

4 Disease diagnosis and specific treatment

MS is a disease affecting the white matter of the central nervous system (CNS; brain and spinal cord). It is defined clinically by accumulating evidence from the history, examination or investigations that the individual has lesions within the CNS that are scattered in time (ie two or more separate episodes) and space (ie in two or more separate locations). Histological proof (ie under the microscope) is rarely available in life, and there is no single test or investigation that can 'prove' the diagnosis. Consequently, people who may or may not have MS and clinicians advising them need to live with uncertainty; the diagnosis is never proven '100%' and the prognosis is always uncertain.

This section covers the management of MS at the level of pathology (ie the disease process). It deals with the diagnosis of the disease and all treatments that may affect the disease process itself (in contrast to the secondary symptoms and signs). Within this section the term *acute episode* is used in place of *relapse* in many instances because the first episode, which cannot logically be called a relapse, will usually require the same management in terms of diagnosis and treatment. When used, the term 'relapse' refers to a clinically presumed episode of acute demyelination.

The topics covered are:

- making the diagnosis of MS
- involving the person with MS in the diagnostic process
- diagnosis of acute episodes
- treatment of acute disease episodes (including optic neuritis and transverse myelitis)
- treatments to modify the course of the disease (prevention of relapses using drugs, and drugs to slow down progression*)
- other actions that may influence relapse rate.

4.1 Making the diagnosis of MS

In medicine the process of diagnosis may include:

- confirming (or determining the probability) that a diagnosis is true
- making or excluding an alternative diagnosis
- classifying the disease further, to help determine prognosis and/or responsiveness to specific treatments.

All three aspects of diagnosis will be considered here. While the diagnostic process is most important when the person first presents with symptoms or signs, the diagnosis should always be considered when the person presents with completely new or unexpected problems. The principles will be similar.

* This section includes the treatment of MS with interferon beta or glatiramer acetate but has not reassessed the evidence for them as this was excluded from the scope of this guideline by NICE see note on p 59 (Section 4.6).

The diagnosis of MS is made clinically.⁵⁵ It depends upon obtaining evidence of characteristic neurological lesions:

- located in different parts of the CNS
- that have occurred at different points in time.

MS may cause potentially almost any neurological symptom. There is no definitive diagnostic test for MS and confirmation of the diagnosis may require several neurological tests and clinical evaluation over a period of time (see algorithm). In many instances, even with all available investigations, it is not possible to reach a definite diagnosis in the early stages and it is important to explain this to anxious patients.

In practice, an accurate diagnosis can sometimes be reached either on clinical grounds alone, or by following a clinical diagnostic strategy using appropriate investigations. However, even among specialist neurologists there may be disagreement.⁵⁶

The algorithm in Appendix G explains how investigations such as MRI can be used to reduce the stressful delay which can result while the required clinical evidence is obtained over a period of time. An international panel, meeting in 2000, published recommended criteria to utilise MR in this way.⁵⁵ Although these criteria are not above criticism, they are probably the best currently available. The criteria were developed by consensus using an internationally renowned group of experts. Initial evidence supports the McDonald criteria (see below) and we have agreed to follow their recommendations. When considering the recommendations it must be remembered that making a diagnosis is a process that logically depends as much on excluding reasonable alternative diagnoses as it does on confirming a diagnosis, especially in MS where there is no confirmatory test. Consequently in practice when faced with an individual the clinician must:

- have a diagnostic strategy, and not depend upon a single feature (eg investigation)
- recognise that no single feature can confirm or refute the diagnosis
- consider which investigation is most likely to help given the specific prior likelihood of a diagnosis.

The classification of MS is likewise controversial. Although commonly used, there is little firm epidemiological evidence to validate any of the categorisation schemes used and there are no studies of the reliability of the classification. Nonetheless, classifications may be useful both in research and in clinical practice, not least in relation to trials of new drugs.

The categorisation most commonly used is a subset of that published in 1996.⁵⁷ This categorisation was based on an international survey of 215 people actively involved in research in MS, of whom 125 (58%) replied. Several clinical types were recognised, with the first three remaining in common use:

- **relapsing-remitting:** clearly defined disease relapses with full recovery or with sequelae and residual deficit upon recovery; periods between relapses characterised by a lack of disease progression. About 80% have relapsing-remitting disease at onset
- **secondary progressive:** initial relapsing-remitting course followed by progression with or without occasional relapses, minor remissions and plateaux. About 50% of people with relapsing-remitting MS develop secondary progressive MS during the first 10 years of their illness
- **primary progressive:** disease progression from onset with occasional plateaux and temporary minor improvements allowed. About 10–15 % have primary progressive disease at onset.

In addition this group recognised other categories which are not widely used:

- **progressive-relapsing:** progressive from onset with clear acute relapses but with progression in between relapses (this is probably comparable to primary progressive disease)
- **benign:** disease in which the patient remains fully functional in all neurologic systems 15 years after onset
- **malignant:** disease with a rapid progressive course, leading to significant disability in multiple neurologic systems or death in a relatively short time after disease onset.

One other category was put forward, 'relapsing progressive', but no consensus was achieved.

Several points need emphasis. This classification reflects the person's history up to that point and it is not a classification that can be made prospectively. It has been used as a way of selecting or excluding patients for clinical trials of disease-modifying agents, and for the application of some of these treatments in clinical practice. There is evidence that the classification changes over time.⁵⁸ It is also important to stress that these categories do not reflect pathologically different types of disease and are poor predictors of subsequent behaviour of the disease in any one individual.⁴

▷ Evidence statements (all diagnostic studies)

A total of 33 studies met inclusion criteria. These studies assessed the diagnostic accuracy of 143 tests or test combinations. Of these studies, nine used a diagnostic case control design and the remainder were diagnostic cohort studies. The reference standard (the method to determine whether patients truly had MS) used was based upon clinical examination in all studies. For the diagnostic cohort studies patients were generally followed up for a period of time to determine if they developed MS. Only three of the studies^{59–61} followed up patients for five years or more and were determined to have used an appropriate reference standard. The introduction of the McDonald criteria (see the algorithm in Appendix G) potentially changes matters because the reference standard may have changed.

All but one⁶² of the studies reported sufficient data to construct a 2×2 table of test performance, although one additional study did not report sufficient data to construct a 2×2 table for one of the tests investigated.⁶³ These studies reported areas under the receiver operating curve (ROC). The 2×2 table data was extracted and used to calculate sensitivity, specificity and the diagnostic odds ratio (DOR) for each of the tests evaluated.

The DOR gives an overall (single indicator) measure of the diagnostic accuracy of a diagnostic test (see the appendices). It is calculated as the odds of positivity among diseased persons, divided by the odds of positivity among non-diseased. The DOR combines sensitivity and specificity into one measure. When a test provides no diagnostic evidence then the DOR is 1.0. The higher the DOR, the better the test and, generally speaking, a DOR greater than 100 provides convincing diagnostic evidence, and a DOR greater than 25 provides strong diagnostic evidence. In studies of diagnostic accuracy there is a trade off between having a high sensitivity (correctly identifying those people who have the condition), and having a high specificity (ie not diagnosing people as having the condition when they don't have the condition). For MS the use of this measure can be misleading. The proportion of confirmed MS patients with an abnormal visual evoked potential is about 90% but in suspected cases, at the time when you need such

tests, it may be less than 70%. However, it is a very reliable test of optic nerve disease and, in the appropriate case, can allow a confident diagnosis of MS. It is as important to detect all patients with MS as it is to avoid mistakenly diagnosing someone as suffering from MS.

The tests evaluated were grouped into four categories – clinical criteria, imaging, cerebrospinal-fluid tests, evoked and event related potentials – and combinations of tests. DORs varied considerably, both overall and within categories, either for technical reasons or more usually because of differences in the mix of patients being submitted to the test. Overall, DORs ranged from less than 1 to 2,091. They were generally higher in studies that did not include an appropriate range of patients. An appropriate range of patients was defined as a group of patients in whom the test would be used in practice, ie patients suspected of having MS but in whom the diagnosis had not been confirmed

Clinical criteria

One study evaluated the accuracy of the McDonald criteria applied at three months and one year after initial presentation. This study used the Poser criteria at three year follow-up as the reference standard.⁶⁴ The McDonald criteria use a combination of clinical features and MRI findings to make a diagnosis of MS, these are detailed in Appendix G. This study found that the McDonald criteria was an average diagnostic test at three months with a DOR of 24 and a good diagnostic test at one year with a DOR of 82. Both these figures were obtained when the diagnosis was made using a combination of clinical signs and MRI findings. When MRI evidence of dissemination in time and space alone were used to make the diagnosis, the diagnostic performance dropped to a DOR of 19 at three months and 24 at one year. When interpreting these figures it should be noted that the reference standard is unlikely to have correctly classified all patients, and so these figures may be biased.

Imaging

Twenty four studies assessed the accuracy of imaging in the diagnosis of MS, including a total of 61 test evaluations.^{59–82} The majority of these assessed MRI (59), two assessed the diagnostic accuracy of computerised tomography (CT).

The DOR for magnetic resonance imaging (MRI) showed great variation, ranging from less than 1 to 2091. In 29 of the comparisons the DOR was less than 25, suggesting poor overall test performance. The DOR ranged from 25–50 in a further 16 evaluations, suggesting good diagnostic performance, and was greater than 100 in nine evaluations, suggesting excellent test performance. One study reporting two evaluations of MRI (different cut-off points) reported the area under the receiver operating curve (ROC) and reported an area under the curve (AUC) of 0.96.⁶² This suggested excellent diagnostic performance, but this study did not include an appropriate spectrum of patients.

The wide variations in the DORs estimated from these studies makes it difficult to draw conclusions regarding the accuracy of MRI for the diagnosis of MS. The variations appear related to a number of factors, mainly the spectrum of patients included in the study and the cut-off point used to determine a positive test result. Generally speaking, the studies which reported the higher estimates of test performance did not include an appropriate spectrum of patients, suggesting that estimates of test performance obtained from such studies are likely to

be biased. Of the 29 studies in which the DOR was less than 25, five (17%) did not include an appropriate spectrum. Of the 17 studies that reported a DOR between 25 and 100, nine (52%) did not include an appropriate spectrum of patients. Only one of the eight comparisons with a DOR greater than 100 included an appropriate spectrum of patients.

