The National Collaborating Centre for Chronic Conditions

Funded to produce guidelines for the NHS by NICE

MULTIPLE SCLEROSIS

National clinical guideline for diagnosis and management in primary and secondary care

With joint leadership from

The Royal College of Physicians

The Chartered Society of Physiotherapy

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Contents

Preface

It is a pleasure to welcome you to this guideline on the management of multiple sclerosis (MS). It describes best practice for the health care management of a complex disorder that affects individuals and their carers in many and varied ways. This variability has made it hard to plan a cohesive or effective NHS service, and the challenge now is for all those involved in health care (those that commission care, those that deliver care, and the patient and carer groups) to ensure that these guidelines are used.

We would particularly direct readers to the six key messages set out in the Executive Summary at the front of the document and to the audit/implementation criteria (Section 7) for measuring the implementation process. If these are acted upon, then service provision will be improved and those with MS will enjoy a better quality of life and less disability in the future.

The guideline has been developed by National Collaborating Centre for Chronic Conditions (NCC-CC) with a commission from the National Institute for Clinical Excellence (NICE). The commission stipulated that the guideline should concentrate on the health (ie NHS) aspects of multiple sclerosis, and that while it would include the interface with other agencies including social services, it would not discuss their detailed provision. An additional stipulation was that topics already covered by an existing NICE appraisal report would be incorporated without further assessment.

For many areas of MS there is little evidence upon which to base recommendations, and the gaps between the evidence have been filled with recommendations, based on a formal consensus of the experts on our guideline groups. In each section of the document the level of supporting evidence is made clear on the understanding that the stronger the evidence the greater likelihood that the recommendations based on it are sound. However the reader should not equate level of evidence with strength of recommendation – some of the most important recommendations, with the greatest consequences for the health service or for people with MS, have been made by group consensus because there was inadequate evidence. This is what the experts believe to be best practice – what they would recommend for their patients or relatives.

While the detail of local implementation of this guideline may vary (according to local facilities and geography), the main aims ought to be common across England and Wales, and if adopted should lead to better standards of care and thus better outcomes from this often distressing condition. There may be some readers who will find particular recommendations, especially those reached by consensus, hard to accept, and to them the challenge is to go out and produce and publish evidence to either confirm or refute what this guideline sets out. This additional research and thought applied to multiple sclerosis could make future versions of this guideline even stronger.

Mike Pearson FRCP
Director, National Collaborating Centre for Chronic Conditions

Executive summary

Multiple sclerosis (MS) is diagnosed in 3.5 to 6.6 people per 100,000 of the population each year, equivalent to about 1,800 to 3,400 people each year in England and Wales. Prevalence is between 100 to 120 per 100,000 of the population, equivalent to about 52,000 to 62,000 people with MS in total in England and Wales.

Some people with MS develop few symptoms, but for others the disease and society's interactions with them lead to problems affecting all aspects of their lives. The disease often has an impact upon the family.

Many people with MS need to make extensive use of primary and secondary health care, and social services. This guideline suggests how clinical services for people with MS can be improved both in terms of delivery and in terms of specific interventions. The needs of people with MS are similar to those of many other patients with long-term conditions, and this guideline will have general lessons which can be applied more widely than just MS.

The following recommendations have been identified as priorities for implementation.

▷ Specialised services

MS is a relatively rare condition often leading to complex problems that require expert services. We recommend that *specialist neurological and neurological rehabilitation services should be available to every person with MS when they need them, usually when they develop any new symptom, sign, limitation on activities or other problem, or when their circumstances change.* We have made suggestions about what this might mean for commissioners in the audit criteria section of the guideline (Section 7).

▷ Rapid diagnosis

Once a patient has experienced symptoms suggestive of MS, a rapid diagnosis is needed. This ensures that any required treatments are started, and reduces anxiety and uncertainty. We recommend that *an individual who is suspected of having MS should be referred to a specialist neurology service and seen rapidly within an audited time. The individual should be seen again after all investigations necessary to confirm or refute the diagnosis have been completed (also rapidly within an audited time).**

▷ Seamless services

People with MS often have complex problems requiring input from many different groups both within and outside the NHS. Many find that bureaucracy and border disputes lead to stress and

* The Guideline Development Group debated the meaning of the word 'rapidly'. In this context, it is taken to mean that the exact time will vary according to clinical need but should, in the opinion of the development group, be no longer than six weeks from referral to being seen by a neurologist, and a further six weeks until any necessary investigations are completed.

delays in even the simplest of actions. Current policies should lessen this, but still we recommend that *every health commissioning organisation should ensure that all organisations in a local health area agree and publish protocols for sharing and transferring responsibility for and information about people with MS, so as to make the service seamless from the individual's perspective.* We recommend that these protocols are publicly available and that the timescales involved are audited to ensure that unnecessary delays do not occur.

▷ A responsive service

People with MS can experience one or more of a wide variety of symptoms and difficulties. Each person's needs are unique, and a flexible response is required from the NHS. We recommend that *all services and service personnel within the health care sector should recognise and respond to the varying and unique needs and expectations of each person with MS. The person with MS should be involved actively in all decisions and actions.* In other words, services should be patient centred. A patient-led system of audit can help address some of the difficulties in monitoring this.

▷ Sensitive but thorough problem assessment

The great variety of possible problems that people with MS may have can make it difficult for health care professionals to detect all relevant changes. We have recommended that *health service professionals in regular contact with people with MS, should consider in a systematic way whether the person with MS has a 'hidden' problem contributing to their clinical situation, such as fatigue, depression, cognitive impairment, impaired sexual function or reduced bladder control.* The main text of the guideline details the various problems that a person with MS may have and appropriate ways of treating these problems.

▷ Self-referral after discharge

There is no predictable pattern or progress of the condition in any individual with MS, but problems may arise quickly at any time. Some people therefore have routine appointments 'to keep in touch', which is wasteful and perpetuates a dependent approach, while many others 'fall out' of the system until a crisis occurs. We have strongly recommended that *every person with MS who has been seen by a specialist neurological or neurological rehabilitation service should be informed about how to make contact with the service when he or she is no longer under regular treatment or review. The individual should be given guidance on when such contact is appropriate.* This recommendation should mean that each specialist service (neurology, and neurological rehabilitation) has in place a mechanism for accepting and responding to direct contact by someone with MS, even when they are no longer under regular treatment or review by that service.

Conclusion

The full document gives specific advice to clinical staff on a huge range of issues such as the management of bladder problems, the treatment of spasticity, therapy for reduced walking ability and the identification and management of difficulties in swallowing. One strong message

is that clinical staff need to be systematic in their approach to each person with MS so that all remediable problems are identified and managed effectively. This depends upon a well-trained body of staff working in a team with appropriate support from information systems.

Finally, the document emphasises the importance of prevention of ill health, which is a vital function of the NHS. Prevention is especially important in people with long-term conditions because they are often at risk of many specific secondary conditions. For example people with MS may experience infections, contractures, and falls. However, the occurrence of a pressure ulcer is perhaps the most serious and the best marker of service quality. We have suggested that the occurrence of a pressure ulcer in someone with MS should be considered an adverse event worthy of formal investigation.

If the NHS can deliver a good service to people with MS then it will also be delivering a good service not simply to other people with neurological disability but to all people with long-term conditions. This guideline should help set the NHS on course for this.

Glossary

Activities of daily living (ADL)
This phrase refers to activities or tasks undertaken as part of day-to-day life such as getting dressed, cooking or shopping. They can be subdivided into personal ADL, domestic (household) ADL, and community ADL.

Adverse events
Sometimes known as side effects. Adverse events are any event that is not to the benefit of the person. Some are predictable, and some are only rare and unexpected. Adverse events from drugs might include, for example, rashes, feeling fatigued and being depressed. Adverse events can also follow rehabilitation treatments and might include falling while learning to walk and pain from stretching a joint.

Allied health professionals
Health care professionals, other than doctors and nurses, directly involved in the provision of health care. Includes several groups such as physiotherapists, occupational therapists, dieticians, etc. (Also known as professions allied to medicine or PAMs.)

Alternative therapies
A term that is difficult to define because the classification of therapies is not fixed. This usually refers to treatments of any type which are not prescribed or recommended by doctors, or are not given by health care professionals practicing within the NHS.

Applicability
The extent to which the results of a study or review can be applied to the target population for a clinical guideline.

Appraisal of evidence
Formal assessment of the quality of research evidence and its relevance to the clinical question or guideline under consideration, according to predetermined criteria.

Area under curve (AUC)
See *receiver operating curve (ROC)*.

Association of British Neurologists (ABN)
The professional body to which all neurological specialist physicians belong.

ATG
Anti-thymus globulin.

Bias
Systematic errors in the design and execution of a study which may lead to an over- or underestimation of the 'true' effect of a treatment or intervention.

Blinding
The practice of keeping the investigators or subjects of a study ignorant of the group to which a subject has been assigned or of the population from which the subject has come. For example, a clinical trial in which the participating patients or their doctors are unaware of whether they are taking the experimental drug or a placebo (dummy treatment). The purpose of 'blinding' is to protect against bias.

British National Formulary (BNF)
The BNF is the recognised authoritative source of up-to-date information on drugs and pharmaceutical products for health care professionals. The emphasis is on those that are prescribed in the UK, rather than over-the-counter medicines. It is a joint publication of the British Medical Association (BMA) and the Royal Pharmaceutical Society of Great Britain (RPSGB).

CAM
Complementary and alternative medicine, eg acupuncture, homeopathy.

Cardiorespiratory fitness
The extent to which the heart and lungs are able to respond to demand. Fitness depends upon a) muscles, primarily in the legs and b) the heart and lungs.

Case-control study
A study that starts with the identification of a group of individuals sharing the same characteristics (eg people with a particular disease) and a suitable comparison (control) group (eg people without the disease). All subjects are then assessed with respect to other factors, such as things that happened to them in the past, eg things that might be related to getting the disease under investigation.

Ceiling effects
See *floor and ceiling effects*.

Cerebro-spinal fluid (CSF)
Fluid produced in hollow structures within the brain that circulates around the outside of the brain and also down the spinal canal. CSF is removed when a lumbar puncture is undertaken.

Clinical audit
A systematic process for setting and monitoring standards of clinical care. Patients' notes and other clinical records are examined as part of the

audit process. Clinical audit should cover the practice of all relevant health care professional groups, as opposed to medical audit which only looks at the doctor's role in patient care. Whereas 'research' defines what the best clinical practice should be, 'audit' investigates whether best practice is being carried out.

Clinical effectiveness
How well a drug, treatment or package of care works to produce good outcomes for patients.

Clinical importance
The importance of a particular guideline recommendation compared with other aspects of clinical management that may be under consideration.

Clinical trial
Research study conducted with patients, usually to evaluate a new treatment or drug. Each trial is designed to answer scientific questions and to find better ways to treat individuals with a specific disease. See also *randomised controlled trial*.

Clinician
A health care professional providing patient care, eg a doctor, nurse or physiotherapist.

Cochrane Library
The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration). The Cochrane Library is available on CD-ROM and on the Internet.

Cognitive status
Cognition refers to the processes involved in thinking, concentrating, planning, solving problems, learning, analysing sensations and remembering. A person's cognitive status is the extent to which they can use their brain to undertake these processes.

Cohort study
A cohort study takes a group of patients and follows them forward in time and measures their outcome (eg disease or mortality rates). Patient subgroups are then identified from information collected about patients and these groups are compared with respect to outcome, eg comparing mortality between one group that received a specific treatment and one group which did not (or between two groups that received different levels of treatment). Cohorts can be assembled in the present and followed into the future (a 'concurrent cohort study') or identified from past records and followed forward from that time up to the present (a 'historical cohort study'). Because patients are not randomly allocated to the two groups, the groups may be quite different in their characteristics and some adjustment must be made when analysing the results to ensure that the comparison between groups is as fair as possible.

Competence
In legal terms, this refers to the ability of someone to make an informed judgement and it depends upon being able to understand written or spoken material sufficiently, hold the information in the memory and use the material to make a considered judgement.

Complementary therapies
See *alternative therapies*.

Computerised tomography (CT)
A technique whereby X-rays are used to map the inside of the body, especially the brain.

