](#) (NICE guideline NG5) was identified.

### Impact statement

The evidence that was identified is supportive of the current recommendation.

New evidence is unlikely to change guideline recommendations.

## 1.7 Relapse and exacerbation

### **Recommendations in this section of the guideline**

#### **Treating acute relapse of MS with steroids**

- 1.7.1 Develop local guidance and pathways for timely treatment of relapses of MS. Ensure follow-up is included in the guidance and pathway.
- 1.7.2 Non-specialists should discuss a person's diagnosis of relapse and whether to offer steroids with a healthcare professional with expertise in MS because not all relapses need treating with steroids.

#### **Recognising a relapse**

- 1.7.3 Diagnose a relapse of MS if the person:
- develops new symptoms **or**
  - has worsening of existing symptoms and these last for more than 24 hours in the absence of infection or any other cause after a stable period of at least 1 month.
- 1.7.4 Before diagnosing a relapse of MS:
- rule out infection – particularly urinary tract and respiratory infections **and**
  - discriminate between the relapse and fluctuations in disease or progression.
- 1.7.5 Assess and offer treatment for relapses of MS, that affect the person's ability to perform their usual tasks, as early as possible and within 14 days of onset of symptoms.
- 1.7.6 Do not routinely diagnose a relapse of MS if symptoms are present for more than 3 months.

#### **Treating a relapse**

- 1.7.7 Offer treatment for relapse of MS with oral methylprednisolone 0.5 g daily for 5 days.
- 1.7.8 Consider intravenous methylprednisolone 1 g daily for 3–5 days as an alternative for people with MS:
- in whom oral steroids have failed or not been tolerated **or**
  - who need admitting to hospital for a severe relapse or monitoring of medical or psychological conditions such as diabetes or depression.
- 1.7.9 Do not prescribe steroids at lower doses than methylprednisolone 0.5 g daily for 5 days to treat an acute relapse of MS.
- 1.7.10 Do not give people with MS a supply of steroids to self-administer at home for future relapses.

#### **Information about treating a relapse with steroids**

- 1.7.11 Discuss the benefits and risks of steroids with the person with MS, taking into account the effect of the relapse on the person's ability to perform their usual tasks and their wellbeing.
- 1.7.12 Explain the potential complications of high-dose steroids, for example temporary effects on mental health (such as depression, confusion and agitation) and worsening of blood glucose control in people with diabetes.
- 1.7.13 Give the person with MS and their family members or carers (as appropriate) information that they can take away about side effects of high-dose steroids in a format that is appropriate for them.
- 1.7.14 Ensure that the MS multidisciplinary team is told that the person is having a relapse, because relapse frequency may influence which disease-modifying therapies are chosen and whether they need to be changed.

#### **Medical, therapy and social care needs at time of relapse or exacerbation**

- 1.7.15 Identify whether the person having a relapse of MS or their family members or carers have social care needs and if so refer them to social services for assessment.
- 1.7.16 Offer inpatient treatment to the person having a relapse of MS if their relapse is severe or if it is difficult to meet their medical and social care needs at home.
- 1.7.17 Explain that a relapse of MS may have short-term effects on cognitive function.
- 1.7.18 Identify whether the person with MS having a relapse or exacerbation needs additional symptom management or rehabilitation.

### **Surveillance decision**

This recommendation should not be updated.

### **Editorial amendments**

None.

## **2018 surveillance summary**

### **Treating a relapse**

A systematic review included 6 RCTs (n=419) comparing the efficacy and safety of oral versus intravenous (IV) steroids for treatment of acute relapses in patients with MS. There were no significant differences in measures of disability, relapse rate or relapse freedom at 6 months between groups receiving oral versus IV steroids. For adverse events, there was a significant association

between oral administration and insomnia. [75]

A systematic review included 5 RCTs (n=369) assessing the efficacy, safety and tolerability of oral versus intravenous methylprednisolone for MS relapses. A meta-analysis of the pooled data revealed that there were no significant differences in relapse improvement at day 28 between oral and IV methylprednisolone; there was no evidence of heterogeneity among the trials; and no differences in safety or tolerance, except that insomnia was

reported as more likely to occur in the oral compared with IV group. [76]

### Intelligence gathering

No new evidence was identified.

### Impact statement

Evidence was only identified concerning the efficacy, safety and tolerability of oral versus IV steroids for treating a relapse. This evidence indicates that administration route does not have an impact on these

outcomes, expect possibly in an increase in insomnia when methylprednisolone is administered orally. Information on dosage and duration of methylprednisolone given orally or by IV was not specified and as such the impact of this evidence on the current recommendations cannot be fully explored.