In summary, although difficult to draw conclusions from these results given the large variation in DORs, it would appear that MRI is a reasonable although not excellent investigation when making the diagnosis of MS. In addition, the studies used many different definitions of a positive test result. Due to time limitations however, it was not possible to investigate the influence of this.

CT using X-rays was found to be a poor predictor of MS in both studies in which it was investigated.^{63,66} The first found a DOR of 2.4 which corresponded to a sensitivity of 38% and specificity of 80%.⁶⁶ The other did not report data to construct a 2 × 2 table but instead reported the area under the receiver operating curve (ROC). This was found to be 0.5 which indicates that CT was no better than chance alone at diagnosing MS. This study also assessed the diagnostic accuracy of MRI and found this to be significantly higher than that of CT (AUC was 0.82 for MRI and 0.52 for CT).⁶³ Both studies were of reasonable quality.

Evoked potentials and event-related potentials

Evoked potentials (EPs) and event-related potentials (ERPs) were assessed in eight studies,^{66,72,78–80,83–85} including 40 test evaluations. Generally, ERPs were found to be less accurate than MRI with DORs ranging from 0.6 to 90. The majority of the evaluations (28) reported DORs less than 25, suggesting poor diagnostic performance. The remaining evaluations suggested good diagnostic performance. As with the evaluations of MRI, studies which did not include an appropriate range of patients tended to produce higher estimates of test performance. Of the 28 evaluations which reported DORs less than 25, 15 (53%) included an appropriate range of patients. This compares to one (8%) of the 12 evaluations which reported DORs greater than 25.

The studies assessed a variety of different EPs/ERPs including: visual evoked potentials (VEP) ($n = 18$), auditory event-related potentials (AERP) ($n = 1$), brainstem auditory evoked potentials (BAEP) ($n = 4$), long latency auditory evoked potentials (LLAEP) ($n = 2$), middle latency auditory evoked potentials (MLAEP) ($n = 2$), motor-evoked potentials (MEP) ($n = 2$), somatosensory evoked potentials (SEP) ($n = 6$), sympathetic skin response (SSR) ($n = 1$), and various combinations of these ($n = 4$). Overall, VEPs appeared to be the most accurate in diagnosing MS. Six of the eight included studies assessed more than one ERP.^{66,72,78–80,85} These studies varied in terms of which ERP was found to be most accurate in diagnosing MS. Three of the studies found that the VEP was the most accurate,^{66,72,79} one found that MEP was the most accurate,⁷⁸ one MLAEP⁸⁵ and the other BAEP.⁸⁰ Two of the studies which found that VEP was the most accurate did not assess MEPs.^{66,79} In summary, there is disagreement regarding which EP is the most accurate for the diagnosis of MS. Overall, ERPs do not provide strong diagnostic evidence for the diagnosis of MS.

Cerebrospinal fluid

Various cerebrospinal fluid (CSF) tests were evaluated in 15 studies^{60,66,68–70,78–80,86–92} reporting a total of 37 test evaluations. The DORs ranged from 0 to 378.8. In 26 (70%) of evaluations, the DORs were less than 25, in seven (20%) the DOR was between 25 and 100 and in four (10%) evaluations the DOR was greater than 100. Of the evaluations reporting a DOR less than 25, 20 (77%) included an appropriate range of patients. In comparison only half of the studies with DORs between 50 and 100 included an appropriate range of patients. However, in contrast to the studies included in the other sections, three of the four studies reporting DORs greater than 100 included an appropriate range of patients.

The tests evaluated in the studies varied. The most commonly investigated test was the presence of oligoclonal bands. This was assessed in 15 test comparisons, including all four comparisons which found convincing diagnostic evidence.^{70,86,88,89} A further three of these studies reported DORs between 25 and 100,^{89,90,92} two of these included an appropriate range of patients.^{89,92} The remaining studies, all of which included an appropriate range of patients, reported DORs between 0 and 24. This illustrates a wide discrepancy in the estimates of diagnostic performance for the presence of oligoclonal banding. The reasons for the heterogeneity in estimates are unclear. There appears to be some evidence from reasonable quality studies that the presence of oligoclonal bands may be an accurate test for the diagnosis of MS, although this is not supported by all studies. Other tests which provided strong diagnostic evidence (DOR >50) were the IgG index^{91,92} and the IgG synthetic rate.⁹¹ However, the study which investigated both tests did not include an appropriate range of patients.⁹¹ The IgG index was investigated in a further two studies which reported DORs of 4.0⁷⁹ and 12.2.⁸⁹ The value of this test in the diagnosis of MS using CSF is therefore unclear. Other evaluated tests which did not provide strong or convincing evidence included: IgG synthesis ($n = 3$); level of IgG in CSF ($n = 4$); the presence of antibodies to various disease in CSF ($n = 1$); CSF total protein ($n = 1$); CSF/serum albumin ratio ($n = 1$); IgG albumin ratio ($n = 1$); the presence of myelin basic protein in CSF ($n = 1$). There is no evidence to suggest that these tests are accurate for the diagnosis of MS. Five comparisons included various combinations of tests.^{68,78,90} For all of these the DOR was less than 25.

Test combinations

Two studies, reporting four evaluations, assessed the accuracy of combinations of tests.^{68,69} All four evaluations assessed the effectiveness of combined measures based on oligoclonal bands and MRI. For three of the evaluations the DOR was less than six, suggesting that this combination is not accurate for the diagnosis of MS.^{68,69} The fourth evaluation reported a DOR of 42.2 (sensitivity 96%, specificity 63%) for the presence of at least two oligoclonal bands only in CSF and an MRI diagnosis based on the presence of three quarters of Barkhof's criteria.⁶⁹

Economic evidence

There were no economic studies of CSF, EPs or ERPs.

MRI

Magnetic resonance imaging (MRI) is a relatively expensive diagnostic technology (costing approximately £200 per scan), and a relevant question is whether the benefits of MRI are worth the additional cost. Unfortunately this is a difficult question to answer as there is a large amount of uncertainty around the diagnostic accuracy of MRI in MS and the influence of a MRI-backed diagnosis on disease management.

Benefits from MRI in diagnosis of MS may arise from the medical information it provides (which in turn informs disease management), and also from the potential psychological value of the information to the patient. In addition, MRI may reduce the need for other tests, and in particular the need for EPs and CSF examination has diminished in recent years.

In MS the majority of interventions are targeted at symptoms rather than the disease itself, and the extent to which symptom management is influenced by diagnosis is unclear. The availability of the disease-modifying therapies (DMTs) interferon beta and glatiramer acetate under the risk sharing scheme (see section 4.6 for further details) may have implications for the use of MRI in diagnosing MS. The ABN criteria, which determine the eligible population for DMTs, are not dependent on diagnosis using MRI and it is unclear how many of the eligible population would require an MRI scan to confirm diagnosis before access to treatment (the majority of people will already have had an MRI scan before this point). Nevertheless, in countries where DMTs have been more commonly used than the UK, MRI is often used to aid the decision on whether to start, stop or modify therapy. This may mean that the risk sharing scheme does increase the requests for MRI scans.

Only two relevant existing studies were identified.^{93,94} These looked at the targeting and cost-effectiveness of MRI for people with equivocal neurological symptoms who may have MS. Both studies employ decision analytic models, which are particularly valuable in evaluating diagnostic technologies since they enable modelling of alternative scenarios with their associated costs and benefits given available information. They also allow the identification of key areas of uncertainty around clinical utility and cost-effectiveness which can guide future research. The two studies are by the same authors and represent developments of the same piece of work; only the latest study is included in the evidence tables.⁹³

This study made good use of information available at the time (the early 1990s) and also employed comprehensive sensitivity analysis to deal with the large amount of uncertainty surrounding the key model parameters. The study concluded that MRI was not cost effective in people with low prior probability of MS (unless the diagnostic information has a very high psychological value to patients). As the probability of disease increases, further MRI use becomes cost effective. Given the fact that this study is relatively old (and in an area where the technology is developing) and that it is based in the US, there is little value in citing specific cost-effectiveness ratios. Nevertheless, the results do question the usefulness of the routine use of MRI in people where the probability of MS being present is low unless there is a reasonable probability of an alternative diagnosis that can also be diagnosed using MRI being present.

The results from both studies illustrate that the key areas of uncertainty are the diagnostic accuracy of MRI and the value of the diagnostic information to patients; both of these factors will have an important influence on the cost effectiveness of the technology. While evidence on the former may have improved since this study was published, evidence on the latter is virtually

non-existent. In addition, these studies were carried out before the availability of the DMTs interferon beta and glatiramer acetate, so they do not take account of any additional benefit arising from speeding up access to these therapies.

For more detail see Appendix I.

▷ From evidence to recommendations

Linking these evidence statements to recommendations depends upon a clear understanding of the diagnostic process. When making a diagnosis a doctor will start with a reasonable estimate of the probability that someone has a particular disease, and may have a list of other diagnoses that might also be present. Consequently, investigations are used as much to exclude alternative diagnoses as to confirm the suspected diagnosis, and most diagnostic studies do not evaluate this two-pronged approach. The doctor will (or should) also use a strategy appropriate to the particular situation, choosing the test most likely to clarify matters before undertaking further tests.

In practice, neurologists will often use an MRI scan first for three reasons.

- 1) To rule out other disorders, eg spinal cord compression in a patient with a spinal cord lesion.
- 2) To establish the presence of clinically-silent lesions in other parts of the CNS, and/or
- 3) To demonstrate new lesions appearing since the last clinical episode. However other considerations, such as the need to exclude a disease through examining CSF or a patient's claustrophobia, may dictate an alternative strategy. The recommendations made draw on the evidence, but also draw on the strategy implied.⁵⁵ They should give a useful clinical diagnostic strategy.

RECOMMENDATIONS

There is no single specific diagnostic test available, but in practice, the diagnosis can be made clinically in most people.