Confidence interval
This helps us assess the likely effect of a clinical intervention by describing a range of possible effects that are consistent with the results of a study (or of a combination of studies). A wide confidence interval indicates a lack of certainty or precision about the true size of the clinical effect and is seen in studies with too few patients. Where confidence intervals are narrow they indicate more precise estimates of effects and a larger sample of patients studied. We usually interpret a 95% confidence interval as the range of effects within which we are 95% confident that the true effect lies.

Confounding factor
Something that introduces uncertainty and bias into an observed outcome, complicating interpretation.

Consensus methods
A variety of techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic.

Consistency
The extent to which the conclusions of a collection of studies used to support a guideline recommendation are in agreement with each other. See also *homogeneity*.

Control group
A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) – in order to provide a comparison for a group

receiving an experimental treatment, such as a new drug.

Controlled clinical trial (CCT)
A study that includes some form of control that is not randomised.

Correlation
A measure of the strength of association between two or more variables. For example in children height, weight and age are all correlated because older children tend to be taller and heavier. A positive correlation indicates that one variable has been observed to increase as the other increases, a negative correlation indicates that one decreases as the other increases.

Cost-benefit analysis
A type of economic evaluation where both costs and benefits of health care treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.

Cost-effectiveness
How expensive treatment and care are compared to how much benefit they offer to patients. In cost-effectiveness analysis, the outcomes of different interventions are converted into health gains for which a cost can be associated, for example, cost per additional heart attack prevented.

Crossover study design
The administration of two or more experimental treatments one after the other in a specified or random order to the same group of patients.

Decision analytic model
A method, in health economics, of establishing the best course of action when evidence, both clinical and cost, is uncertain.

Department of Health
A generic term for four UK government departments responsible for the health and well-being of people in England, Wales, Scotland and Northern Ireland, and having specific responsibility for the National Health Service (NHS) and Social Services Inspectorate (SSI).

DGH
District general hospital (non-teaching hospital).

Diagnostic odds ratio (DOR)
DOR is used as a summary measure of the accuracy of a diagnostic test. It is calculated as the odds of a correct positive result, divided by the odds of a false positive result. When a test provides no diagnostic evidence then the DOR is 1.0, but a valuable diagnostic test will tend to have a high DOR.

Diagnostic study
Any research study aimed at evaluating the utility of a diagnostic procedure. The methods employed are generally different to those in a *clinical trial* aimed at evaluating an *intervention*.

Diagnostic work-up
The process of making a diagnosis through tests, clinical history and clinical judgement.

Disease modifying therapies (DMTs)
Any treatment that slows down, stops or reverses the processes that damage the nervous system in MS.

Disease progression
This specifically refers to increasing damage to the nervous system. There is only a weak relationship between damage to the nervous system and increasing symptoms or signs. And some episodes of worsening are simply due to another illness (eg bladder infection) and not progression of the damage to the nervous system.

Dominant
An economic term for an intervention which is cheaper and clinically more effective than the alternative(s).

Dysarthria
Difficulty of articulating words caused by disease of the central nervous system, typically characterised by slurred speech, imprecise articulation and disorders of intonation.

Economic evaluation
Comparative analysis of alternative courses of action in terms of both their costs and consequences.

Effectiveness
The extent to which a specific treatment or intervention, when used under usual or everyday conditions, does what it is intended to do, eg control or cure an illness. (Clinical trials that assess effectiveness are sometimes called 'management trials'.)

Efficacy
The ability of a drug or other treatment to control or cure an illness. In research terms, 'efficacy' refers to the extent to which a specific intervention produces the intended (beneficial) result under ideally controlled conditions, eg in a laboratory.

Episode of care
A technical, Department of Health term that refers to the whole of a treatment episode from hospital admission to discharge or from starting to stopping a course of treatment.

Evidence-based
The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.

Evidence table
A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.

Evoked potentials
Electrical changes in the brain that follow stimulation of the nervous system. The commonest example is to flash lights in the eyes, when an electrical change will occur over the occiput (back of the head) about 1/10th of a second later. They can only be detected using computers and many repeated stimulations because the potentials are so small.

Experimental study
A research study designed to test if a treatment or intervention has an effect on the course or outcome of a condition or disease.

Extrapolation
The application of research evidence based on studies of a specific population to another population with similar characteristics.

Floor and ceiling effects
Problems encountered in some *outcome* measures where there are limits to how low or high a numerical value they can assume, eg it is impossible to measure more than 100%. These can make it difficult to assess the true effect of an *intervention*.

Focus groups
Method of group interview or discussion of between 6 and 12 people focused around a particular issue or topic. The method explicitly includes and uses the group interaction to generate data.

Functional status
An individual's ability to continue normal social and physical activities.

Grade of recommendation
A code (eg A, B, C) linked to a guideline recommendation, indicating the strength of the evidence supporting that recommendation.

Guideline
A systematically developed tool which describes aspects of a patient's condition and the care to be given. A good guideline makes recommendations about treatment and care, based on the best research available, rather than opinion. It is used to assist clinician and patient decision making about appropriate health care for specific clinical conditions.

Guideline recommendation
Course of action advised by the guideline development group on the basis of their assessment of the supporting evidence.

Health technology
Health technologies include medicines, medical devices such as artificial hip joints, diagnostic techniques, surgical procedures, health promotion (eg the role of diet *vs* medicines in disease management) and other therapeutic interventions.

Health technology appraisal (HTA)
A health technology appraisal, as undertaken by NICE, is the process of determining the clinical and cost-effectiveness of a *health technology*. NICE health technology appraisals are designed to provide patients, health professionals and managers with an authoritative source of advice on new and existing health technologies.

Heterogeneity
Or lack of *homogeneity*. The term is used in *meta-analyses* and *systematic reviews* when the results or estimates of effects from separate studies seem to have different magnitude or even different sign or direction. Differences in the patient populations, outcome measures, definition of variables and duration of follow-up of the studies included in the analysis create problems of non-compatibility. See also *homogeneity*.

Hierarchy of evidence
An established hierarchy of study types, based on the degree of certainty that can be attributed to the conclusions of a well-conducted study. Well-conducted randomised controlled trials (RCTs) are at the top of this hierarchy. (Several large statistically significant RCTs which are in agreement represent stronger evidence than, say, one small RCT.) Well-conducted studies of patients' views and experiences would appear at a lower level in the hierarchy of evidence. See also *randomised controlled trial*.

History, clinical
The information collected and considered by a health care professional regarding an individual's previous health-related experiences.

Homogeneity
This means that the results of studies included in a systematic review are similar and there is no evidence of *heterogeneity*. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance. See also *consistency, heterogeneity* and *systematic review*.

HTA
See *health technology appraisal*.

Iatrogenic
Caused by a health care treatment.

Incidence
The rate of new occurrences of a condition or disease, often given as people per year or episodes per year.

Inclusion criteria
See *selection criteria*.

Intention to treat analysis
An analysis of a clinical trial where patients are analysed according to the group to which they were initially randomly allocated, regardless of whether or not they had dropped out, fully complied with the treatment, or crossed over and received the alternative treatment.

Intervention
Health care action intended to benefit the patient, eg prescribing drugs, surgical procedures, psychological therapy, etc.

Intervention groups
In a *clinical trial*, groups to which participants are allocated. Typically, these groups will receive different *interventions* or a *placebo*.

Level of evidence
A code (eg 1a, 1b) linked to an individual study, indicating where it fits into the hierarchy of evidence and how well it has adhered to recognised research principles. See also *hierarchy of evidence*.

Literature review
A process of collecting, reading and assessing the quality of published (and unpublished) articles on a given topic.

Local protocols
See *protocol*.

Low vision service
Any local health service provided to cater for people experiencing visual problems.

Magnetic resonance imaging (MRI)
An imaging technique which uses powerful magnetic fields rather than radiation to obtain accurate images of soft tissue inside the body. Some people cannot safely be scanned with MRI, for example those with pacemakers.

Meta-analysis
Results from a collection of independent studies are pooled, using statistical techniques to synthesise their findings into a single estimate of a treatment effect. A systematic review may or may not include a *meta-analysis*. It is always appropriate and desirable to systematically review a series of results but it may sometimes be inappropriate, or even misleading, to statistically pool results from separate studies. See also *systematic review* and *heterogeneity*.

Methodological quality
The extent to which a study has conformed to recognised good practice in the design and execution of its research methods.

Methodological weakness
Any problem in the way in which a study has been conducted, which throws doubt on the conclusions. See *methodological quality*.

Methodology
The overall approach of a research project, eg the study will be a randomised controlled trial, of 200 people, over one year. See also *randomised controlled trial*.

Multimodal intervention
An *intervention* comprised of more than one aspect which can affect outcomes for the patient.

Musculo-skeletal pain
Pain arising from the muscular and skeletal systems, as distinct from neurogenic pain.

National Institute for Clinical Excellence (NICE)
NICE is a special health authority responsible for providing patients, health professionals and the public with authoritative, robust and reliable guidance on current 'best practice'. NICE commissioned and funded the development of this guideline.

Neurogenic
Arising from the nervous system.

Neuropathic
Pertaining to disorders of the nervous system.

Non-experimental study
A study based on subjects selected on the basis of their availability, with no attempt having been made to avoid problems of bias.

Objective measure
A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and study participants.

Odds ratio
Odds are a way of representing probability, especially familiar for betting. In recent years odds ratios have become widely used in medical reports. They provide an estimate (usually with confidence interval) for the effect of an intervention. Odds are used to convey the idea of 'risk' and an odds ratio of 1 between two treatment groups would imply that the risks of an adverse outcome were the same in each group. For rare events the odds ratio and the relative risk (which uses actual risks

and not odds) will be very similar. See also *control group, relative risk*.

Oligoclonal banding
A phenomenon which can be detected by testing *cerebro-spinal fluid*. It can help to diagnose MS.

Optic neuritis
Inflammation of the optic nerve, which carries visual information from the eye to the brain.

Orthodox therapies
See also *alternative therapies*. Any medical or physical therapy which is usually used or recommended by health care professionals working within the NHS

Outcome
The end result of care and treatment and/or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the effectiveness of care/treatment/rehabilitation. Researchers decide what outcomes to measure before a study begins. Outcomes are then assessed at the end of the study.

Palliative care
Care aimed at alleviating symptoms, pain and distress, and hence improving quality of life, rather than at curing or slowing progression of a disease or condition. It is often associated with, but is actually not limited to, the end of life.

PCT
See *primary care trust*.

Pilot study
A small scale 'test' of the research instrument. For example, testing (piloting) a new questionnaire with people who are similar to the population of the study, in order to highlight any problems or areas of concern, which can then be addressed before the full-scale study begins.

Placebo
A pill, medicine, or other treatment that has no physiological effect and is used as a dummy treatment. A placebo may be used as a comparison (control) in tests on new drugs etc.

Placebo effect
A beneficial (or adverse) effect produced by a placebo and not due to any property of the placebo itself. See *placebo*.

Pooled estimate
An estimate of the effect of a treatment, arrived at through a *meta-analysis*.

Postpartum
After childbirth.

Pre-post study
A study design which measures outcomes in one group of people, first before, and then after, an intervention is given or initiated.

Prevalence
The proportion of a population of people who are experiencing a condition or disease at a given time.

Primary care
Health care delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other health care professionals, dentists, pharmacists and opticians.

Primary care trust
A primary care trust is an NHS organisation responsible for improving the health of local people, developing services provided by local GPs and their teams (called primary care) and making sure that other appropriate health services are in place to meet local people's needs.

Prior probability
In a *diagnostic study*, the proportion of the population which has the condition in question, regardless of what the test result subsequently is.

Probability
How likely an event is to occur, eg how likely a treatment or intervention will alleviate a symptom.

Prognostic factor
Patient or disease characteristics which influence the course of a particular condition. In a randomised trial to compare two treatments, chance imbalances in variables (prognostic factors) that influence patient outcome are possible, especially if the size of the study is fairly small. In terms of analysis these prognostic factors become confounding factors. See *confounding factor*.

Prospective study
A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. Prospective studies may be of several types, including cohort or randomised controlled trials. See *cohort study* and *randomised controlled trial*.