New evidence is unlikely to change guideline recommendations.

## 1.8 Other treatments

### Recommendations in this section of the guideline

#### Vitamin D

1.8.1 Do not offer vitamin D solely for the purpose of treating MS.

#### Omega fatty acids compounds

1.8.2 Do not offer omega-3 or omega-6 fatty acid compounds to treat MS. Explain that there is no evidence that they affect relapse frequency or progression of MS.

### Surveillance decision

This recommendation should not be updated.

### Editorial amendments

None.

### 2018 surveillance summary

#### Vitamin D

A systematic review of RCTs (number of studies and participants = NR) assessed the impact of vitamin D use in patients with MS. A meta-analysis indicated that Vitamin D3 as an add-on treatment was associated with a very small but significant increase in annual relapse rate and had no significant effect on EDSS score in patients with MS. [77]

A systematic review included 37 RCTs (n=NR) evaluating interventions that target risk factors for MS progressions. This included 5 RCTs that reported there was no significant difference in EDSS scores after vitamin D supplementation compared with placebo (described by authors as very low quality evidence). [34]

An RCT (n=NR) assessed the immunological effects of high-dose vitamin D3 in people with MS compared with healthy controls. All participants were

randomised to either placebo, 5,000 IU or 10,000 IU vitamin D3/day over 24 weeks. There were no significant immunological differences found between groups. Vitamin D3 was reported as well tolerated, with no safety signals. [78]

A pilot RCT (n=40) assessed whether vitamin D3 supplementation (14,000IU/day) compared with placebo reduces depressive symptoms in people with relapsing-remitting MS when taken over a 48 week period. While there were significant decreases in depression (Hospital Anxiety Depression Scale-depression subscale) in the intervention group at the end of the trial, there were also decreases in depression in the placebo group and no significant between group differences. [79]

### **Omega fatty acids compounds**

No evidence was identified.

### **Intelligence gathering**

No new evidence was identified.

### **Impact statement**

Evidence indicates that vitamin D supplementation in people with MS provides no significant benefit in managing MS symptoms. This supports the content of recommendation 1.8.1 to not offer vitamin D solely for the purpose of treating MS.

New evidence is unlikely to change guideline recommendations.

## **Research recommendations**

### **2.1 Cognitive rehabilitation**

What is the clinical and cost-effectiveness of cognitive rehabilitation for people with MS?

### **Summary of findings**

The new evidence identified in the [Rehabilitation](#) section indicates that rehabilitation programmes can lead to improvements in memory in people with MS. This evidence should be considered in an update to the guideline. No cost-effectiveness studies of cognitive rehabilitation for people with MS were identified.

### **Surveillance decision**

This research recommendation will be considered again at the next surveillance point unless a new research recommendation is made as part of the update process.

## 2.2 Continued relapses

Is intravenous methylprednisolone more clinically and cost effective than oral methylprednisolone in people with relapsing–remitting MS and people with secondary progressive MS with continued relapses?

### Summary of findings

The new evidence identified in the [Treating a relapse](#) section indicates that IV methylprednisolone is not more clinically effective than oral methylprednisolone in people with MS who have a relapse. No cost-effectiveness studies were identified.

### Surveillance decision

This research recommendation will be considered again at the next surveillance point unless a new research recommendation is made as part of the update process.

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## 2.3 Mobility

What is the optimal frequency, intensity and form of rehabilitation for mobility problems in people with MS?

### Summary of findings

The new evidence reported in the sections on [mobility](#) may provide an insight into the optimal frequency, intensity and form of rehabilitation for mobility problems in people with MS and should be considered in an update to the guideline.

### Surveillance decision

This research recommendation will be considered again at the next surveillance point unless it is removed or a new research recommendation is made as part of the update process.

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## 2.4 Spasticity

What non-pharmacological interventions are effective in reducing spasticity in people with MS?

## Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing research.

## Surveillance decision

This research recommendation will be considered again at the next surveillance point.

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## 2.5 Vitamin D

Can vitamin D slow down the progression of disability in MS?

## Summary of findings

The new evidence on [vitamin D](#) shows that the use of vitamin D supplementation in people with MS provides no significant benefit in slowing the progression of disability in MS.

## Surveillance decision

This research recommendation will be considered again at the next surveillance point unless it is removed or a new research recommendation is made as part of the update process.

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