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| R26 | When an individual presents with a first episode of neurological symptoms, or signs suggestive of demyelination (and there is no reasonable alternative diagnosis), a diagnosis of MS should be considered. | D |
| R27 | When an individual presents with a second or subsequent set of neurological symptoms, which are potentially attributable to inflammatory or demyelinating lesions in the central nervous system (and again, there is no reasonable alternative diagnosis), the person should be referred to an appropriate expert for investigation. | D |
| R28 | A diagnosis of MS should be made clinically: <ul style="list-style-type: none">● by a doctor with specialist neurological experience● on the basis of evidence of CNS lesions scattered in space and time● primarily on the basis of the history and examination. | D |
| R29 | When doubt about the diagnosis remains, further investigation should: <ul style="list-style-type: none">● exclude an alternative diagnosis, or● find evidence that supports the potential diagnosis of MS. (Dissemination in space | D |

should usually be confirmed, if necessary, using an MRI scan, interpreted by a neuroradiologist if possible, using agreed criteria such as those described by McDonald and colleagues⁵⁵ (see Table G1 in Appendix G). Dissemination in space may also be confirmed using evoked potential studies. Visual evoked potential studies should be the first choice. Dissemination in time should be confirmed clinically, or by using the MRI criteria described (in Table G1 in Appendix G).

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| R30 | Other tests supportive of the diagnosis of MS, such as analysis of CSF, should only be used either when the investigation is being undertaken to exclude alternative diagnosis or when the situation is still clinically uncertain. | D |
| R31 | The diagnosis of MS is clinical and an MRI scan should not be used in isolation to make the diagnosis. | DS |
| R32 | A CT brain scan should only be used to exclude alternative diagnoses that can be diagnosed using that investigation. | DS |
| R33 | Any CSF samples taken from individuals who may have MS should be tested for the presence of oligoclonal bands and should be compared with serum samples. | DS |
| R34 | The evidence supporting the diagnosis and its degree of certainty should always be documented formally in the medical notes and letters discussing the diagnosis. This allows the diagnosis to be reviewed critically and reinvestigated if necessary. | D |

LOCAL IMPLEMENTATION POINT

Local guidelines will need to consider and define how urgent referrals of potential cases of MS should be made from primary care trusts (PCTs) and local health groups (LHGs) to a specialist neurological service.

4.2 Involving the person with MS in the diagnostic process

This covers the involvement of the patient in the diagnostic process from first presentation to a doctor to confirmation of the diagnosis and being informed of the diagnosis. It must be emphasised that making and telling the diagnosis is a process that may extend over some time, and that recommendations made elsewhere concerning communicating with the patient (see Section 3) should also be consulted. It is known that people with MS often have strong views about the process of making and telling the diagnosis, usually feeling that it could have been done better.¹⁴ Two comments from people with MS attending the focus groups (for further details see Section 2.3 and Appendix B) exemplify this:

‘Every test you go for no one tells you the results – you have to go back to the neurologist and go back to the GP – he didn’t know anything ... In the end it’s a relief just to be told you have it.’

‘The diagnosis was handled particularly badly by a particular junior doctor who was doing his neurology rotation in the hospital – in a very matter of fact manner as if the diagnosis was made. Go away to your GP and he will sort it out from there, was almost the attitude.’

▷ Evidence statements

Diagnosis

Two SRs were identified that assessed communication at the time of diagnosis of a potentially chronic or fatal disease, not MS^{95,96} (Ia). A review of 21 studies assessing the effect of physician-patient communication found that the quality of communication in both the history taking segment and during discussion of the management plan influenced patient health outcomes.⁹⁵ Positive effects were observed in patients' emotional health, symptom resolution, general functioning, physiological measures and pain control. The results indicated that patients should be involved in the consultation and in decisions about care. A review of different strategies for communicating 'bad' news to newly diagnosed patients showed mixed result.⁹⁶ Overall the use of an information package, follow-up telephone call or provision of a consultation summary only influenced patients' knowledge and satisfaction levels in half of the trials. No differences were seen in patients' psychological adjustment between the control and intervention groups.

Four studies were identified that examined patients' response to the diagnosis of MS⁹⁷⁻¹⁰⁰ (III). Two studies assessed patients' responses to undergoing a diagnostic work-up.^{97,100} The first study assessed the effect of diagnostic information on patients' sense of well-being.⁹⁷ The results indicated that most patients felt better having received diagnostic information, although this varied according to sub-groups of patients. Those in whom no definitive diagnosis emerged tended to be more anxious, whilst individuals with 'positive' work-ups became less anxious and expressed favourable feelings about the diagnosis despite now facing a chronic disease. The second study assessed the effect of diagnostic testing on patients' health perceptions.¹⁰⁰ Overall, the results indicated a significant and generally beneficial change in patient health perceptions with the neurological 'work-up' in suspected MS, irrespective of the final diagnosis. Two further studies explored patients' reaction to being diagnosed as having MS.^{98,99} The first of these focussed upon whether patients wish to know their disease status and how they had been informed of this.⁹⁹ The results showed that 83% favoured knowing the diagnosis, 13% were indifferent and less than 4% preferred not to know the diagnosis. Almost a quarter of patients had discovered the diagnosis for themselves, and all respondents thought that the consultant was the person who should convey the diagnosis. The second study explored the individual's experience of having symptoms and then being told they had MS.⁹⁸ The narrative synthesis indicated that diagnosis disclosure had been a painful and unexpected event for participants, but also viewed by some as a relief.

Information and education

Three reviews evaluated the effectiveness of information strategies in patient care, not especially MS¹⁰¹⁻¹⁰³ (Ia). The first review of nine studies assessed the provision of lectures, leaflets, booklets or manuals for stroke patients and their caregivers.¹⁰¹ The results provided some evidence that information combined with educational lectures improved knowledge and was more effective than providing information only. However, information only had no effect on mood, perceived health status or quality of life for patients or carers. The second review evaluated the use of audio-taped interviews, audio-visual aids, individual patient care records and written information for patients with cancer.¹⁰² The review showed positive effects on patient outcomes such as recall and knowledge, symptom management, satisfaction,

preferences and health care utilisation. The interventions had no effect on psychological indices, and there was an interaction between disease prognosis and intervention. Where prognosis was poorer added information was detrimental. The last review of eight studies assessed the effects of providing recordings or summaries of their consultation to people with cancer.¹⁰³ The results support the use of recordings or summaries as an aid to information recall. However, they had little effect upon the level of patients satisfaction with the information provided and no effect upon patients' level of anxiety or depression.

Two RCTs were identified that assessed patient support through education or the provision of information in people with MS^{104,105} (Ib). The first study examined the effectiveness of an educational program for newly diagnosed patients with MS.¹⁰⁵ The results indicated no significant differences between the groups on measures of physical and occupational functioning, emotional well-being and general contentment, nutrition and health or family and social relationships. A positive effect was observed for levels of patients' self-worth. However, the sample size was too small for any robust conclusions to be drawn. The second study assessed the provision of an information booklet to aid medication compliance.¹⁰⁴ The results showed that the booklet had a positive effect on patients' understanding of medication information, but had no effect on either correct medication usage or their level of medication compliance.

A further three studies in patients with MS examined patient information needs at the time of initial diagnosis and during periods of disease exacerbation^{106–108} (III). The first study explored information needs and sources of information.¹⁰⁷ Biological information was prioritised by patients as information they personally required, whilst they advised encouragement and supportive information for others recently diagnosed. The most common sources of information besides the neurologist were other patients, patient-authored books and the MS society. Another study examined the information needs and information seeking behaviours of patients within the context of an acute exacerbation.¹⁰⁶ The results indicated gaps in patients' knowledge about physical symptoms experienced, emotions and treatments. Generic information on MS was not seen as being helpful and the major barrier identified was the dearth of current, realistic and up-to-date information. The last study assessed the utility of an information pack on symptoms and treatments, dietary advice and local and national resources for individuals with MS.¹⁰⁸ The results showed that 90% of the participants would have liked the information pack within six months of being diagnosed, and that usage of the pack was dependent upon the individuals' experience of managing their symptoms.

▷ From evidence to recommendations

The evidence reviewed is difficult to use directly because the research rarely explored explicit questions or gave answers that translate into recommendations. However, the focus groups and much written descriptive research emphasise that people with MS attach great importance to involvement in and clear communication throughout the diagnostic process. Additionally, the evidence did not suggest any harmful effects. The GDG reached strong consensus on the recommendations made, which reflect the main areas of concern expressed by people with MS.

RECOMMENDATIONS

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| R35 | An individual should be informed of the potential diagnosis of MS, as soon as a diagnosis of MS is considered reasonably likely (unless there are overwhelming patient-centred reasons for not doing so). This should occur before undertaking further investigations to confirm or refute the diagnosis. | C |
| R36 | Throughout the process of investigating and making the diagnosis of MS, the health care professional should: <ul style="list-style-type: none"> ● find out what and how much information the individual wants to receive (this should be reviewed on each occasion) ● discuss the nature and purpose of all investigations, especially the likely outcomes and their implications for the individual. | C
D |
| R37 | If a diagnosis of MS is confirmed, the individual should be told by a doctor with specialist knowledge about MS (usually a consultant or experienced specialist registrar). See also the recommendations for good communication (Table 2). | C |
| R38 | After the diagnosis has been explained, the individual should be: <ul style="list-style-type: none"> ● offered in the near future* at least one more appointment to see wherever possible the doctor who gave the original diagnosis ● put in touch with, or introduced to, a skilled nurse or other support worker, ideally with specialist knowledge of MS and/or other neurological conditions and counselling experience ● offered written information about local and national disease-specific support organisations, including details of local rehabilitation services ● offered information about the disease, preferably in the form of an information pack, specific to the newly diagnosed. | D
D
C
D
A |
| R39 | Within six months of diagnosis, the individual should be offered the opportunity to participate in an educational programme to cover all aspects of MS. | B |

LOCAL IMPLEMENTATION POINTS

Local services should establish:

- a mechanism for keeping an up to date register of which doctors (consultants and trainees) should confirm and give the diagnosis
- a list of all relevant local and national organisations involved with MS, with a mechanism of keeping it up to date
- an agreed mechanism for putting a person newly diagnosed with MS in touch with a nurse or other support worker with knowledge of MS
- develop a set of information suitable for newly diagnosed people, including information on local services, and ensure that it is kept up to date.