Protocol
A policy or strategy which defines appropriate action. A research protocol sets out, in advance of carrying out the study, what question is to be answered and how information will be collected and analysed. Guideline implementation protocols set out how guideline recommendations will be used in practice by the NHS, at both national and local levels.

P-value
If a study is done to compare two treatments then the P-value is the probability of obtaining the results, or something more extreme, if there really was no difference between treatments. Suppose P = 0.03. What this means is that if there really was no difference between treatments then there would only be a 3% chance of getting the kind of results obtained. Since this chance seems quite low we should question the validity of the assumption that there really is no difference between treatments. We would conclude that there probably is a difference between treatments. By convention, where the value of P is below 0.05 (ie less than 5%) the result is seen as *statistically significant*. Where the value of P is 0.001 or less, the result is seen as highly significant. P values just tell us whether an effect can be regarded as statistically significant or not. In no way do they relate to how big the effect might be, for which we need the *confidence interval*.

Qualitative methods
Research techniques used to describe life's experiences and give them meaning, using a systematic, subjective approach. This type of research is conducted in order to describe and promote understanding of people's experiences, feelings, motivations and behaviour. Examples of qualitative methods include focus groups, in-depth interviews and participant observation. These techniques generate non-numerical data, eg a patient's description of their pain rather than a measure of pain.

Quality-adjusted life years (QALYs)
A measure of health outcome. QALYs are calculated by estimating the total life-years gained from a treatment and weighting each year with a quality of life score.

Quantitative methods
Research techniques that generate numerical data or data that can be converted into numbers. For example, census questions such as the number of people living in a household.

Quasi-experimental study
This is a study in which the treatment comparison groups are not assigned by randomisation.

Randomised controlled trial
A trial in which people are randomly assigned to two (or more) groups: one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was.

Receiver operating curve (ROC)
A mathematical method of comparing diagnostic procedures involving their *specificity* and *sensitivity*. The closer the area under the curve (AUC) is to 1, the better the test.

Reference standard
In *diagnostic studies*, the test being evaluated is often compared to the best known diagnostic procedure, which is known as the reference standard or gold standard.

Rehabilitation
Rehabilitation is a process that focuses on ability and aims to optimise social participation and to minimise distress and stress for both the person with MS and any carers involved, mainly through a problem-solving approach that will involve multi-focal interventions from a specialist team over time.

Relative risk
A summary measure which represents the ratio of the risk of a given event in group of subjects compared to another group. When the 'risk' of the event of interest is the same in the two groups the relative risk is 1. Relative risk is sometimes used as a synonym for *risk ratio*. In a treatment comparison study a relative risk of 2 would indicate that patients receiving one of the treatments had twice the risk of an undesirable outcome than those receiving the other treatment.

Relative risk-benefit ratio
A method of comparing two interventions, balancing the risk and benefit of each to a defined population.

Reliability
Reliability refers to a method of measurement that consistently gives the same results. For example, someone who has a high score on one occasion tends to have a high score if measured on another occasion very soon afterwards. With physical assessments it is possible for different clinicians to make independent assessments in quick succession – and if their assessments tend to agree then the method of assessment is said to be reliable.

Review
Summary of the main points and trends in the research literature on a specified topic. A review is considered non-systematic unless an extensive literature search has been carried out to ensure that all aspects of the topic are covered and an objective appraisal made of the quality of the studies.

Sample
A part of the study's target population from which the subjects of the study will be recruited. If subjects are drawn in an unbiased way from a particular population, the results can be generalised from the sample to the population as a whole.

Sampling
Refers to the way participants are selected for inclusion in a study.

Secondary
Conditions and symptoms which are brought about by an existing disease or condition are described as secondary. For example, secondary pain can result from restrictions in mobility because of MS. The pain in this case is secondary to the MS.

Secondary care
Care provided in hospitals.

Selection criteria
Explicit criteria used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.

Self-report measure
An outcome measure which uses the views and experience of the person with MS rather than clinical measurements.

Sensitivity
The sensitivity of a diagnostic test is the proportion of people with MS who, when tested, have a true positive result.

Sensitivity analysis
A mathematical process, often employed in good quality health economics studies, which assesses the sensitivity of the conclusions to inaccuracy in the estimates regarding cost, clinical effectiveness of the treatments, and the structure of the health service.

Sequelae
A condition occurring as a consequence of a disease.

Significance, statistical
Also 'significant difference' or 'significant effect'.

Specialist
Health care professional with relevant qualifications, necessary knowledge and skills.

Specificity
The specificity of a diagnostic test is the proportion of people without MS who, when tested, have a true negative result.

Stakeholder
Any national organisation, including patient and carers' groups, health care professionals and commercial companies with an interest in the guideline under development.

Standard deviation
A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean to describe numerical data.

Survey
A study in which information is systematically collected from people (usually from a random sample within a defined population).

Systematic
Methodical, according to plan; not random.

Systematic review
A review in which evidence from scientific studies has been identified, appraised, and synthesised in a methodical way according to predetermined criteria. May or may not include a *meta-analysis*.

Systemic
Involving the whole body.

Tertiary centre
A major medical centre providing complex treatments, which receives referrals from both primary and secondary care. Sometimes called a tertiary referral centre. See also *primary care* and *secondary care*.

Transverse myelitis
Inflammation with neurological symptoms, caused by lesions on the spinal cord.

Trial of treatment
A planned period during which a person with MS receives a treatment to find out if it will be of benefit to them as individuals.

Trust
A trust is an NHS organisation responsible for providing a group of health care services. An acute trust provides hospital services. A mental health trust provides most mental health services. A primary care trust buys hospital care on behalf of the local population, as well as being responsible for the provision of community health services.

Validity
Assessment of how well a tool or instrument measures what it is intended to measure. See also *external validity, internal validity*.

Well-being
A concept combining an individual's health, their quality of life, and their satisfaction. There is no universally agreed definition that is useful in the context of health care.

DEVELOPMENT OF THE GUIDELINE

1 Introduction

1.1 Guideline aim

Multiple sclerosis (MS) is a condition of the central nervous system (brain and spinal cord) that usually starts in early adult life. Once present the disease never goes; there is no cure and the person lives with the condition for life but a significant proportion of people have few or no problems. The impact of MS on the individual is variable but one constant feature is uncertainty. The condition also has an impact on family members

Many people with MS may need to make extensive use of health services and social services. Consequently, the aim of this guideline is to ensure that people with MS benefit from a coherent and consistent response from services, to minimise their problems as far as can be achieved.

1.2 Who is the guideline intended for?

A guideline has been defined as 'a systematically developed statement that assists clinicians and patients in making decisions about appropriate treatment for a specific condition'.[1]

These guidelines are aimed at helping health care professionals provide optimal services for those with MS by:

- providing individual clinicians with a set of explicit statements on the best way to manage most common clinical problems to maximise the effectiveness of the service
- providing commissioning organisations and provider services with specific guidance on the best way to organise complex services, to maximise efficiency and equity.

Others, including the general public, may find the guideline of use in understanding the clinical approach to MS. Separate short-form documents for a) the public and b) clinical staff are available which summarise the recommendations without full details of the supporting evidence.

1.3 Clinical context

MS is diagnosed in 3.5 to 6.6 people per 100,000 of the population each year, equivalent to about 1,820 to 3,380 new people being diagnosed each year in England and Wales (population 52 million). Life expectancy in the majority is more or less normal. The prevalence (frequency in the population) is between 100 to 120 per 100,000, equivalent to two people for each general practitioner or 52,000 to 62,400 people in total in England and Wales.[2–4] In comparison, the incidence of stroke is 240 per 100,000 each year, equivalent to about 124,800 new cases each year in England and Wales. The prevalence is about 700 per 100,000, equivalent to about 14 per GP or 364,000 people in England and Wales in total.

Multiple sclerosis is usually diagnosed between the ages of 20 and 50 years. Once diagnosed, people often recognise that they have had the condition for many years. It affects two women for each man affected. The cause is unknown, but it is thought to have several different 'causes' because the evidence suggests that there are both genetic (inherited) and environmental factors at play.

The disease process involves episodes where white matter within the brain or spinal cord becomes inflamed and then damaged by the person's own immune system. These inflamed areas become scarred, giving the disease its name: *multiple* areas of hardening (*sclerosis*) within the brain and spinal cord. Many episodes do not cause any symptoms, but when sudden symptoms occur the person is said to have had a relapse. In some people there is simply a slow progressive increase in symptoms.

Although there is no cure, there are positive roles for the health service. These include making the correct diagnosis, trying to reduce the disease progression, and trying to help the person (if necessary) experience as few symptoms and functional problems as possible.

1.4 The challenge

The challenge facing both organisations and individual clinicians is major. MS is an extremely variable condition. The specific symptoms or signs experienced by an individual can vary. Each person will have a unique combination of symptoms, signs, personal circumstances and wishes. Furthermore, the prognosis for an individual patient is unpredictable. Through their disease pathway people with MS may present to any one of a wide range of health care professionals in any one of a wide range of specialist services. They also present to a wide range of non-health care professionals with their problems, and these professionals may know little or nothing about the condition and yet need to make decisions. Moreover, the evidence needed by a professional to make an informed decision is often difficult to find. Consequently many people with MS are seen by individuals who have relatively little expertise or knowledge, and who cannot find relevant advice easily, and who often are working in isolation away from co-ordinated services, and the service is suboptimal both for the patient in terms of effectiveness and for society in terms of efficiency and equity.

Several studies have highlighted the poor provision of services to people with MS in the UK. Freeman and Thompson surveyed an opportunity sample of 150 patients in contact with the NHS, and found many people with significant disability failed to receive services.[5] An audit of services in Oxfordshire showed the extent of the disorganisation, and the problems faced by individual patients.[6]

Large resources are needed to help people with MS. A recent survey of people with MS at three specialist centres in England estimates a mean total cost per patient of £17,000 per year, suggesting a total burden to society of around £1.34 billion per year.[7] Informal care accounts for 26% of this total, and direct medical cost only 16%. A cost of approximately £3,400 per patient per year falls on the NHS, and the remainder is borne by patients and their families and carers. As well as this financial cost, the quality of life of people with MS is affected by the physical limitations imposed by the disease, and also by the social limitations that follow from this and the emotional problems that may also arise.

1.5 Underlying guideline principles

The main principles behind the development of these guidelines were that they should:

- consider all issues that are important in the health care of people with MS
- use published evidence wherever this is available
- be useful to and usable by all professionals

- take full account of the perspective of the person with MS and their family
- indicate areas of uncertainty or controversy needing further research.

The problems presented by people with MS are complex, covering many aspects of illness and lifestyle. As any set of hospital notes will illustrate dramatically, it is difficult to describe their problems in a simple way. This complexity also makes it difficult to construct a set of guidelines.

The solutions to address this complexity in terms of the guidelines are:

- to use a systematic model of illness, the World Health Organization (WHO) International Classification of Functioning (ICF) model
- to consider the different aspects of the management processes separately
- to recognise that
  - people with MS have different needs
  - many people with MS will have very complex needs at different stages of their disease
  - many people may have few or no needs.

The model of illness used is the WHO's International Classification of Functioning, Disability and Health (ICF) framework (see Appendix A).[8] This allows the description of a person with MS's situation at four levels – disease, symptoms and signs, behaviour, and social situation. It also recognises three different environmental or contextual factors – the social environment, the physical environment, and the person's own internal environment (ie their beliefs, wishes and expectations). It has a specific terminology that has been preferred throughout this document, but the older terminology is also used in places for two reasons: it is sometimes simpler, and it may be more familiar to some readers. More details are given in Appendix A.

1.6 How to use this document

The document is large, covers many topics and gives much background information. The reader is strongly recommended to use the contents page to find his or her way to the relevant part and a glossary is provided at the back of the book to clarify terminology. **The recommendations made in Section 3 apply to all other recommendations, and should be read first.**

Once the relevant part has been found, the reader will probably first look at the recommendations. Generally these follow a logical order from problem identification through simple interventions suitable in most cases, on to complex interventions that will only be used rarely. If the reader wants, he or she can then read the evidence statements above and look at the tables to understand more about why the recommendation was made.

1.7 The structure of the document

The document is divided into sections, each of which covers a set of related topics. For each topic the layout is similar.