* The GDG debated the meaning of the words ‘in the near future’. In this context, it is taken to mean that the exact time will vary according to clinical need but should be, in the opinion of the development group, no longer than four weeks.

4.3 Acute episodes: diagnosis

An acute episode, often referred to as a relapse, is a neurological event that occurs in people diagnosed with MS that lasts more than 24 hours. It has no better explanation, and is assumed to be due to an episode of acute inflammation within the CNS. Consequently, treatments designed to reduce CNS inflammation have been tried.

Two specific acute clinical syndromes are recognised, optic neuritis and transverse myelitis. Each is particular a) because it is often the first manifestation of MS in the person concerned and b) because only a proportion of patients presenting with the syndrome have or go on to develop MS itself. Nonetheless they share many features with other acute relapses, and may occur in someone known to have MS, and so are considered within this section.

Establishing whether a recent change in a patient's state is due to an episode of demyelination is important. First, it may determine specific treatment such as steroids. Second, it may determine the need (and eligibility) for preventative treatments. Third, there may be another treatable reason for the apparent decline in neurological function.

However, there are major difficulties in defining and diagnosing a relapse, given the natural variability of the condition. First, it is well known that many new lesions seen on MRI scans are clinically silent.^{109,110} Second, incidental illnesses such as influenza and possibly other stressors may cause marked neurological deterioration that clinically cannot be distinguished from a relapse. Third, if access to specific treatment depends upon the diagnosis (or otherwise) of a relapse, bias is inevitable.

This section considers the diagnosis of people with MS who present with symptoms suggestive of an acute episode with onset within the previous four weeks (a time chosen because most studies have this time limit).

4.3.1 General diagnosis

▷ Evidence statement

There were no studies on the validity or reliability of the diagnosis of a relapse that fulfilled the inclusion criteria.

▷ From evidence to recommendations

The absence of any studies on the validity and reliability of the clinical diagnosis of a relapse concerned the GDG. However it was essential to make some recommendations, if only because the Department of Health risk sharing scheme depends absolutely on the diagnosis of relapses. Therefore a clinical consensus was reached, without difficulty, on the recommendations that follow.

RECOMMENDATIONS

- R40** If a person with MS has a relatively sudden (within 12–48 hours) increase in neurological symptoms or disability, or develops new neurological symptoms, a formal assessment should be made to determine the diagnosis (that is, the reason for the change). This should be recorded clearly. **D**

- R41 This diagnostic assessment should: D
- be undertaken within a time appropriate to the clinical presentation
 - consider the presence of an acute infective cause
 - involve a GP or acute medical/neurological services.
- R42 Further neurological investigation should not be undertaken unless the diagnosis of MS itself is in doubt. D

LOCAL IMPLEMENTATION POINTS

Local clinicians will need to set out protocols for:

- which specialists should be approached by GPs and how
- agreed local criteria for further neurological investigation.

4.3.2 Optic neuritis: diagnosis

Optic neuritis is an acute demyelination of the optic nerve. Optic neuritis is often the first manifestation of MS. Many attacks of optic neuritis are asymptomatic, but symptoms may include pain in or around the eye and altered visual acuity, presenting as blurring, or altered colour perception. It is one of two specific clinical diagnoses that often but not always indicate an acute attack of MS (the other is transverse myelitis, discussed next). In the context of an already established diagnosis of MS the management is little different from that of any other acute relapse. However if this is the first clinical attack then there are specific considerations relating to the likelihood of eventually developing further clinical evidence of MS. The risk can be estimated using MRI brain scanning, and people with no abnormalities on MRI scanning are at low risk of developing MS within five years.^{111,112} This section covers the approach to optic neuritis as the first neurological manifestation in a patient, but the guidelines will apply even in the context of a known diagnosis.

▷ Evidence statement

Two diagnostic accuracy studies examined the effectiveness of different tests for the diagnosis of optic neuritis. The first assessed the use of the Aulhorn Flicker Test in which the luminance of a visual field varies at flicker rates between 0–50 Hz and subjective ratings of this are recorded. The results showed that a decrease in the brightness sensation at medium frequencies and a brightness enhancement at 1–3 Hz, the ‘late maximum’, gives a sensitivity of 98% and a specificity of 86% for the diagnosis of florid optic neuritis. Overall this gives a DOR of 300, indicating that the test provides strong diagnostic accuracy, being able to differentiate between patients in the florid stage of optic neuritis and those in the recovery phase.¹¹³ The second study examined the utility of three different optotype contrast sensitivity charts in the diagnosis of optic neuritis. The results indicated that the 3% chart with a cut-off point of 2.25 lines was best able to discriminate between patients with optic neuritis and normal controls. At this cut-off point the test yielded a DOR of 873, which is indicative of a test with convincing diagnostic accuracy. However as the patient range was composed of patients with unilateral/bilateral optic neuritis and normal healthy controls this is highly likely to have inflated the diagnostic accuracy of the test.¹¹⁴

- ▷ From evidence to recommendations

The main issues to be considered are ensuring that people with potential optic neuritis are seen by a specialist for diagnosis of MS and deciding on what actions to take following the diagnosis. The recommendations therefore reflect the clinical issues, and were made by consensus without difficulty

RECOMMENDATIONS

- | | | |
|-----|--|---|
| R43 | Every individual presenting with an acute decline in visual acuity, with or without associated pain, should be seen by an ophthalmologist for diagnosis. | D |
| R44 | If the diagnosis is confirmed as optic neuritis, without any other specific cause and possibly due to MS, the ophthalmologist should discuss the potential diagnosis with the individual (unless there are overwhelming patient-centred reasons for not doing so; see R35). A further referral to a neurologist for additional assessment should be offered. | D |

LOCAL IMPLEMENTATION POINTS

These will need to cover:

- which local ophthalmologists are interested in neuro- or medical ophthalmology
- how urgent referrals are made both to the ophthalmologist and, if necessary, to the neurologist.

4.3.3 Transverse myelitis: diagnosis

Transverse myelitis is a reasonably rapid (several hours to a few days) onset of impairment of motor control, sensory function, and control over bladder, bowel and sexual functions that has a specific spinal cord level and no demonstrated structural cause (eg herniated disc). It may be the first manifestation of MS, although about a third of patients have no further attacks.¹¹⁵

- ▷ Evidence statement

No diagnostic accuracy studies were identified.

- ▷ From evidence to recommendations

As with optic neuritis, the main clinical concerns are that people with potential transverse myelitis are diagnosed correctly, especially to ensure that there is no alternative treatable diagnosis, and that appropriate actions then taken. Evidence concerning investigations of acute spinal syndromes and prognosis was not sought. The recommendations were made by consensus without difficulty

RECOMMENDATIONS

- | | | |
|-----|--|---|
| R45 | Every person presenting with symptoms and signs of acute spinal cord dysfunction should be investigated urgently, especially to exclude a surgically treatable compressive lesion. | D |
|-----|--|---|

- R46 If a diagnosis of transverse myelitis is made (and there is no previous history of neurological dysfunction), the individual should be informed that one of the possible causes is MS. D

4.4 Treatment of acute episodes

Acute episodes of neurological symptoms that lead to first presentation or to the recognition of a relapse are thought to be secondary to an episode of demyelination. Hence treatments that affect the inflammatory process and immune system are used, especially corticosteroids. Currently, the use of corticosteroids is recommended as the standard treatment of acute MS relapses but clinical practice varies widely.¹¹⁶ Several preparations of steroids exist, and the recent trend has been away from adrenocorticotrophic hormone (ACTH) (no longer available) and oral prednisolone to more potent preparations such as methylprednisolone and dexamethasone. Although there are many studies, they often address different questions making a synthesis of the evidence difficult. Furthermore many doctors use (and many patients prefer) oral corticosteroids and again the evidence about the efficacy or otherwise of this is simply absent. Lastly it should be recognised that both acute short-term and longer-term use of steroids may have side effects but, again, evidence on the clinical importance of this risk, and relative risk-benefit ratios is absent.

This section will consider optic neuritis and transverse myelitis as acute episodes, and will review the evidence for all three conditions and make one set of recommendations. This approach has been taken to reduce repetition.

4.4.1 General treatment

▷ Evidence statements

The effectiveness of treatments for patients suffering an acute worsening of symptoms was evaluated in three systematic reviews (Ia) and 14 RCTs (Ib).

Steroids

Three systematic reviews^{117–119} assessed the effectiveness of steroids in the treatment of acute worsening (Ia). The first review of six RCTS, reported that both methylprednisolone and ACTH showed a protective effect against the disease getting worse within five weeks of treatment.¹¹⁹ The review found no significant difference in terms of drug (methylprednisolone or ACTH), route of administration or treatment duration (five days vs 15 days). Only one study reported data for long-term follow-up, and reported no significant effect of treatment in terms of improvement or the number of new exacerbations between the methylprednisolone and placebo groups. All of the studies included in the second review of five studies were included in the first review.¹¹⁷ The third review performed two separate analyses.¹¹⁸ The first of these analyses involved the evaluation of studies which compared high dose methylprednisolone with placebo. The studies included for this section of the review were also included in the other two reviews. All three reviews reported similar results.

A further two RCTs,^{120,121} not included in any of the reviews compared the effects of ACTH (combined with bed rest in one study) to control (placebo in one RCT and bed rest in the other) (Ib). One RCT¹²¹ only reported a beneficial effect for three of the seven outcomes assessed, and these effects were only observed in the first six weeks. The second¹²⁰ reported within rather than between group differences and so it is not possible to draw any conclusions from this study.¹²⁰ Both studies reported significantly more minor adverse effects in the ACTH group including rounding of the face, ankle oedema and mood elevation, which occurred in most of the patients treated with ACTH.