The **background** to the topic is described in one or two paragraphs which simply set the recommendations in context.

Then the **evidence statements** are given and these summarise the evidence given in the **evidence tables**, which are Appendix I. In addition, there may be an evidence statement about the health

economic evidence where this is available. In many parts there is a brief statement explaining how recommendations relate to the evidence.

The main **recommendations** follow. These are graded to indicate the strength of the evidence behind the recommendation.

The main recommendations are followed by **local implementation points**: these are specific areas where local clinicians need to develop local policies or guidelines to facilitate the implementation of national guidelines at the local level. They often require collaborative working between NHS services and other local statutory and voluntary sector agencies.

1.8 Guideline limitations

The document and recommendations are subject to various limitations.

The commissioning authority, NICE, is primarily concerned with health services, and so these recommendations only indirectly refer to social services, housing and so on. Nonetheless, the importance of other agencies cannot be overstated and in each locality they should become actively involved.

Not all evidence used comes from MS-specific studies. A systematic approach was used to locate and appraise the evidence. Due to the magnitude of the literature potentially relevant to MS specific inclusion or exclusion criteria were applied. The inclusion/exclusion criteria aimed to limit the included studies to those of a higher quality conducted primarily in people with MS. Where these were not available, well-conducted studies outside MS, or lower-level studies in people with MS, were included.

A general principle behind the search strategy was the use of studies relevant to the clinical situation. Where the situation was specific to MS, for example diagnosis, then the study population was limited to those with MS. However, where the situation was an impairment arising from neurological damage then the search is usually focused upon that impairment when it arose from other neurological diseases causing similar damage. Variation between people with MS is far greater than the variation between people with the same impairment arising from different neurological conditions. Therefore this was not deemed to be extrapolation and the evidence was graded directly.

In areas which primarily relate to organisational matters or general principles such as communication, full systematic searching was not undertaken because priority was given elsewhere. In these areas, existing reviews and other information readily available was considered.

The evidence base was current as of October 2002. Since then additional research findings have become available. However, it is unlikely that these would have a significant impact upon the recommendations.

Using a systematic approach coupled with the grading of evidence used means that some relevant evidence may be omitted. It also means that some recommendations appear without evidence because the recommendation seems self-evident and good practice; no one will consider researching into the area (and ethical considerations might also preclude it). We recognise that much current practice without evidence may in fact be ineffective, but we also recognise that much current practice without evidence may be highly effective and may never

acquire evidence. Consequently, we must emphasise that the lack of evidence cannot be used alone to justify a reduction or withdrawal of resources.

Finally it must be emphasised that these guidelines refer to recommended best clinical practice. It is not the purpose of these guidelines to specify what resources are needed or how appropriate resources are devoted to any particular recommendation.

1.9 Plans for guideline revision

The process of reviewing the evidence is expected to begin four years after the date of issue of this guideline. Reviewing may begin earlier than four years if significant evidence that affects the guideline recommendations is identified.

2 Methodology

2.1 The developers

The National Collaborating Centre for Chronic Conditions (NCC-CC) is housed by the Royal College of Physicians (RCP) but governed by a multi-professional partners board inclusive of patient groups and NHS management. The collaboration was set up in 2000 to undertake commissions from the National Institute for Clinical Excellence (NICE), to develop clinical guidelines for the National Health Service. NICE originally commissioned the RCP and the Chartered Society of Physiotherapy (CSP) to develop this guideline. When the NCC-CC was formed, it assumed the management responsibility, but with continuing leadership from the executive leads of the CSP and RCP.

Editorial responsibility for the guideline rests solely with the development group.

Each commission is systematically developed from the current evidence base. Two multi-professional groups, supported by a technical team from the NCC-CC, were involved in the development of the guideline:

- a small **Guideline Development Group** (GDG) that met monthly and undertook the detailed evidence assessment and recommendation drafting
- an enlarged group, the **Consensus/Reference Group** (CRG), which met early in the development to ensure the clinical questions and aims were appropriate. At the end of the process, the CRG met again to review the recommendations drafted by the GDG and to consider clinically important areas where there was insufficient evidence, and where formal consensus techniques were required to develop recommendations.

Membership details can be found on page iii of this document. The groups were formed by inviting nominations from stakeholder organisations selected by the NCC-CC to ensure an appropriate mix of clinical professions and patient groups. Each nominee was expected to serve as an individual expert in their own right and not as a mandated representative, although they were encouraged to keep their parent organisation informed of the process. All group members made a formal 'declaration of interests' at the start and provided updates during the development. The NCC-CC and the group leader monitored these.

2.2 The scope of the guideline

The scope for this guideline (see Appendix J) was developed utilising the NICE stakeholder consultation process. In summary, the guideline is required to be relevant to adults of all ages with MS, and to consider the full range of care that should be routinely available from the NHS. This includes appropriate use of mainstream pharmacological, physical therapy, rehabilitation and psychosocial treatments. Existing NICE guidance relating to interferon beta and glatiramer acetate is to be incorporated into the guideline. Since this is a guideline for the NHS, it should comment on the interface with other sectors but will not consider them in detail.

2.3 Involvement of people with MS

The NCC-CC was keen to ensure that the guideline development process was informed by the views of people with MS and their carers. This was achieved in two ways:

- by securing patient organisation representation on the guideline development groups
- by carrying out focus groups and interviews to ensure that the views of people directly affected by MS informed the guideline development process.

The Multiple Sclerosis Society and the Multiple Sclerosis Trust had a representative each on the development groups. They were therefore involved at every stage of the guideline development process and were able to consult with their wider constituencies throughout the process.

Before the first meetings of the development groups, focus groups were held to identify issues that people with MS consider important when describing the impact of MS on their lives. The study had three stages:

- focus groups with people with MS (one for people with mild to moderate MS and one for people with moderate to severe MS)
- focus group with carers of people with MS (one group)
- one-to-one interviews with people with severe MS who were fully dependent.

The patient organisation representatives helped to recruit people with MS to participate in each of the groups. Trained facilitators from the NICE Patient Involvement Unit based at the College of Health ran the groups and interviews.

Further information about this study can be found in a separate document (to be issued later). A summary of the key findings from the study and how these have informed the guideline recommendations can be found in Appendix B.

2.4 Searching for the evidence

There were three stages to this process.

1) First, the technical team set out a series of specific clinical questions that covered the issues identified by the project scope. The CRG met to discuss, refine and approve these questions as suitable for identifying appropriate evidence within the published literature.
2) The information scientist then developed a search strategy to identify the evidence for each question. Identified titles and abstracts were reviewed for relevance to the agreed clinical questions and full papers obtained as appropriate. Full papers were assessed for inclusion according to predefined criteria (Appendix C).
3) Finally, the full papers were critically appraised and the relevant data entered into evidence tables (see Table 1) which could be reviewed and analysed by the GDG as the basis upon which to evaluate recommendations.

Limited details of the searches with regard to databases and constraints applied can be found in Appendix C. Grey literature was searched for using the System for Information on Grey Literature in Europe (SIGLE) database. Stakeholder evidence identified via the NICE process[9] was incorporated where appropriate.

In some sections systematic searches were not undertaken because the issue under consideration was not MS specific. Non-systematically retrieved supporting information for these sections is presented.

Evidence on cost-effectiveness was extracted from the main searches wherever it existed, this was rare but was necessary to undertake a separate search for information on the potential costs and benefits of the interventions and management strategies considered in this guideline. This search was carried out by the information resources section in the School for Health and Related Research at the University of Sheffield, and was designed in collaboration with the health economist. The GDG realised that few formal cost effectiveness analyses would be identified, therefore the search for economic evidence was very broad and designed to identify information about the resources used in providing a service or intervention and/or the benefits that can be attributed to it. No study design criteria were imposed *a priori*, ie the searches were not limited to randomised controlled trials (RCTs) or formal economic evaluations. Further details of the searches for economic evidence are given in Appendix D.

Identified titles and abstracts from the economics searches were reviewed by the health economist, and full papers obtained as appropriate. The health economist critically appraised the full papers and the relevant data was conveyed to the group alongside the clinical evidence for each question. Given that the economics searches were so broad and that no standard measure of assessing the quality of economic evidence is available, careful consideration was given to each study design and the applicability of the results to the guideline context.

A further important aim of the economics searches was to identify the key gaps in evidence on potential costs and benefits; hence the titles and abstracts were mapped to the clinical questions at an early stage, so that the GDG could decide which areas to prioritise for further work (see below).

Identifying relevant literature and evidence, evaluating the strength of that evidence, and collating it into a usable form required great efforts. It has to be recognised that:

- Relevant, often important evidence is scattered very widely, often in sources that are not easily available and sometimes not indexed.
- Much of the relevant evidence is not specific to MS (for example, evidence on the management of neuropathic pain is of great relevance but few studies are exclusively based on MS). This applies to most impairments and activities.
- Much of the evidence on costs and benefits comes from the US health care system and is therefore of limited applicability to a UK guideline.
- The scope of the topic is such that there is a great volume of evidence that the GDG considered to be of very variable quality.

2.5 Synthesising the evidence

Each paper was assessed for its methodological quality against pre-defined criteria (based upon CRD report 4 for RCTs and systematic reviews (SRs)[10] and the QUADAS tool for diagnostic accuracy studies[11] (full details are available on request)).

Papers that met the inclusion criteria were then assigned a level according to Table 1 (overleaf).[12]

The clinical question dictated the appropriate study design that should be sought and the level was then assigned as above. RCTs were the most appropriate study design for a number of clinical questions and RCTs lend themselves particularly well to research into medicines.

Table 1 Grading scheme and hierarchy of evidence*

Recommendation grade	Evidence
A	Directly based on category I evidence.
B	Directly based on category II evidence, *or* extrapolated recommendation from category I evidence.
C	Directly based on category III evidence, *or* extrapolated recommendation from category I or II evidence.
D	Directly based on category IV evidence, *or* extrapolated recommendation from category I, II or III evidence.
DS	Evidence from diagnostic studies.
HSC	Health service circular 2002/2004.
Evidence category	**Source**
Ia	Evidence from meta-analysis of randomised controlled trials.
Ib	Evidence from at least one randomised controlled trial.
IIa	Evidence from at least one controlled study without randomisation.
IIb	Evidence from at least one other type of quasi-experimental study.
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case–control studies.
IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities.

*Adapted from Eccles M, Mason J.[12]

However, they were not the most appropriate study design for some other questions, particularly in the area of rehabilitation where interventions are often tailored to the needs of the individual. The result is that evidence on pharmaceutical interventions tended to receive higher levels than for other equally valid interventions. This should not be interpreted as a preference for a particular type of intervention nor as a reflection on the quality of the evidence for questions where non-RCT evidence is valid and appropriate.

2.6 Health economics evidence

The mapping exercise, based on the titles and abstracts identified in the broad search for economic evidence, confirmed that very little information on cost effectiveness was available; of the 464 papers identified there were only nine economic evaluations based on RCTs. In general the economic information came from studies that considered either costs or outcomes but not both. In addition the majority of studies did not investigate specific interventions or services, but rather considered the overall cost of MS to society and/or the individual with the condition, or they dealt with measuring quality of life in general in MS. This evidence could only be of limited use in informing the recommendations.

The health economics input was therefore distinguished according to whether or not formal economic evaluations were available. Where this type of evidence did exist it was presented alongside the clinical evidence with advice on the quality of the evidence and its applicability to the recommendations. However, in the majority of areas there was no formal economic evidence and this problem was exacerbated by a lack of systematic and readily available information on:

- the potential costs and benefits of any of the specific interventions or models of service delivery considered – this is particularly problematic in relation to benefits, as costs can often be estimated from other sources
- the current resource use associated with MS both in the NHS and wider society
- the current range of clinical practice within the NHS.

While health economic analysis can provide a framework for collating information from a variety of sources in order to estimate, and systematically compare, costs and benefits, this is a complex and labour intensive process and it does require a level of clinical evidence that is not readily available in MS. As a result the group prioritised those areas, which they believed would benefit most from additional information on costs and benefits. Priorities were assessed on the basis of:

- potentially large health benefits
- a potentially large effect on NHS resources (positive or negative)
- considerable uncertainty surrounding the benefits and resources
- potentially large service impact
- important equity considerations.

A number of areas were suggested by the health economist and the clinical advisor, and the GDG identified three priorities: the use of magnetic resonance imaging (MRI) scans in the diagnosis and continued management of MS; the delivery of high dose corticosteroids for acute relapse; and the issue of specialist *vs* generalist services for the provision of care. This third area was not explored in detail due to time constraints. Details of the work carried out in the first two areas are included in Appendices E and F.

2.7 Drafting the recommendations

Evidence for each topic was extracted into tables and summarized in graded evidence statements. The clinical advisor used this evidence to draft recommendations that were provided to the group prior to the meetings. The GDG reviewed the recommendations and their grading at their meetings and reached a group opinion. Recommendations were explicitly linked to the evidence that supports them and then graded according to the level of the evidence upon which they were based. Although the grade given to a recommendation reflects the level of evidence on which it is based, it does not necessarily reflect the importance attached to the recommendation. Furthermore, the level of evidence is based on a single hierarchy of research design, but in reality different designs are appropriate for different types of research problem. Specifically in research into rehabilitation and research involving people with long-term conditions, other designs and methodology such as single case studies, quasi-experimental designs, qualitative studies and correlational studies based on prospective observational cohorts will often be stronger than randomised controlled studies. Consequently many of the recommendations that received a grade D were nonetheless those that the GDG felt were the most important.

2.8 Agreeing the recommendations

A one-day meeting of the CRG was held after the evidence review had been completed and when an early draft of the guideline produced by the GDG was available. The CRG considered the draft guideline in two stages using a Rand modified nominal group technique,[13] first via a pre-meeting vote and again in a formal meeting:

1) Are the evidence-based statements acceptable and is the evidence cited sufficient to justify the grading attached?
2) Are the recommendations derived from the evidence justified and are they sufficiently practical so that those at the clinical front line can implement them prospectively? There were three types of recommendation to be considered:
    a) A recommendation from the GDG based on strong evidence – usually non-controversial unless there was important evidence that had been missed or misinterpreted.
    b) A recommendation that was based on good evidence but where it was necessary to extrapolate the findings to make it useful in the NHS – the extrapolation approved by consensus.
    c) Recommendations for which no evidence exists but which address important aspects of MS care or management – and for which a consensus on best practice could be reached.

The formal consensus methods that have been established within the NCC-CC, drawing on the knowledge set out in the health technology appraisal,[13] and practical experience. It made full use of electronic communication and voting techniques and will be fully described in separate publications

2.9 Writing the guideline

The guideline was drawn up by the technical team in accordance with the decisions of the guideline development groups. The draft guideline was circulated to stakeholders according to the formal NICE stakeholder consultation and validation phase[9] prior to publication, and modifications, approved by the GDG, were made as a result.

THE GUIDELINE

3 General principles of care

An effective, efficient and high quality service depends as much upon its organisation and style as it does upon individual competence. For example, there is little point in having an excellent service for people with continence problems if less than 20% of that group are ever seen in the service or have the problem identified. There is much evidence that patient dissatisfaction with services is primarily focused on organisational matters and communication.[14] Consequently this section covers various topics that apply to the overall management of MS.

This section is divided into five main interlinked areas:

1) Interaction between the professional and person with MS
2) Interactions between the team and the person with MS
3) Service organisation and inter-relationships between services
4) Within-team communication – a conceptual framework
5) Provision of services over time.

Evidence on the areas covered in this section is generally scant and difficult to synthesise, and with little of it specific to MS. For example, the evidence supporting specialist stroke services could be used to support some of the recommendations.[15] Systematic searching was not undertaken for this section, but supporting evidence is provided.

These guidelines cannot cover all general aspects of good patient care; this section will emphasise those areas that specifically concern people with MS. Specific aspects have been given specific recommendations, and important general aspects that apply to all patients with any condition are found in the accompanying tables.

The recommendations made in this section stress the importance of patient-centred teamwork and the need to consider all aspects of a person with MS's situation.

3.1 Interaction between the professional and person with MS

Most studies of the experience of service users[14] show that many professionals appear to have an inappropriate attitude towards people with MS, who often feel deprived of the information and support they want. There are also discrepancies in perception between people with MS and professionals concerning health care needs.[16] These findings suggest the need for improvements in:

- style and manner of communication, especially of initial diagnosis
- accuracy and detail of information given
- recognition of the emotional consequences of the information given
- acknowledgement that people with MS have expertise and have views that should be taken into account
- encouragement of self-management by people with MS.

3.1.1 Communicating and giving information

Many studies have emphasised the importance of good communication between individuals and health care professionals.

Anyone can now access vast amounts of information on any topic using the Internet, and there are books available in public libraries on almost any topic. However much of this information is of low quality, inaccurate, and/or difficult to understand. Therefore it is vital for health care professionals to take seriously the provision of accurate, relevant and appropriately presented information to people with any disease.

Many people with MS have some impairment of cognitive skills, and some have visual impairment. These are two important factors to consider in all communication. All the basic principles of good practice apply (see Table 2) and information provided in the section on 'Encouraging autonomy/self-management' (3.1.3) is also of relevance.

▷ Health economic statements

It is not possible to say anything certain about the economic implications of improved information provision and communication. It is not clear what NHS resources are currently devoted to this, but they are unlikely to be substantial. Improvements in co-ordination of information could potentially result in savings through increased efficiency, and this is particularly true of the interface between primary and secondary care and between the NHS and social services. Good information provision may directly improve patient well-being by reducing uncertainty, relieving stress and contributing to empowerment if the patient is more involved in decisions about care. This may also have subsequent effects in terms of functional status. In addition, information may change the pattern of service use and this will also have the potential to benefit patients, carers and their families. However, if current provision is very poor, then substantial resource increases may be required in order to improve the situation. A significant part of this will be required to equip health professionals with the necessary skills to assess individual patient needs for information.

RECOMMENDATIONS

R1 All communication with all people with MS should comply with the general principles of good communication, shown in Table 2. **D**

R2 Some people with MS may not be able to follow everything fully or remember complex details. This includes people who have no obvious disability. So, when talking to the person with MS, the health care professional should: **D**

- be straightforward
- check the person has understood
- back up what was said with written (and other) material
- reinforce as necessary.

LOCAL IMPLEMENTATION POINTS

Local services will need to:

- provide leaflets and other information for the people with MS detailing local NHS, social care and voluntary sector resources

- ensure that information is accurate and up to date and takes into account local ethnic and language needs
- ensure that there are mechanisms for disseminating information to those who need it.

Table 2 Principles of good communication in health care

Principle (what the health care professional should do in any communication)	Comment
Communicate in a suitable environment, usually a quiet area or room free from distraction or interruption.	Privacy and quiet are important.
Seek agreement from the person with MS that anyone present can be there and ensure that as far as possible anyone she or he wants present is there.	Consider especially students and family.
Start by asking what the person knows or believes already.	Establishes expectations.
Establish the nature and extent of the information that the person wishes to receive.	Establishes expectations.
Consider carefully the balance between the benefits and the risks associated with giving each item of information.	Once given information cannot be withdrawn.
Tailor the communication to the person's: • specific situation • communicative and cognitive abilities • culture.	Makes information relevant.
Limit information given to that within your own knowledge, referring on to others as necessary for more detailed information.	Do not give information if uncertain about it.
Clarify specifically any options and choices the person may need to choose, specifying: • likely outcomes of each choice • benefits and risks of each choice.	Both in diagnosis and treatment.
Offer back-up with information being given: • in different ways (eg written leaflets, tapes) • by different people (eg specialist nurse) • at another time (eg follow-up appointment).	Information is often forgotten.
Inform the person with MS about any recommended local or national sources of further information including employment and voluntary sector sources.	Allows person with MS to follow-up and take more control.
Consider need for emotional support during process, especially if the information might be stressful, and arrange emotional support if needed.	Should be considered an intrinsic part of the process (see R3).
Document in notes and inform other healthcare staff closely involved what has been communicated, especially to the general practitioner.	Ensures consistency over time and across settings.

Failure in communication between health care professionals and people with MS was a common theme in the focus groups. The development group there felt it was essential to have recommendations on communication, and indeed took this as the first topic to consider. The development group reviewed the evidence summarised in 4.2 and took into account all the evidence of factors (such as poor memory and visual disturbance) that might affect communication. During several long discussions and debates, a series of specific recommendations were derived, primarily through consensus. In the interest of brevity and clarity, these were then converted to this table of recommendations.

3.1.2 Giving emotional support to people with MS

MS is a disease that causes emotional distress in many ways:

- it often starts at a young age when individuals are anticipating marked life development
- it is unpredictable and causes much uncertainty
- it has a bad 'reputation' and expectations are often worse than reality
- it can lead to many cumulative losses over many years
- feelings of control can be lost
- the effects on family members and changing interactions between family members can also increase emotional distress.

The management of anxiety and depression is covered in Section 6. Here we consider the emotional support that may be required by any person, at any time, and which is frequently requested by people with MS, especially in the early stages.[17] When reading the evidence and considering the recommendations, we have taken the following into account. *Counselling* is a word used both in relation to giving information, and in relation to giving emotional support. *Emotional support* may take two forms: a formal therapeutic process (eg psychotherapy) that usually requires training and expertise, and an informal process that, although it may be improved by training, is part of many personal interactions which occur between the person with MS and both professionals and non-professionals.

This section is primarily concerned with informal emotional support. Within the process of informal emotional support given by knowledgeable professionals there is also inevitably a component of giving information (another aspect of 'counselling'), which may itself reduce emotional distress.

▷ Evidence statements

Three RCTs that assessed the utility of neuropsychological compensatory training, psychotherapy and coping skills training for persons with MS were identified (**Ib**). The first RCT assessed the effectiveness of traditional psychotherapy compared to participation in a 'current affairs' topic group or no intervention. The results showed psychotherapy to be superior on two of the four outcome measures assessed, namely depression and locus of control. However, it had no significant effect on either anxiety levels or levels of self-esteem.[18] The second RCT examined a coping skills group compared to non-directive peer telephone support. The coping skills group entailed formal therapist support and considerable contact time, whilst the telephone support group was informal and only entailed one hour a month. No overall differences between the groups were observed on any of the five outcome measures.[19] The last RCT compared neuropsychological compensatory training to supportive psychotherapy. The results indicated beneficial effects on measures of social aggression, but no difference between the groups on measures of depression or personality change.[20]

One controlled clinical trial (CCT) compared client-centred psychotherapy to a no-treatment control in patients with MS. The results indicated beneficial effects on four of the seven outcome measures assessed, with all of these being within inter- or intra-personal domains[21] (**IIa**). Two further CCTs were identified that examined therapeutic groups for persons with either MS or spinal cord injury. However, both of these studies reported only within subject results and therefore no comparison could be made as to the efficacy of the interventions between the groups.[22,23]

Two uncontrolled pre-post studies examining coping skills training and stress management instruction were also included. The first study assessed coping skills training in patients with MS. The results showed an overall beneficial effect on measurements of depression, physical mobility and emotional reaction.[24] The second study examined the efficacy of stress management instruction in patients with disease of mixed aetiology. The results showed a positive effect on two of the four outcome measures assessed[24,25] (**III**).

▷ Economic statements

The current resources devoted to emotional support are not known. Any recommendation to increase assessments for psychological symptoms and offer various types of counselling will result in increased resource use. However, savings may result from increased efficiency if counselling is being used inappropriately at present, and also if counselling reduces the need for other health interventions. The benefits for patients, carers and their families are potentially very large, including reduced stress and anxiety and improved functional status. Good quality cost effectiveness analyses of psychological support for people with MS, including the different ways in which this support could be provided, are required.

▷ From evidence to recommendations

Formal psychotherapy may require many resources, and we felt that the evidence reviewed was insufficient to allow any firm recommendations to give formal therapeutic intervention. However the evidence suggests some possible benefits for giving emotional support in some way which leads to our consensus recommendations.

RECOMMENDATION

R3 A person with MS may benefit from emotional support; this should be considered by each individual and team in contact with the individual. Where possible, that emotional need should be met directly or through referral to a suitable resource. **D**

LOCAL IMPLEMENTATION POINT

Local services will need to agree which individual people or services locally, both within the NHS and elsewhere, are sufficiently expert and knowledgeable about MS to provide emotional support to people with MS who have particularly great need.