One review¹¹⁸ also included studies comparing high and low dose methylprednisolone (Ia). No differences were found in Expanded Disability Status Score (EDSS) scores among patients treated with high and low dose methylprednisolone. An additional RCT, not included in the review, also compared high (2g/day) and low dose (1g/day) intravenous methylprednisolone (IVMP). No differences were seen on any of the outcome measures assessed at three week follow-up.¹²² One further RCT compared the effects of high dose (2g/day) and low dose (0.5g/day) methylprednisolone combined with 300mg ranitidine daily (Ib). This study found no significant differences between groups in terms of EDSS scores, but did find a positive effect in favour of the high dose treatment group for two MRI measures.¹²³ Minor side effects were reported in both groups. Two RCTs compared intravenous and oral methylprednisolone (500mg). Both studies found no significant differences between the two treatment groups.^{124,125} One study¹²⁴ reported more withdrawals in the oral treatment group and both groups reported similar minor side effects.

Two RCTs^{126,127} compared short-term treatment (15 days) with ACTH and methylprednisolone (Ib). These studies reported no significant differences in the effects of the two treatments either in the short-term or at long-term follow-up (18 months). Adverse events were relatively minor and were similar between the two groups in one study,¹²⁶ while in the other all side effects were reported in the ACTH group and included ankle oedema and glycosuria.¹²⁷ A third RCT compared intravenous ACTH, intravenous dexamethasone (8mg daily maximum) and methylprednisolone (40mg daily maximum) in the short-term treatment of patients suffering an acute relapse. The average EDSS score improved significantly more in patients treated with dexamethasone compared to those receiving ACTH or methylprednisolone. Significantly more patients showed a lowering of the EDSS score of at least one point in the groups treated with ACTH and dexamethasone compared to those receiving methylprednisolone.¹²⁸ Adverse events were not reported.

One RCT compared the effectiveness of intrathecal triamcinolone acetonide crystal suspension and oral methylprednisolone. No significant differences were found between the two treatment groups in EDSS scores.¹²⁹

Side effects were reported in two of the systematic reviews and two RCTs. These included herpes simplex, herpes zoster, severe ankle oedema, fractured neck of femur, acute anxiety and severe depression;¹¹⁷ weight gain, oedema, gastrointestinal symptoms and psychological symptoms;¹¹⁹ raised blood glucose;¹²⁶ infection and raised blood pressure.¹²¹ One review reported that the major side effects were significantly more frequent in the intervention group compared to the control group. The frequency of minor side effects was high in all the studies.

Other interventions (all Level Ib)

One RCT¹³⁰ assessed the effects of plasma exchange combined with ACTH and oral cyclophosphamide to a control group receiving ACTH, oral cyclophosphamide and sham plasma exchange. This study found no significant differences between the two treatment groups.

Ciclosporin A was compared to prednisolone in one RCT. At the end of treatment there were no significant differences between the two groups but after three month follow-up there was a significant improvement in EDSS score in the prednisolone group compared to the ciclosporin group.¹³¹ There were reports of side effects including nausea and paraesthesia of the extremities all in the ciclosporin group.

ATG combined with ACTH was compared to treatment with ACTH alone. The RCT¹³² reported a significant improvement in DSS score in those in the combined treatment group compared to those receiving ACTH alone. Side effects occurred in both groups and so the treatment period was reduced from 28 to 14 days.

One RCT assessed the efficacy of ginkgolide B at different doses compared to placebo. This study found no significant differences between the treatment groups for any of the three outcomes assessed.¹³³ Adverse effects were similar between the groups although hiccups were reported more commonly in the ginkgolide group.

▷ Economic evidence on methylprednisolone in the treatment of acute relapses in MS

The use of high-dose steroids to manage acute relapse in MS was deemed an important area for economic analysis; in particular the group was interested in the potential costs and benefits of different methods of administering high-dose steroids.

Clinical practice varies greatly and the only formal clinical evidence comes from two RCTs comparing oral methylprednisolone with intravenous administration as a hospital day case;^{124,125,134} these show equal efficacy. This evidence is of limited relevance as a recent survey of consultant neurologists suggested that only 7% could offer administration as a day case.¹¹⁶

Formal economic modelling was not deemed worthwhile given the lack of relevant clinical data. Instead a 'think piece' was prepared which attempted to itemise the potential costs and benefits of alternative methods of administration in a way that facilitates comparisons.

The three alternative methods of administration considered were:

- hospital IV (inpatient or day case)
- home IV
- oral.

The potential costs and benefits were classified under six headings:

- effectiveness
- NHS resources
- quality of life
- patient and carer costs
- side effects and tolerability
- NHS delivery issues.

Details are given in Appendix E.

One may conclude that many factors should be considered when comparing alternative methods of methylprednisolone delivery and that there is little formal evidence on any of these. As a result there is no clearly dominant treatment in terms of clinical effectiveness or resource use, and the group was unable to make a recommendation for the preferred method of administration of high dose steroids.

▷ From evidence to recommendations

There was much evidence available. However, each study investigated a separate question. The questions were rarely related to each other. They used different steroids at different doses and had different outcome measures at different times. Direct synthesis of an answer to the question ‘What treatment should I give, in what dose, by what route, for how long, and how infrequently?’ was not possible. The GDG debated the issue several times, over several hours in total, and eventually agreed the recommendations unanimously

4.4.2 Optic neuritis: treatment

Many patients with optic neuritis are asymptomatic, and do not even approach their GP. However in those people presenting with symptoms treatment may be considered, either to reduce current problems or to prevent later problems.

▷ Evidence statement

One systematic review of three placebo-controlled RCTs assessed four comparisons of the effects of steroids on short- and long-term functional improvement.¹¹⁷ Two studies assessed ACTH, one assessed prednisone and one intravenous methylprednisolone. The overall results showed that there were no beneficial effects on functional improvement at eight days, but a small significant beneficial effect at thirty days. However, there was no long-term effect on functional improvement or on relapse occurrence. A number of the studies also reported both major and minor side effects associated with steroid treatment¹¹⁷ (Ia). Two further studies, one RCT and one CCT, not included in the review also examined the effects of methylprednisolone. The RCT compared intravenous methylprednisolone against mecobalamin. No overall beneficial effects on any of the six outcomes measures assessed were observed at one year follow-up¹³⁵ (Ib). The CCT compared methylprednisolone against vitamin B1. The results showed no significant beneficial effects on any of the three outcome measures assessed¹³⁶ (IIa).

A further four placebo-controlled RCTs met the inclusion criteria. The first examined intravenous immunoglobulin and was terminated at one year follow-up due to lack of efficacy of the intervention. No beneficial effects were observed for any of the four outcome measures assessed and the incidence of both major and minor side effects in the treatment group was high.¹³⁷ The second RCT evaluated the use of corticotrophin gel in patients with unilateral optic neuritis. The results showed no significant benefits for treatment on any of the six outcome measures assessed.¹³⁸ The last two RCTs both examined the use of a single injection of triamcinolone. The first trial reported a significant beneficial effect for overall visual improvement at three-month follow-up.¹³⁹ However, the second trial reported no significant differences between the groups on any of the outcome measures at six months¹⁴⁰ (Ib).

▷ From evidence to recommendations

The evidence, although extensive, is difficult to use because the research has not considered many of the questions such as the relative effectiveness of different doses, different durations of treatment, different preparations, or different routes of administration. The guideline developers discussed the matter extensively and the recommendations below draw upon the evidence, experience and evidence in other areas of medicine, and current practice. We agreed that a single set of recommendations covering acute episodes including optic neuritis (and transverse myelitis, where there was no evidence) would be appropriate.

RECOMMENDATIONS

- R47 Any individual who experiences an acute episode (including optic neuritis) sufficient to cause distressing symptoms or an increased limitation on activities should be offered a course of high-dose corticosteroids. The course should be started as soon as possible after onset of the relapse and should be **either**:
- intravenous methylprednisolone, 500mg – 1g daily, for between three and five days **A**
 - or
 - high-dose oral methylprednisolone, 500mg – 2g daily, for between three and five days. **A**
- R48 An individual should be given a clear explanation of the risks and benefits involved in taking corticosteroids. **D**
- R49 Frequent (more than three times a year) or prolonged (longer than three weeks) use of corticosteroids should be avoided. **D**
- R50 Other medicines for the treatment of an acute relapse should not be used unless as part of a formal research protocol. **D**

LOCAL IMPLEMENTATION POINTS

The local services will need to set guidelines on:

- who may prescribe or recommend methylprednisolone
- where and how intravenous methylprednisolone is to be administered if used
- how patients are linked in to appropriate disability services (see next section).

4.5 Acute episodes: rehabilitation

An acute episode will usually cause some increased limitation on activities, and the increased disability will itself often require urgent intervention, if only the provision of additional support to the person with MS. Sometimes hospital admission is the only way to manage the increased dependence. The general aspects of the management of increased dependence are covered later. The specific features of increased dependence associated with an episode are its relatively sudden onset and the likelihood that recovery will occur over three to six months, albeit not necessarily complete recovery.

▷ Evidence statements

One RCT¹⁴¹ compared the efficacy of planned multidisciplinary team assessment and intervention combined with IVMP (1g/day for three days) to standard ward routine care combined with IVMP for acute relapse. The results showed significant beneficial effects on four of the five outcome measures at three-month follow-up in favour of the group who had received the multidisciplinary team intervention.

▷ From evidence to recommendations

Although there was only one trial that specifically considered rehabilitation after acute relapse, the additional evidence (reviewed elsewhere in this document) confirming the benefits of specialist neurological rehabilitation coupled with the strong evidence supporting rehabilitation after stroke (which is similar in presenting with sudden onset complex neurological disability) meant that the GDG had no difficulty in supporting the recommendations made.

RECOMMENDATION

R51 When a person with MS experiences a sudden increase in disability or dependence the individual should be:

- given support, as required and as soon as practical, both in terms of equipment and personal care D
- referred to a specialist neurological rehabilitation service. The urgency of the referral should be judged at the time, and this referral should be in parallel with any other medical treatment required. A

LOCAL IMPLEMENTATION POINTS

Local services will need to specify and agree:

- arrangements for swift access to a neurological rehabilitation service for post-relapse support
- how equipment and home care should be provided for relapse and post-relapse support
- arrangements for accessing neuro-ophthalmology and low vision services.

4.6 Interventions affecting disease progression

The primary aim of medical intervention is generally to cure pathology, by preventing disease progression and/or removing or stopping the disease process. In MS therefore it is to prevent relapses and progressive demyelination once a diagnosis of MS is confirmed. Demyelination has an inflammatory component, and therefore most treatments target the immune system.*

* NB There are three interferon beta products: Avonex (manufactured by Biogen) and Rebif (Serono) are interferon beta-1a products licensed only for the treatment of relapse-remitting MS (RRMS). Betaferon (Schering) is interferon beta-1b and is licensed for the treatment of both RRMS and secondary progressive MS.

The evidence relating to interferon beta and glatiramer acetate has not been reviewed for this document. The National Institute for Clinical Excellence (NICE) reviewed the clinical and cost-effectiveness evidence and concluded that, 'On the balance of their clinical and cost-effectiveness neither interferon beta nor glatiramer

continued

▷ Evidence statements

Steroids

The studies in this part are distinguished by taking patients who were *not* in an acute relapse.

The effectiveness of steroids in the long-term treatment of MS was investigated in one systematic review (Ia), six RCTs (Ib) and one CCT (IIa). The review¹¹⁷ included four placebo-controlled RCTs comparing the effects of ACTH ($n = 1$), prednisolone ($n = 1$) and methylprednisolone ($n = 2$) given for 9–18 months. It reported no significant effect on long-term functional improvement or on relapse occurrence. The review also reported the occurrence of both major and minor side effects including herpes simplex, herpes zoster, severe ankle oedema, femur fracture, acute anxiety and severe depression.¹¹⁷ Four of the controlled trials also compared steroids to placebo. Two RCTs, one of ACTH and the other of two different doses of zinc hydroxide corticotrophin, found no effect of treatment on any of the outcomes investigated.^{142,143} One reported a greater incidence of adverse effects including steroid diabetes, increased blood pressure, oedema, acne and hirsutism in the intervention groups.¹⁴² A placebo-controlled RCT¹⁴⁴ of methylprednisolone daily for five days followed by oral prednisone for a further four days reported beneficial effects for four (pyramidal function, cerebellar symptoms, sensitivity disorders and overall EDSS scores) of the eight outcomes investigated. This study only included patients with primary progressive MS. A second placebo-controlled RCT investigated a combination treatment of prednisolone, azathioprine and anti-lymphocyte globulin. This study found no effects on relapse rate or EDSS score but did report a positive effect on VEP latency.¹⁴⁵ One RCT and one CCT compared the regular administration of intravenous methylprednisolone to treatment with methylprednisolone during relapses.^{146,147} Both studies included only patients with relapsing remitting MS, and both reported positive effects of treatment. It should be noted that the CCT was of very poor quality,¹⁴⁶ and the RCT was only of average quality.¹⁴⁷ The CCT reported only mild side effects, however, the RCT reported two serious adverse effects (acute glomerulonephritis and severe osteoporosis) in the group receiving regular steroid treatment.

Aminopyridines

The effectiveness of aminopyridines was assessed in one systematic review (Ia), three placebo-controlled crossover RCTs and one pragmatic crossover RCT (Ib). The systematic review, which included five crossover trials, reported significantly greater improvements in a variety of outcomes in those receiving 4-aminopyridine or 3,4-diaminopyridine.¹⁴⁸ It reported that six

acetate is recommended for the treatment of multiple sclerosis (MS) in the NHS in England and Wales'. The guidance also invited the Department of Health and National Assembly for Wales 'to consider the strategy outlined in Section 7.1 [of TA 32] with a view to acquiring any or all of the medicines for this guidance in a manner that could be considered to be cost effective'.

Subsequently the Department of Health and National Assembly for Wales set up a risk sharing scheme with the pharmaceutical companies concerned (see HSC 2002/004 and WHC 2002/016) so that these drugs will be funded for use in selected people with MS. Selection is undertaken using the guidelines developed by the Association of British Neurologists (see www.theabn.org/downloads/msdoc.pdf), both for starting and stopping the drugs. A subset of people with MS, who agree, will be monitored using a standard protocol.^{141a,141b,141c}

It is worth noting that there is no evidence relating to the validity or reliability of making the diagnosis of the type of multiple sclerosis or the occurrence of a relapse, both important components of the current policy.

major side effects occurred in the 144 treated patients included in the review. These included acute encephalopathy, confusion and seizures. All three of the placebo-controlled studies not included in the review found no overall significant differences between the treatment groups, 4-aminopyridine in two and 3,4-diaminopyridine in the other, and those receiving placebo.^{149,150} The study using 3,4-diaminopyridine reported that over half the participants experienced side effects when in the active treatment group compared to around 10% when receiving placebo.¹⁴⁹ The studies were of good quality. One reasonable quality crossover RCT compared the effects of 3,4-diaminopyridine and 4-aminopyridine.¹⁵¹ This study reported that 4-aminopyridine appeared more effective than 3,4-diaminopyridine. More patients withdrew during treatment with 3,4-diaminopyridine as they believed their condition had deteriorated.

Cytotoxics

The effects of cytotoxics were investigated in one systematic review (Ia), two RCTs (Ib) and three CCTs (IIa).

The review included two RCTs which compared the effects of cladribine to placebo, and an additional placebo-controlled RCT of cladribine also met inclusion criteria. The review reported that one study reported a beneficial effect of cladribine but the other did not.¹⁵² The RCT reported no difference in the two treatment groups in terms of clinical outcomes but reported a beneficial effect of cladribine on MRI outcomes.¹⁵³ The review highlighted the cladribine is a potentially toxic immunosuppressive agent.

Mitoxantrone was compared to placebo in two RCTs included in the review, and two RCTs and one CCT not included in the review. An additional RCT compared mitoxantrone to methylprednisolone. The review found that both RCTs reported significant delays in progression and reductions in relapse rate, although one trial was of short duration.¹⁵² Both studies not included in the review supported these findings. The first RCT included a large number of participants and was of reasonable quality.¹⁵⁴ It reported a beneficial effect of treatment for all five outcomes investigated.¹⁵⁴ The second RCT compared high (12mg/m) and low-dose (5mg/m) mitoxantrone to placebo. The results showed a significant beneficial effect of high-dose treatment compared to placebo on EDSS scores, AI scores and the number and severity of relapses. There were no significant differences between the placebo and low-dose groups.¹⁵⁵ The CCT reported a beneficial effect on mean exacerbation rate in those receiving mitoxantrone, although it found no significant effects on EDSS score.¹⁵⁶ This study was of poor quality and only included 20 patients. Mitoxantrone has significant cardiac side effects and cannot be given for more than two years. The pragmatic RCT found no difference between treatment with mitoxantrone and methylprednisolone in terms of EDSS score, disease progression or the number of patients with clinical improvement. However, mitoxantrone was more effective than methylprednisolone in terms of the number of relapses and MRI lesions.¹⁵⁷

Cyclophosphamide was investigated in the review and also in two CCTs.* The review included five placebo-controlled RCTs of cyclophosphamide, in four of these it was combined with corticosteroids.¹⁵² Delays in progression were reported in two trials but this was not confirmed

* A Cochrane review – La Mantia, Milanese C, Mascoli N, Incorvaia B *et al.* Cyclophosphamide for multiple sclerosis. Cochrane Library, Issue 4, 2002 – also met the inclusion criteria. The review however did not include any trials not already included.

by the other three, a wide range of side effects were reported in all studies.¹⁵² An additional poor quality placebo-controlled CCT was identified which was not included in the review. This study compared two different regimes of cyclophosphamide compared with corticotrophin and also included a no-treatment group. Both cyclophosphamide groups showed beneficial effects on time to progression and there were no differences between the two intervention groups.¹⁵⁸ The second poor quality CCT compared three different treatment regimes. It found no significant differences between the groups in terms of EDSS score but found that time to progression was improved in those receiving a slightly higher total mean dose of cyclophosphamide than those receiving the lowest dose.¹⁵⁹

Immunoglobulin

One systematic review which included three placebo-controlled trials of intravenous immunoglobulin (IVIg) (Ia), and three further placebo-controlled trials not in the review met inclusion criteria, two of which were randomised (Ib) and one of which was a controlled trial (IIa). An RCT of gamma-globulin (Ib) and a controlled trial of anti-lymphocyte globulin also met the inclusion criteria (IIa). The review reported that two of the three trials reported no effect on disease progression, although the third small trial did report an effect. Relapse rate was reduced in all three trials. A wide range of side effects including headache were reported in all trials.¹⁵²

The remaining three placebo-controlled studies all reported some beneficial effects of treatment. The RCT reported a beneficial effect on disease progression (as assessed by the EDSS score) and on the number of relapses, but found no effect on muscle strength or depression.¹⁶⁰ The randomised crossover trial found a beneficial effect on the period of no exacerbation but not on any of the other four outcomes assessed, during IVIg treatment.¹⁶¹ This study also reported a high number of common adverse events during the IVIg phase. The CCT reported a positive effect on both the number of exacerbations and the severity of exacerbation and reported no side effects during treatment.¹⁶² The second CCT which investigated a combination of interventions including anti-lymphocyte globulin (with combinations of azathioprine, prednisolone and thoracic-duct drainage), did not report appropriate results and so it is not possible to draw conclusions from this study.¹⁶³ One small placebo-controlled RCT investigated the effects of gamma-globulin and found no difference between the intervention and control group.¹⁶⁴

Immunostimulants

Two reasonable quality placebo-controlled RCTs investigated the effects of **levamisol**. The first reported no effect on disability or neurological function,¹⁶⁵ while the second reported a reduction in the number of patients experiencing an exacerbation.¹⁶⁶ Both studies reported that side effects, although minor, were more common in the intervention group.