3.1.3 Encouraging autonomy/self-management

People with MS have their disease for life, and may only see any individual professional for a short time. Moreover, the person with MS has to live with the consequences of any decisions made and in the absence of firm evidence for most decisions, it is especially appropriate to involve the individual in all decisions as far as they wish. Encouraging self-management is consistent with recent moves towards the 'expert patient',[26] which aims to use patients to give other patients the skills, knowledge and confidence to participate actively in all aspects of their own health care.

▷ Evidence statements

One RCT assessed the effect of a self-care program for patients with MS living in the community. Overall, the results showed no positive benefit with significant changes only on two out of six of the items assessed.[27]

▷ Health economic statements

The economic implications of encouraging patient autonomy are uncertain. An intensive patient education programme for self-management in people with asthma resulted in improved outcomes in the intervention group with no significant difference in costs.[28] However, the patient group and the geographical location (Finland) undermine the relevance of these to the population of people with MS in the UK. The balance of resource burden between the NHS and the patient and their family is an important factor in any move towards self-management.

▷ From evidence to recommendations

The evidence specific to MS is sparse. However, the GDG also took into account emerging evidence in other areas of health care, and the move from NHS towards encouraging greater patient autonomy. It therefore reached strong consensus behind the recommendations made.

RECOMMENDATIONS

R4 People with MS should be enabled to play an active part in making informed decisions in all aspects of their MS health care by being given relevant and accurate information about each choice and decision. **D**

R5 As far as possible, people with MS should be helped to manage their own general health through the following information and advice provided in written, audio or other media on: **D**

- specific activities that promote health maintenance and prevent complications
- changes in their health that may require them to take further action
- the condition and its management, including both local and national sources of further information and support in clear and accessible language.

This function should be fulfilled by working in conjunction with local voluntary organisations and through acquiring the skills needed to:

- seek, evaluate and use advice and help available
- communicate effectively with health care professionals (for example, through participation in the Expert Patient Programme (**http://www.doh.gov.uk/cmo/progress/expertpatient/index.htm**)).

LOCAL IMPLEMENTATION POINTS

Local services will need to discuss and specify:

- who is responsible for providing information on self-management for people with MS
- who is responsible for providing access to self-management programmes (such as the Expert Patient Programme) for people with MS
- making all screening and disease-prevention programmes accessible to people with long-term illness.

3.1.4 Support to family and informal carers

Family members, and sometimes close friends, of a person with MS may play three roles, related to the MS, and often need help with these.

1) They may provide physical assistance or supervision. While many families will do this willingly, there is a risk that a normal family relationship may change to a patient-carer relationship.
2) They may become the main social contact for the person with MS, making the relationship increasingly intense. This may then lead to significant interpersonal strains, and distress both the person with MS and the family member(s).
3) They may take over responsibility for family roles once held by the person with MS, such as earning money, running the household or being a parent. This may cause stress on the family member if other roles are not relinquished, may upset the person with MS and may stress family relationships.

Such informal supporters and carers often live under the same roof, but some may perform these roles at a distance. Children (sometimes of a young age) are often involved in one or more of these roles and the effects of having a parent with a disabling condition can be severe.

The recognition of these factors and the provision of assistance where possible may benefit both the person with MS and the family itself. Sometimes the needs and wishes of family members may conflict with those of the person with MS, and this must be acknowledged. One must bear in mind that a) the person with MS and the family member(s) may have different general practitioners and social workers and b) the primary responsibility of the health care team is usually to the person with MS.

▷ Evidence statements

Three studies assessed the effectiveness of support for caregivers of people after stroke. One RCT and one CCT assessed the benefits of an educational group for patients who had suffered a stroke and their main caregiver. The RCT that compared a stroke educational program to the use of standard stroke unit information leaflets showed beneficial effects only in terms of the patient and carer's knowledge about stroke. No differences were observed between the groups on any measure of either patients' or carers' health status, activities of daily living (ADL) or levels of anxiety and depression[29] (**Ib**). The CCT compared a group educational program to home visits or no intervention for patients caregivers. The results showed beneficial effects for both programs compared to no intervention on two of the four outcome measures, but no significant difference between the different program groups[30] (**IIa**). The last RCT examined the utility of Stroke Association family support compared to normal care. The results showed beneficial effects on two out of the four measures assessed for carers, but no difference between groups on any outcome measures for the patients[31] (**Ib**).

▷ From evidence to recommendations

Consensus was used to agree recommendations as the evidence available neither supported nor refuted the benefits of providing carer support.

RECOMMENDATION

R6 Family members (including any school children) living in the same house as a person with MS, and family members delivering substantial support (even if living elsewhere), should be supported by: **D**

- asking about their physical and emotional health and well-being, especially in the case of children aged 16 years or less, and offering advice and referring on for additional support if necessary
- providing them with general factual information about MS; this should only be extended to include more specific information related to the person with MS with the permission of that person
- ensuring that they are willing to undertake support of personal activities of daily living (such as dressing and toileting), are safe and competent at such tasks, and that the person with MS is happy for them to provide such assistance
- informing them about social services and their entitlement to carer assessment and support procedures.

LOCAL IMPLEMENTATION POINTS

Local services should:

- identify services able to assess and support children of people with MS
- collate and publicise information about statutory and non-statutory support services available for families and carers locally and how to access them.

3.2 Team approaches to rehabilitation

3.2.1 Interactions between the team and the person with MS: approaches to rehabilitation

Specific aspects of rehabilitation are covered in later sections; here we consider the general approach to rehabilitation. Because few of these issues are specific to MS, no systematic review has been undertaken.

▷ Assessment and measurement

The process of assessment refers both to the collection and to the interpretation of data needed to identify problems (screening) and to inform the solutions. The process of assessment may or may not include measurement, which is the quantification of data against some metric. In other words, an assessment procedure may be considered to have two purposes which may be distinct or combined:

- the **detection** of a phenomenon (ie diagnosis); and,
- the **measurement** of a phenomenon.

Evaluation of a diagnostic tool in one setting is not necessarily transferable: a measure for use in one context, such as research with a small, homogenous group, may be unsuitable for day-to-day clinical practice. Few studies have evaluated measures in different settings or in comparison with each other. Consequently we have not systematically reviewed the evidence and cannot make any specific recommendations about which measures to use (see Table 4 and Appendix H).

A common approach across all services will make assessment more efficient, less repetitious for the person with MS, and provide an impetus towards an integrated delivery of services.

The specific issues relating to the detection (diagnosis) of specific problems arising in people with MS are that the person:

- may have or develop one or more of a large range of specific problems
- may have problems that are not always obvious, and which may come on insidiously so that even the person with MS is unaware
- may be unaware that something can be done to alleviate problems and so may not mention them
- may be in touch with someone who focuses on only one problem, and who may fail to detect or know about others, consequently not referring the patient on to appropriate services for further treatment.

Consequently it is important to have systems in place that:

- check at appropriate intervals whether the person with MS has common problems
- do not waste the time of the person with MS or the health care professional.

The specific issues relating to the measurement of problems arising in people with MS are that:

- the person with MS may have many problems that could be measured, and each measure may take considerable time and effort that may waste resources unless each measurement has a clear and relevant purpose
- many measures are available for almost every single phenomenon but there is minimal data available to guide the choice of measure, and none may be appropriate
- the presence of multiple impairments in one person may make the measurement of some phenomena either difficult or impossible, and also may complicate interpretation of the data.

One solution in many clinical situations is for the team members to identify and specify their goals as a method for evaluating an intervention. This is often referred to as 'goal attainment scaling' which has become well recognised as a useful method for evaluating complex and varied interventions.[32–34]

The recommendations made here are intended to ensure that the person with MS has any difficulties detected as soon as possible so that the difficulty is managed, often by referring on to the appropriate service for expert further assessment and management. The recommendations are also intended to give general guidance on measurement. Because the clinical situation and time course of people with MS can vary so greatly, this section uses an 'episode of care' to mean any series or programme of interactions with health care staff or teams concerned with the same underlying problem. It is trying to ensure that problems are not overlooked without overloading the health care system or the person with MS.

The guidelines have not recommended any specific, named measures for use in any specific situation. A quick review of the evidence tables will show that over 60 different measures have been used in research and apart from the Expanded Disability Status Score (EDSS) few have been used on more than 10 occasions (see Appendix H). There is very little research comparing the utility of different measures in different situations. Indeed, relatively few measures have any evaluative data published at all. Systematically reviewing the available evidence would be a major undertaking, and because the number of measures supported by different people and

organisations is large, consensus will not be achieved. Therefore we agreed not to recommend any specific measures.

RECOMMENDATIONS

R7 The review checklist shown in Table 3 should be used each time a person with MS starts a new 'episode of care' (including initial diagnosis), and whether or not the presenting issues relate to the MS. The health care professional should: **D**

- record the information for future comparison
- refer to the specific recommendations made in this document if any problem is identified.

R8 Health care staff who frequently undertake MS-specific assessments or treatments should: **D**

- be familiar with simple methods for detecting impairment and limitations on activities
- be trained in their use and interpretation (if used).

R9 All health care staff within a local health community should use the same simple methods for common assessments. **D**

R10 When initially assessing a person, and when undertaking any treatment, health care staff should consider the characteristics of a measure (see resource pack on the NICE website: **www.nice.org.uk/pdf/cg008_msresourcepack.pdf**) recognising that: **D**

- formally evaluated measures may not exist or be practical
- personalised measures should be considered, including comparing the outcome against goals agreed (goal attainment scaling).

R11 Before embarking on any course of treatment, the health care professional should be satisfied that the individual fully understands the implications of the treatment, and is able to participate in it as necessary. **D**

Further guidance may be found at the Department of Health consent website at **www.doh.gov.uk/consent/index.htm**

LOCAL IMPLEMENTATION POINTS

Local services will need to set guidelines on:

- the specific measures and assessment procedures to be used locally for common problems
- training of all staff in the use of simple screening methods for impairment, and in the use of simple measures of activities.

3.2.2 Teamwork and goal setting

People with MS often have several problems that need resolution and consequently will usually need actions from more than one person. Co-ordination of interventions, often delivered by several people over time, requires teamwork from a group of individuals working together towards a single goal or set of goals. A group of individuals who happen to work with one person with MS is not a team but a workgroup;[35] a team must communicate and work jointly. The difficulties and weaknesses of community teams in the UK have been discussed[36–38] and clinical standards have been produced for rehabilitation teams both in hospitals and in the community.[39,40]

Table 3 Review checklist*

Initial question

It is best to start asking an open-ended question such as, *Since you were last seen or assessed has any activity you used to undertake been limited, stopped or affected?*

Activity domains

Then, especially if nothing has been identified, it is worth asking questions directly, choosing from the list below those appropriate to the situation based on your knowledge of the person with MS.

Are you still able to undertake, as far as you wish:

- ❑ vocational activities (work, education, other occupation)?
- ❑ leisure activities?
- ❑ family roles?
- ❑ shopping and other community activities?
- ❑ household and domestic activities?
- ❑ washing, dressing, using toilet?
- ❑ getting about (either by walking or in other ways) and getting in and out of your house?
- ❑ controlling your environment (opening doors, switching things on and off, using the phone)?

If restrictions are identified, then the reasons for these should be identified as far as possible considering impairments (see below), and social and physical factors (contexts).

Common impairments

It is worth asking about specific impairments from the list below, again adapting to the situation and what you already know.

Since you were last seen, have you developed any new problems with:

- ❑ fatigue, endurance, being over-tired?
- ❑ speech and communication?
- ❑ balance and falling?
- ❑ chewing and swallowing food and drink?
- ❑ unintended change in weight?
- ❑ pain or painful abnormal sensations?
- ❑ control over your bladder or bowels?
- ❑ control over the movement?
- ❑ vision and your eyes?
- ❑ thinking, remembering?
- ❑ your mood?
- ❑ your sexual function or partnership relations?
- ❑ how you get on in social situations?

Final question

Finally, it is always worth finishing with a further open-ended question. *Are there any other new problems that you think might be due to MS that concern you?*

*This is not a list of questions to be asked of every person with MS on every occasion. It is a list to remind clinicians of the wide range of potential problems that people with MS may face, and which should be actively considered as appropriate. A positive answer should lead to more detailed assessment and management

Table 4 Characteristics of a useful measure

When considering measuring the effect of a treatment or the extent of some aspect of a person's situation, any potential measure should be considered against the following characteristics.

Domain	Questions
Feasibility	• Can the measure be used in this situation? • Will the process be acceptable to the person with MS?
Utility	• Is this measure going to be useful? • Will the time and effort required be worthwhile?
Validity	• Is this measure going to measure whatever it is I am interested in? • Does this measure also include unrelated phenomena that reduce its validity?
Reliability	• How much variation occurs from time to time when there is no 'real' change? • How much variation occurs between observers?
Sensitivity	• Will this measure detect the change or difference that I am looking for? • Does the measure cover the whole range of possible change?
Communicability	• Can I communicate this result? • Will other people involved understand the result?

The agreeing of goals is one way of facilitating effective teamwork. Goal setting refers to the identification of, and agreement on, an outcome or group of outcomes that the person with MS and family, therapist or team will work towards over a specified period of time. The important characteristics of goal setting in a rehabilitation service have been the subject of a non-systematic review.[41]

Recommendations are needed to ensure that efficient and effective teamwork occurs.

RECOMMENDATIONS

R12 When several health care and other professionals are involved with a person with MS, they should work together with the person and his or her family, as a team: **D**

- towards common agreed goals
- using an agreed common therapeutic approach.

R13 The goals set should: **D**

- be agreed as relevant and important by the person with MS
- cover both short-term specific actions and longer-term outcomes
- be challenging or ambitious but achievable
- be set both at the level of individuals and at the level of the team as a whole
- be formulated in such a way as to leave no doubt as to when they have been met.

R14 Goal attainment scaling should be considered as one way of setting goals and evaluating progress. **D**

LOCAL IMPLEMENTATION POINTS

Local services need to discuss and agree common:

- approaches to therapies to be used within and between teams
- terminology to be used within and between teams
- documentation to be used within and between teams.

3.3 Service organisation

Specific recommendations made in later sections can only be successful if a) services are organised so that they can be used efficiently by the person with MS, and b) service staff have appropriate knowledge and skills to advise on the specific problem. An audit in Oxfordshire documented the long and tortuous routes people traversed to resolve specific problems,[6] suggesting that people with MS are often seen by people without appropriate skills to solve specific problems.

In terms of service organisation, effectiveness and efficiency depend upon two separate matters:

- the *grouping* of people with different skills into named services, and
- the *timing* of actions undertaken by the organisation.

This section makes recommendations concerning specialisation and timing.

Expertise is a key issue here. For this document the following definitions will apply:

- a *specialist* is a health care professional with the necessary knowledge and skills in managing people with the problem concerned, usually evidenced by having a relevant further qualification, and keeping up to date through continuing professional development
- a *specialist team or service* is a group of specialists *who work* together regularly managing people with a particular group of problems, and who between them have all the necessary knowledge and skills to assess and resolve over 90% of all problems faced.

In practice, the person with MS will rarely present with a new problem to a specialist, and so it is important that clear and unhindered routes of referral exist, but at the same time it must be recognised that many problems can be resolved by clinicians and services with less MS-specific expertise. In other words, all health staff should work within their level of competence:

- *competence* is defined as the sufficient knowledge and skills to assess and resolve the problem and to recognise when further, more specialist help is needed.

A single service will be unlikely to cover all problems presented to it. Many problems will be simple, only peripherally related to MS, or well within the competence of the service first approached. Specialist services, on the other hand, can only retain expertise if they are not overwhelmed by simpler problems. Consequently it is inevitable that some people will need to be referred on from one service to another (or even to two or more others). Recommendations need to take this into account.

Lastly, services will be developed over time, and it is important that people with MS are involved in discussions about the development of services used by them.

3.3.1 Specialist services

The evidence in support of specialisation in general, and relating to specialisation in the management of people with MS in particular, has not been searched systematically. It is widely accepted that specialisation can deliver many benefits in terms of effectiveness and efficiency, for example to patients with conditions such as cancer or vascular disease.

The benefits of specialist services have been well demonstrated in stroke where specialised stroke units are effective in research settings[15] and also have better processes in practice.[42] Similarly, specialist neurological rehabilitation teams can improve outcome after head injury.[43,44] The Health Select Committee, in its report on Rehabilitation after Traumatic Brain Injury,[45] drew attention to the inefficiencies resulting from the fragmented management structure for rehabilitation in most NHS trusts, and recommended that the best single way to avoid such fragmentation of NHS rehabilitation services would be for every NHS trust providing rehabilitation to appoint a named general manager to be responsible for all elements of the rehabilitation services operated by the trust.

At least five studies have investigated the effect of a specialist neurological rehabilitation team specifically in the management of MS, and found benefits.[46–51]

The evidence is given in more detail later (4.5, 5.2). In summary, one study has shown that the input of a specialist rehabilitation team was associated with improved outcome three months after an acute relapse; one study showed that a two week inpatient specialist rehabilitation was associated with sustained benefits at six months; one study showed that outpatient specialist rehabilitation was associated with sustained benefits; one study showed that specialist rehabilitation lead to positive change at 15 weeks; and two controlled clinical trials have demonstrated sustained benefits after input from a specialist neurological rehabilitation team. This must be set in the context of a much greater volume of evidence for specialist neurological rehabilitation services in other neurological conditions such as stroke and head injury.

This section makes general recommendations concerning specialist services, without detailing the model of service delivery or resource implications. There are particular difficulties in specifying a 'core team' because people with MS may need help from almost any profession or service at some point. The recommendations are based on consensus informed by the existing studies, studies in other areas, and the logical consequences of the many recommendations made elsewhere in this guideline.

▷ Health economics statements

Many of the recommendations made in this section and elsewhere in this guideline imply an increase in the number of specialists and specialist centres that can diagnose and treat people with MS. At present, the provision of services is inadequate and geographically variable. It is well established that there is a shortage in the required number of consultant neurologists in the UK. There are currently around 350 consultant neurologists, giving a population ratio of 1:177,000 – much lower than other European countries. In some areas, like the South East, the ratio is 1:100,000, whereas in less well-served areas it is 1:250,000. An Association of British Neurologists (ABN) survey in 2001 revealed that the average waiting time to see a consultant neurologist from GP referral varied from 13 weeks in North West Thames to 51 weeks in Wales.[52]

Anecdotal evidence suggests that for specialist MS services the situation is worse, but there is no formal evidence to back this up. The vast majority of people with MS are treated as outpatients so they will suffer from the long waiting times reported here. In addition they are adversely affected by the lack of specialist centres where multidisciplinary team-based care can be provided. Preparatory work for the UK health departments risk-sharing scheme (see Section 4.6) shows that 66 centres in the UK have self-nominated as 'specialist' centres, but the number of centres that can actually provide multidisciplinary team-based care is probably around half of this number. The result is that only the minority of people with MS have access to a specialist centre and many do not even have access to a neurologist.

We have not attempted to estimate the resource increase that will be needed to provide these improved services, and neither do we have appropriate evidence to make judgements on the cost-effectiveness of using NHS resources in this way; this is an important area for future research. It is not simply a matter of making finance available, as the implications for the training of health professionals are also important. As a minimum, the ABN, for example, suggests that the number of consultant neurologists must be doubled to provide an acceptable service. They have estimated that this could be achieved by 2008 if the number of trainees was increased by two per year (from the current figure of around 158). Future research should investigate the need for improved services, the potential benefits to the NHS, people with MS and their families, and the resources involved, including any potential resource savings that might accrue elsewhere in the health care system.

RECOMMENDATIONS

R15 Every health care commissioning authority should ensure that all people with MS have ready access to a specialist neurological service for: **D**

- diagnosis of MS initially, and of subsequent symptoms as necessary
- provision of specific pharmacological treatments, especially disease-modifying drugs, and enacting the risk-sharing scheme for interferon beta and glatiramer acetate.

R16 The health care commissioning authority should also ensure that its population has ready access to a specialist neurological rehabilitation service. This should be available to all people with MS when the presenting problem is outside the competence of the first point of contact, for: **D**

- undertaking assessment (that is, diagnosis) when the person has complex problems
- undertaking specific pharmacological or other therapies
- providing an integrated programme of rehabilitation when the person has complex problems
- monitoring change, especially when the person with MS has more severe impairments or limitations on activities
- giving advice to other services.

R17 As a minimum, the specialist neurological rehabilitation service should have as integral members of its team, specialist: **D**

- doctors
- nurses
- physiotherapists

- occupational therapists
- speech and language therapists
- clinical psychologists
- social workers.

The team should either have as team members, or through agreed mechanisms, ready access to other local relevant specialist services with expertise in treating neurologically disabled people, to cover: D

- dietetics
- liaison psychiatry
- continence advisory and management services
- pain management services
- chiropody and podiatry
- ophthalmology services.

LOCAL IMPLEMENTATION POINTS

Local services will need to discuss and agree on:

- which specialist services are available to each primary care trust (PCT), or GP
- the most appropriate point of referral into each service in different circumstances
- specific referral pathways and mechanisms
- which health workers are in the local core team and which are additional to the team
- how health care workers who are additional to the team should be contacted.

3.3.2 Interfaces

People with MS present to any one of a large number of people within any one of a large number of organisations, and may in turn be referred on to many different people.[6] One of the main complaints made by people with MS is that they are constantly referred on to other services and have to start from the beginning each time. Referral between services and organisations is inevitable, given the nature of the condition and the organisation of statutory services. Therefore it is vital that the interfaces are made as seamless as possible for the person with MS.

People with MS have stressed the importance of having access to a single contact point to provide on-going information and support, and to provide advice and sign-posting to other services. This coordinating and advising role is important both to the person with MS and to the various health and social service professionals involved.

The roles that are needed include:

- service coordinator with wide local authority and voluntary sector links, eg housing
- information signposter
- resources coordinator
- facilitator for an individual person with MS.

RECOMMENDATIONS

R18 All parts of the health care system, social services and other statutory services should have agreed protocols that specify: **D**

- how responsibility for people with MS is shared with other groups or organisations
- what agreed descriptive information (that is, a common dataset) about the person with MS should always be shared
- the point of contact within any service or organisation, and how contact should be made.

R19 People with MS should be able to identify and contact: **D**

- a named person in their health area who is responsible for all NHS services for local people with MS (including coordination and collaboration with other statutory services)
- a named person in their health area with clinical expertise who is able to respond to any inquiry on clinical problems (and to guide the person to the most appropriate local service)
- a named person within any health care team with which they are involved.

LOCAL IMPLEMENTATION POINTS

Services should discuss and agree:

- referral and funding mechanisms between the following agencies; GPs, PCTs/LHGs, specialist neurological services, the specific neuro-rehabilitation services, social services departments, local authority housing department
- standardised data to be shared across each interface
- who will fulfil the specific roles identified in R19 within the area.

3.3.3 Timing of actions

To be useful (that is, to be effective and efficient) it is important that any intervention is timely. Setting a target time for every recommendation would be both wordy and difficult to base on evidence. There is no evidence on appropriate timing, but the government has set targets for some services. Therefore, we have made some general recommendations about timeliness that reflect government targets, the concerns of people with MS and consensus.

RECOMMENDATIONS

R20 Any action recommended within these guidelines should be undertaken within a time that takes into account: **D**

- risk of direct harm associated with any delay
- distress or discomfort being experienced or likely to occur
- risk of secondary complications associated with delay
- risk of harm to others (for example, carers) associated with delay
- any nationally recommended targets for timing
- action being taken by any other person or service.

LOCAL IMPLEMENTATION POINT

The local commissioners and service providers should agree a set of timed targets which should include, at a minimum, those time targets contained within this guideline.

3.3.4 Involvement with service development

The involvement of service users in service development and research is government policy within the clinical governance framework, so no specific evidence has been sought concerning these issues. Good guidelines have been produced by the Department of Health in relation to the involvement of patients in research.