Immunosuppressives

One systematic review (Ia), nine RCTs (Ib) and two CCTs (IIa) met inclusion criteria. The review, which included one systematic review of seven studies and two RCTs, assessed the effectiveness of **azathioprine**.¹⁵² Three additional RCTs and one CCT also assessed the effectiveness of azathioprine.^{167–170} The review found that both RCTs and the review reported non-

significant delays on progression, and that the placebo-controlled studies reported a reduction in relapse rate of one-third or more. It also reported that azathioprine has unpleasant side effects with around 10% of patients suffering intolerable vomiting.¹⁵² None of the other trials of azathioprine reported an overall beneficial effect of treatment. Three studies found no beneficial effect of treatment^{167–169} and one reported a beneficial effect on MRI lesion load and MEP but not on any of the other outcomes investigated.¹⁷⁰ All studies reported side effects of azathioprine treatment, some of which were severe.

Two placebo-controlled RCTs assessed the effectiveness of cyclosporin. One reported no beneficial effect of treatment,¹⁷¹ the other reported a positive effect on three of the five outcomes investigated.¹⁷² Both studies reported adverse effects associated with cyclosporin. Renal function was adversely affected in almost all patients receiving cyclosporin in both trials, with significant nephrotoxicity occurring in around one fifth of patients in one of the trials.¹⁷² An additional RCT compared cyclosporin with azathioprine and found no significant differences between the two treatment groups.¹⁷³ Side effects occurred in both groups but more severe in the azathioprine treated group.

Other immunosuppressives investigated included 6-mercaptopurine combined with methotrexate,¹⁷⁴ mizoribine,¹⁷⁵ and lenercept,¹⁷⁶ each in one RCT, and antegren in two RCTs.^{177,178} None of these interventions showed an overall beneficial effect of treatment compared to placebo. The systematic review also included two RCTs of methotrexate.¹⁵² There was a significant beneficial effect in one trial when assessed using a composite measure of treatment failure; the other trial, however, reported no effect on relapse rates.

Interferons (excluding interferon beta)

Seven RCTs assessed the effectiveness of α -interferon.^{179–185} None of the RCTs reported a beneficial effect on clinical outcomes, but four of the RCTs did report positive effects on MRI parameters including the number of new and active lesions.^{180,182,183} Adverse events were significantly more common in the interferon-treated groups.

Antiviral

A number of different antiviral treatments have been investigated in the treatment of disease progression. A total of eight RCTs (**Ib**) and two CCTs (**Iia**) met inclusion criteria. These studies investigated the effects of valaciclovir ($n = 1$),¹⁸⁶ isoprinosine ($n = 3$),^{187–189} aciclovir ($n = 1$),¹⁹⁰ influenza vaccine ($n = 3$),^{191–193} tuberculin ($n = 1$),¹⁹⁴ and amantadine ($n = 1$).¹⁹⁵ None of these studies reported an overall beneficial effect of treatment, and the RCT of tuberculin reported a harmful effect of treatment with a greater incidence of exacerbations in the treatment group.¹⁹⁴ One RCT of amantadine¹⁹⁵ reported a positive effect of treatment on two (time to first relapse and number of relapses) of the seven outcomes investigated. All but one of these studies were placebo controlled. The study without placebo control compared isoprinosine with prednisolone and found no difference between the two treatment groups.¹⁸⁸

Anti-inflammatory

Two RCTs (**Ib**) and one CCT (**Iia**) assessed the effectiveness of anti-inflammatory agents; all were placebo controlled. The CCT¹⁹⁶ which investigated D-penicillamine and metacycline, and

one of the RCTs¹⁶⁴ which investigated chloroquine and soluble aspirin, both reported no beneficial effects of treatment. The second good quality RCT investigated the effects of sulfasalazine and reported a beneficial effect of treatment for three (progression rate, relapse rate and MRI T2 lesions) of the six outcomes investigated.¹⁹⁷ Treatment was stopped permanently in eight patients treated with sulfasalazine due to adverse effects including neutropenia, hepatitis, allergy and depression.

Transfer factor

The effectiveness of transfer factor was investigated in three RCTs (Ib) and one CCT (IIa). None of the RCTs reported any beneficial effect of treatment.^{198–200} The CCT reported a beneficial effect for one of the three outcomes investigated.²⁰¹ This study was of very poor quality.

Irradiation

Four placebo-controlled RCTs (Ib) investigated the effects of treatment with total lymphoid irradiation (TLI). One good quality small RCT found no beneficial effects of treatment,²⁰² one reported an initial beneficial effect which was no longer significant after 18 months follow-up,²⁰³ one reported a beneficial effect for one of the two outcomes investigated²⁰⁴ and the other reported an overall beneficial effect of treatment.²⁰⁵ The study which reported an overall beneficial effect of treatment was stopped prematurely due to decreased patient entry because of the availability of β -interferon.²⁰⁵ All studies reported a greater incidence of adverse events in the TLI treated groups. These included nausea, hair loss, amenorrhoea, infections, thrombocytopenia and pancytopenia.

Hyperbaric oxygen

A systematic review (Ia) and one additional RCT (Ib) met the inclusion criteria. The review included 14 RCTs but the results were restricted to eight studies which were judged to be of reasonable quality.²⁰⁶ The review reported that only one of eight trials reported results in favour of hyperbaric oxygen therapy, the others found no clear positive effects. Side effects were generally minor with ear and visual problems predominating. The additional RCT, which was of good quality, reported a positive effect of treatment for all five outcomes investigated and reported only minor adverse events associated with treatment.²⁰⁷

Linoleic acid

One systematic review (Ia) met the inclusion criteria. The review included three RCTs and found that the severity and duration of relapses was reduced in those treated with linoleic acid. It also found that patients with very low disability at trial entry ($EDSS \leq 2$) treated with linoleic acid showed a significantly smaller increase in disability than those in the control group, however, this was not observed in those with higher disability at trial entry.²⁰⁸

Linomide

Three RCTs and two CCTs assessed the efficacy of linomide. The first RCT reported no beneficial effect of treatment,²⁰⁹ the second reported a beneficial effect for a number of MRI

measures but not for any clinical measures,²¹⁰ and the third investigated the effects of two different doses of linomide compared to placebo.²¹¹ This study found no beneficial effect of the lower dose (2.5mg/day) of linomide compared to placebo, but reported a positive effect for this higher dose (5mg/day) for two of the three outcomes investigated.²¹¹ Two of the RCTs^{209,211} were ended prematurely due to an increase in serious adverse events including death (IIb). Both of the CCTs reported overall beneficial effects of treatment with linomide. However, both also support a high number of minor adverse effects in the intervention groups.^{212,213}

Myelin basic protein

Six RCTs (Ib) assessed the effectiveness of various forms of myelin basic protein; all studies were placebo controlled. Five of these reported no beneficial effects of the intervention for any of the outcomes investigated.^{214–218} Interventions investigated in these trials were: HBC,²¹⁴ AG284 (human leukocyte antigen with myelin base protein),²¹⁵ altered peptide ligands at three different doses,²¹⁶ T-cell receptor peptide,²¹⁷ and bovine myelin.²¹⁸ One of these studies was stopped prematurely due to the appearance of a systemic hypersensitivity reaction in 13/142 patients.²¹⁶ One reasonable quality RCT of myelin basic protein reported a significant beneficial effect of treatment for patient self report of various symptoms, no other outcomes were assessed.²¹⁹ This study reported that no adverse effects were observed during the study.

Plasma exchange

One systematic review (Ia) and one CCT (IIa) examined the effects of plasma exchange. The review,²²⁰ which included six RCTs comparing various treatment combinations including plasma exchange to the treatment combination without plasma exchange, found that plasma exchange significantly reduced the proportion of patients who experienced neurological decline at 12 months follow-up. The CCT,²²¹ which only included 16 patients and was of very poor quality, found no beneficial effects of treatment. It reported transient hypotension in one patient in the intervention group but reported no other adverse effects.

Thymectomy

The effects of thymectomy were investigated in two poor quality controlled trials (IIa). Both included three treatment groups, one receiving azathioprine combined with thymectomy, the second receiving thymectomy alone, and the third receiving no intervention. One study reported no beneficial effects of the thymectomy, either alone or combined with azathioprine.²²² The second reported a beneficial effect of thymectomy combined with azathioprine for two of the three outcomes investigated, but found no beneficial effects of thymectomy alone. Neither study reported on adverse events.²²³

Other

A variety of other interventions have been investigated for their effects on disease progression. Five studies were included in this category, four RCTs (Ib) and one CCT (IIa), all included a placebo or no treatment arm. Interventions which were shown to have no effect on disease progression included tolbutamide,²²⁴ atromid,²²⁵ and 8-methoxypsoralen.²²⁶ An average

quality RCT of Padma 28,²²⁷ a herbal mixture, reported a positive effect of treatment on disease progression. A poor quality CCT²²⁸ of Chinese medicine reported a positive effect on the incidence of relapses. Neither study provided any details on adverse events.

▷ Economic evidence

An HTA systematic review of immunomodulatory drugs for the treatment of people with MS was carried out in 1999.¹⁵² This review found no cost-effectiveness studies of azathioprine, cladribine, cyclophosphamide, intravenous immunoglobulin, methotrexate or mitoxantrone. The costs of these drugs vary enormously from around £60 per year to treat one person with methotrexate or cyclophosphamide, to around £9,000 per year for cladribine or intravenous immunoglobulin. There will be considerable extra costs associated with the administration and monitoring of these drugs. Of course, cost savings may also accrue to health and social services due to reduced hospital admissions, reduced disability and maintenance of employment for the person with MS and/or their carer. A full economic evaluation would need to assess the costs along with the benefits, side effects and acceptability of these treatments to people with MS.

▷ From evidence to recommendations

The recommendations made here had to consider not only the evidence reviewed above but also:

- existing NICE recommendations concerning disease-modifying drugs (this evidence was not reviewed for this guideline)
- the Department of Health's risk sharing scheme
- the need to advise against any treatments known to be ineffective or harmful
- the need to encourage caution where there is some evidence that is equivocal, but where the drug may carry significant risks
- the considerable uncertainty surrounding many drugs
- the large number of drugs that have been researched and that some people may still consider or ask about.

The recommendations try to cover all likely drugs in a logical order, starting with the drugs with the strongest recommendations in their favour and finishing with the drugs with the strongest recommendations against them.

Many drugs have been tried for reducing disease progression. The recommendations given have been influenced by several factors:

- in the development of this guideline we referred to the NICE technology appraisal relating to interferon beta or glatiramer acetate
- the Department of Health risk sharing scheme was also outside of our scope
- aminopiridines, which were reviewed in this section, are not intended to effect disease progression, have risks and are not available on the NHS.

Consequently we have not been able to draw comparisons between the various disease-modifying drugs in terms of cost-effectiveness. The recommendations primarily summarise existing guidance with some recommendations concerning other drugs.

RECOMMENDATIONS

- R52** People with relapsing-remitting MS, and those with secondary progressive MS in which relapses are the dominant clinical feature, who meet the criteria developed by the Association of British Neurologists are eligible for treatment under the risk sharing scheme. See Health Services Circular 2002/004 (www.doh.gov.uk/pricare/drugsmultiplesclerosis.htm) and Table 5. HSC

Table 5 Summary of the criteria suggested by the Association of British Neurologists, and agreed by the Department of Health, to determine eligibility for treatment using interferon beta and glatiramer acetate for people with MS within the 'risk sharing scheme'

- A** People with **relapsing-remitting** MS should be offered **interferon beta** (any type) provided that the following four conditions are met:
- can walk 100 metres or more without assistance
 - have had at least two clinically significant relapses in the past two years
 - are aged 18 years or older
 - do not have contraindications (see specific summary of product characteristics (SPC) for details).
- B** People with **relapsing-remitting** MS should be offered **glatiramer acetate** provided that the following four conditions are met:
- can walk 100 metres or more without assistance
 - have had at least two clinically significant relapses in the past two years
 - are aged 18 years or older
 - do not have contraindications (see specific SPC for details).
- C** People with **secondary progressive** MS should be offered **interferon beta** (any type licensed for this use) provided the following five conditions are met:
- can walk 10 metres or more with or without assistance
 - have had at least two disabling relapses in the past two years
 - have had minimal increase in disability due to gradual progression over the past two years
 - are aged over 18 years
 - do not have contraindications (see specific SPC for details).
- D** People with MS offered treatment with **interferon beta** should have the following **stopping criteria** discussed and agreed before starting treatment:
- intolerable side effects
 - becoming or trying to become pregnant
 - occurrence of two disabling relapses within a 12-month period
 - secondary progression with an observable increase in disability over a six-month period
 - loss of ability to walk, with or without assistance, that has persisted for longer than six months.
- E** People with relapsing-remitting MS offered treatment with **glatiramer acetate** should have the following **stopping criteria** discussed and agreed before starting treatment:
- intolerable side effects
 - being pregnant or planning pregnancy
 - occurrence of two disabling relapses within a 12-month period
 - development of secondary progressive MS
 - loss of ability to walk, with or without assistance, that has persisted for longer than six months.

- R53 People with MS should be advised that linoleic acid 17–23g/day may reduce progression of disability. Rich sources of linoleic acid include sunflower, corn, soya and safflower oils. A
- R54 The following treatments should not be used except in these specific circumstances: D
- after full discussion and consideration of all the risks
 - with formal evaluation, preferably in a randomised or other prospective study
 - by an expert in the use of these medicines in MS with close monitoring for adverse events.
- The treatments are:
- azathioprine A
 - mitoxantrone A
 - intravenous immunoglobulin A
 - plasma exchange, and A
 - intermittent (four-monthly) short (1–9 days) courses of high-dose methylprednisolone. A
- R55 The following treatments should not be used (because there is no research evidence for beneficial effects on the course of the condition):
- cyclophosphamide A
 - antiviral agents (for example, aciclovir, tuberculin) A
 - cladribine A
 - long-term treatment with corticosteroids A
 - hyperbaric oxygen A
 - linomide A
 - whole-body irradiation A
 - myelin basic protein (any type). A

LOCAL IMPLEMENTATION POINTS

These should cover:

- which neurological services have responsibility for initiating and monitoring treatment with interferon beta and glatiramer acetate, and funding arrangements for the risk-sharing scheme
- which neurological services are going to be responsible for initiating and monitoring treatment with other specialist treatments
- how patients may be recruited into ongoing trials of disease-modifying agents
- how people with MS, if they so wish, obtain advice on dietary changes needed to achieve the linoleic acid intake recommended.

4.7 Other issues around altering the risk of relapses

There are many beliefs held by those with MS, professionals, relatives and others about factors that might precipitate a relapse. This section covers some of the common areas of concern including:

- infections and immunisations

- pregnancy
- stress (emotional and physical).

4.7.1 Infections and immunisations

People with MS who develop infections often experience worsening of impairments and disabilities. The main reason is probably the rise in temperature, which is known to exaggerate neurogenic impairments in MS. However it has also been suggested that infections may trigger actual relapses of MS, leading some people to try to avoid infection by immunisation. On the other hand, immunisations to reduce the risk of infections have sometimes been avoided in case they also trigger a relapse.

▷ Evidence statements

There are two cohort studies^{229,230} and one case-control study^{193,231} on infections and MS (II). The relevant evidence suggests:

- that relapses are more frequent during the five week period following common infections (particularly upper respiratory tract infections)
- bacterial infections are of less importance in causing relapses.

There are two RCTs (I), two cohort studies and two case control studies (II) looking at the effect of vaccinations and MS.^{191,193,232–235} The evidence suggests that:

- 33% of MS patients experience an acute exacerbation following influenza
- vaccination does not cause relapses.

▷ From evidence to recommendations

Many people with MS and their doctors are concerned about infection and vaccination, and although the evidence does not show unequivocal benefit, it certainly shows lack of harm. The GDG agreed that the recommendations could be derived safely from the evidence.

RECOMMENDATIONS

- | | | |
|-----|--|---|
| R56 | People with MS should be offered immunisation against influenza. | C |
| R57 | People with MS should have any other immunisation they need, with advice that there is no known risk of causing a relapse of their MS. | C |

LOCAL IMPLEMENTATION POINT

The local guidelines should cover how routine influenza immunisation will be offered and mechanisms to ensure that every person with MS is contacted.

▷ Resource implications

The resources currently devoted to immunisation are unknown, but probably small. Setting up and running a prophylactic service would best be achieved by using the existing service for the elderly. General practitioners are given financial incentives to immunise patients at risk (the

elderly) and if patients with MS were added to the group at risk then there would be a small increase in expenditure (1–2 patients/GP). The potential benefits are significant in terms of reduced relapses and so reduced admissions and use of steroids. Furthermore people with MS would generally avoid hospital admission with influenza.

4.7.2 Pregnancy

The possible effect of pregnancy on the course of MS is often a dilemma for those with MS and doctors alike. First, it is perceived that it might alter the immediate or long-term natural history of the disease. Second, any disability might affect both obstetric care and, later, child care.

▷ Evidence statements

The evidence comes from seven cohort studies^{236,237–242} (IIa) and it suggests that:

- the relapse rate is stable or declines during pregnancy particularly in the third trimester
- the relapse rate increases during the first three months post-partum
- the relapse rate returns to pre-pregnancy rate six months post-partum
- there is no association between pregnancy and worsening of long-term disability
- there is no association between oral contraceptive use, breast-feeding, epidural analgesia or the number of pregnancies with MS relapses.

▷ From evidence to recommendations

Only observational evidence was available, but the GDG agreed that the recommendations could be derived safely from the evidence

RECOMMENDATIONS

- | | | |
|-----|---|---|
| R58 | Women with MS who wish to become pregnant should be advised that the risk of relapse decreases during pregnancy, and increases transiently post-partum. | C |
| R59 | When giving birth, women with MS should have the analgesia that seems most appropriate and acceptable to them, without fear of its affecting their MS. | C |

LOCAL IMPLEMENTATION POINTS

Local services should identify:

- an obstetrician and members of the obstetric department with a knowledge of supporting women with disabilities in the decision to try and become pregnant, during pregnancy and at birth
- local services and support groups for new mothers with disabilities.

▷ Resource implications

Currently people with MS already see obstetricians and others, but sometimes are given inappropriate advice. There are few direct resource implications, though some special training might be needed if no one locally has an interest. The benefits would largely accrue to the person with MS and child.

4.7.3 Stress (various types)

There is a widespread belief among people with MS, relatives and some professionals that stress of almost any type may precipitate a relapse and worsen the manifestations of MS. Some patients are advised to avoid certain (but varied) stressors. Putative stresses include emotional stress, trauma, and other medical interventions. This section reviews the topic to draw appropriate recommendations where possible. It covers emotional stress, trauma, and surgical treatments.

▷ Evidence statements

Anaesthesia – There are three cohort studies^{241,243,244} of the effects of anaesthesia/surgery, and the evidence (II) suggests that there is no association between type of anaesthetic and deterioration of MS.

Stress – There are two cohort studies and two case-control studies of emotional stressors^{245–248} and the evidence (II) suggests that:

- there is conflicting evidence regarding an association between stress and MS relapses
- several studies have shown no significant association between stressful life events and psychological stress with MS relapses
- increased conflict and disruption in routine, daily hassles have been reported to increase relapse rate
- there is significantly increased risk of reported stressful events when rate of MS progression higher
- there is significantly increased risk of MS progression when rate of reported stressful events higher.

Trauma – There is one cohort study²⁴⁹ and two case control studies^{247,248} of trauma, and the evidence (II) suggests that:

- there is insufficient evidence to support any significant association between trauma and MS relapses
- head injury and lumbar disk surgery are not associated with the onset of MS
- peripheral fractures are not associated with increased disease exacerbation.

RECOMMENDATION

In the absence of conclusive evidence, it has only been possible to make a recommendation on stress relative to surgery.

- R60 People with MS should be encouraged to have any surgery they need, using whichever anaesthetic technique is appropriate. They should be informed that there is no known increase in the risk of relapse. **B**

LOCAL IMPLEMENTATION POINT

The local service should identify anaesthetists with a particular interest in undertaking anaesthesia in people with MS or other neurological conditions.

▷ Resource implications

There are few resources currently devoted to this specific topic, and there are no great implications because the guidelines relate primarily to advice and information. The benefits are that patients and others will be less concerned and anxious about the consequences of trauma and stress.