People with MS will have several important contributions to make to health service planning and development. First, there will be some services where the issues concern specific MS-related matters. The service responsible for making the original diagnosis and for managing acute relapses and the prescription and monitoring of disease-modifying drugs is the most obvious. However, in practice people with MS probably make more use of, and will be more concerned about an increase in, generic services such as neurological rehabilitation services, continence services, and wheelchair services. Lastly, people with MS should be able to use any other services, with particular attention to health promotion and disease prevention services.

In the first case it is obviously important that people with MS are specifically involved. In the second and third cases it would certainly be appropriate for people with MS to be involved and they are likely to have much to contribute but people with other neurological disabilities could also be involved in addition to, or in place of, people with MS.

It should be emphasised that particular efforts are needed to involve any group of people with disabling conditions, and that their involvement is important because they are active users of most services over most of their lives. However, no specific recommendations will be made because this applies to all patient involvement and is not specific to people with MS.

3.4 Within-team communication

A common vocabulary is fundamental to the success of any complex organisation or service. This will usually depend upon an agreed, comprehensive framework that will facilitate the development of common understanding, and encourage the use of a shared vocabulary that helps communication. This will also increase the likelihood of effective teamwork through the setting of common goals. Although there is no evidence comparing models of illness, the increasing prominence of the World Health Organisation's International Classification of Functioning (see Appendix A) suggests that it should be used, especially as much work has already been devoted to its development. The recommendations made are intended to facilitate cohesive teamwork.

RECOMMENDATION

R21 All individual clinicians, professional groups and organisations involved in the care of those with MS should use WHO's International Classification of Functioning (WHO ICF) model of illness, and its vocabulary. **D**

LOCAL IMPLEMENTATION POINT

The local services will need to agree a vocabulary that is shared across all organisations including social services.

3.5 Provision of services over time (rehabilitation, maintenance, prevention and palliative care)

It is important to consider the management of MS over time, accepting that the disease is inherently unpredictable. Four time phases have been suggested,[53] but only a minority of people with MS will pass through all four and many only experience the first two:

1) *Diagnostic phase:* initial symptoms, and diagnosis (with disease modifying drugs now used).
2) *Minimal disability:* relapsing-remitting phase with episodes of sudden worsening with partial or complete resolution; some disability; probably stops work and becomes dependent upon others for some aspects of community or household activities.
3) *Moderate disability:* progressive increase in limitation on activities at a slower or faster rate; becomes dependent on others for personal activities of daily living.
4) *Severe disability:* more-or-less totally dependent upon others at all times; sometimes in residential care; higher rate of complicating medical illnesses such as chest infection.

In the first phase a service that focuses on diagnostic and disease treatment is appropriate. However, it is never too early to apply general rehabilitation principles: for example, the diagnosis of MS may sometimes call for measures relevant to the person's future family, occupational or financial situation. These considerations apply more urgently in the second phase, when therapeutic interventions may also be indicated, often with a preventive as well as a remedial rationale. In the third phase, services maximising activity and participation are more likely to be involved in adapting the social and physical environment, in addition to continuing therapy interventions. In the fourth phase, service delivery will be centred on the provision of support and of a suitable environment, while still aiming to maintain social participation. Health services have an important role to play in all four phases, but social services will become increasingly involved as the person moves into the third and fourth phases.

Neurological rehabilitation services will be used by many people, and factors which apply specifically to people with MS include:

- people with MS are probably the largest single group of people needing specialist neurological rehabilitation aged under 65 years (with people with stroke and head injury being the next two groups)
- the unpredictable, fluctuating, but generally progressing nature of the disease is different from most diseases
- people with MS also fluctuate on a day-to-day basis
- the disease starts in young adult life.

Services, especially but not only neurological rehabilitation services, therefore need to be able to respond flexibly to the specific situations of individual people with MS and their family and carers. When care needs are extensive, the needs of the carers become especially important.

People with MS are at increased risk of many specific additional pathologies such as pressure ulcers, contractures, osteoporosis and deep vein thrombosis. Services should always try to reduce the risk of these. There is evidence that pressure ulcers and contractures are common, and some evidence is available on how to reduce the risk and treat these complications, discussed in sections 6.5 and 6.17. The significance of other complications such as deep vein thrombosis and osteoporosis is difficult to establish in the absence of evidence, and so most other complications have not been mentioned specifically in this guideline. However, individual clinicians should always consider whether the risk of any person with MS suffering a particular complication can be reduced.

▷ Health economic statements

Little is known about the health economics of long-term health support. The provision of this type of care is complex because it must respond to a broad range of needs and is likely to be provided in a variety of different settings. There is no good evidence on the effects of palliative care on quality of life of people with MS. On the cost side it is important to bear in mind that a significant proportion of the burden of long-term care will fall on the patient and their family and carers. One RCT of the cost-effectiveness of a district coordinating service for people who were terminally ill with cancer in South London revealed no difference in outcomes between the two groups but showed that the service could be delivered with lower resource use than standard care. In particular, savings accrued from reduced inpatient days in acute hospital wards.[54] The authors argue that since people with cancer appear to want to remain at home as long as possible, reductions in hospital stays may generate benefits to patients. It is difficult to know the extent to which these findings are relevant to the population of people with MS. If palliative care is to be provided in residential or nursing homes, this is a particularly expensive type of provision but can produce enormous benefits for patients and their families and carers. More information on the cost-effectiveness of residential care is required.

RECOMMENDATIONS

R22 Services should cater for the varying needs of people with MS over time, by: **D**

- responding in a timely and flexible way to the intermittent acute needs of people with MS, especially in the early phases
- identifying and reducing the risks of complications that might develop in the individual
- making fully available, to people with MS, population-based programmes of health promotion and/or disease prevention (such as screening for cervical carcinoma), specifically taking into account an individual's possible impairments and activity limitations.

R23 When any 'episode of care' (medical or rehabilitation treatment programme) ends (that is, when no further benefit is anticipated), the health care team should: **D**

- ensure that any necessary long-term support needs are met
- ensure that the person with MS knows whom to contact and how to contact them, in the event that the person with MS experiences a change in his/her situation
- discuss with the person with MS whether they want a regular review of their situation and, if so, agree on a suitable and reasonable interval and method of review (for example, by phone, by post or as an outpatient).

R24 Health services should ensure that there are mechanisms to allow good communication between health and social services at all times. **D**

R25 Individuals who are severely impaired and markedly dependent should have their support needs reviewed at least yearly, and they should have these needs met as necessary and in accordance with their wishes, through one or more of the following: **D**

- additional support in the home
- respite care in the home
- respite care in another age-appropriate setting
- moving into a residential or nursing home.

LOCAL IMPLEMENTATION POINTS

Local service commissioners and providers need to agree:

- which specialist rehabilitation service will be responsible for maintaining function and for long-term support
- what local social opportunities exist for people with a range of impairments and limited activities and how they are accessed
- which residential and nursing homes are suitable for younger people
- clear mechanisms for agreeing funding for complex, expensive care home support packages and/or respite support and/or residential care.

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 plateaus 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 one[62] 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 propotion 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 MLAEP[85] 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 4.0[79] 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 base 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.

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: **D**

- 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.

R29 When doubt about the diagnosis remains, further investigation should: **D**

- exclude an alternative diagnosis, or
- find evidence that supports the potential diagnosis of MS. (Dissemination in space

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 colleagues[55] (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).

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 MS[97–100] (**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 MS[101–103] (**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

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:

- find out what and how much information the individual wants to receive (this should be reviewed on each occasion) **C**
- discuss the nature and purpose of all investigations, especially the likely outcomes and their implications for the individual. **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:

- offered in the near future* at least one more appointment to see wherever possible the doctor who gave the original diagnosis **D**
- 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 **D**
- offered written information about local and national disease-specific support organisations, including details of local rehabilitation services **C** **D**
- offered information about the disease, preferably in the form of an information pack, specific to the newly diagnosed. **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 referal 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 adrenocorticotropic 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 RCT[121] only reported a beneficial effect for three of the seven outcomes assessed, and these effects were only observed in the first six weeks. The second[120] 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 review[118] 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 study[124] 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 RCT[130] 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 RCT[132] 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 treatment[117] (**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-up[135] (**Ib**). The CCT compared methylprednisolone against vitamin B1. The results showed no significant beneficial effects on any of the three outcome measures assessed[136] (**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 months[140] (**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 RCT[141] 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-opthalmology 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.*

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* 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 review[117] 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 RCT[144] 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

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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 amantadine[195] 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 CCT[196] which investigated D-penicillamine and metacycline, and

one of the RCTs[164] 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 investigated[204] 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 ≤ 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 CCT[228] 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 study[249] 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.

5 Rehabilitation and maintenance: functional activities and social participation

5.1 General introduction

The guidelines to this point have primarily concentrated upon issues that concern the early phases of MS. At that time most people with MS are leading normal unrestricted lives, but rehabilitation should be considered from the time of diagnosis, especially for anyone who has any symptoms or limitations on activities that concern them. Progression is not inevitable but in those who do worsen, it is likely that roles such as work and active leisure pursuits will be affected first. The smaller number of people who go on to develop more severe limitations on their activities will usually only do so later in their life. Furthermore, even those people who do develop more severe impairments usually still wish to maximise their level of independent activities and social participation.

This rehabilitation section therefore starts by considering those recommendations that specifically concern social participation, activities and contextual factors because a) they are likely to be of greatest concern to most people with MS, b) they will arise before or at the same time as concerns about more basic activities and c) even the recommendations concerning impairments covered in Section 6 will all be set in the context of maximising participation and activities.

One key feature of rehabilitation is that it involves a structured, organised approach to complex problems (ie problems that many factors influence and that require multifocal interventions and/or interventions spread over a long time). Consequently many of the recommendations made in Section 3 concern rehabilitation.

The reader is strongly advised to read Section 3 in conjunction with this section.

It is also worth stressing that many of the interventions that may help people with MS require close collaboration with other statutory and non-statutory services. The most obvious is social services who have, for example, shared responsibility for much equipment supplied and for providing personal care in the home. However, other services such as employment and housing will often be involved. Given the closer collaboration being fostered nationally and the blurred and indistinct boundaries that vary around the country, these guidelines have made some recommendations that will apply to the NHS more in some parts of the country than in others, but that certainly are of importance to the person with MS.

It is therefore important at all times to recall recommendation R18.

While many of the recommendations in this section are generally applicable to the process of rehabilitation, it is important to stress some special features particular to the person with MS. As in any patient, rehabilitation for people with MS should first be directed towards the restoration of activities and functions that have become limited.

In people with MS, rehabilitation must also take account of the fact that the disease process may cause progressive impairment and consequent loss of abilities, so that maintenance of activities

in the face of physical deterioration is a common goal of rehabilitation. Another common goal is to minimise the secondary effects of the disease process such as the development of contractures or pressure ulcers, the stress on relatives, and the emotional consequences for the person with MS. This proactive and preventative approach should if possible be adopted at a very early stage in the condition and is likely to be centred in the individual's home and/or workplace rather than in a rehabilitation unit.

The evidence base specifically concerning rehabilitation for people with MS is relatively limited. Interventions in these areas do not easily lend themselves to the traditional randomised control trial approach because rehabilitation interventions are individually tailored, and outcomes expressed in specific rather than general terms. Research is further complicated by the difficulty in describing accurately but succinctly the nature of the tailored intervention. Comparison groups often tend to be those given traditional or no treatments or those treated after a delay. Few studies specifically investigate rehabilitation in specific domains of disablement.

However the general principles of rehabilitation are similar whatever the disease or domain, and so the recommendations are similar for each part and draw on general evidence from other diseases. Therefore this section has the following structure:

- general rehabilitation recommendations
- recommendations relating to vocational and leisure activities
- recommendations concerning mobility
- recommendations specific to other domains including equipment and environmental alterations.

The whole section depends upon initial recognition that the person with MS has a difficulty in some area of their life that might benefit from further assessment and treatment. R7 to R11 in Section 3 covers this.

5.2 General rehabilitation

Rehabilitation is a process that focuses on increasing performance of activities and aims to optimise social participation and to minimise stress and distress for both the person with MS and any carers involved. The rehabilitation process is mainly a problem-solving approach that will involve multifocal interventions at differing levels (eg impairment, environment) from a specialist team over time. Consequently the process of rehabilitation will only begin when a problem has been recognised, and it starts with a detailed assessment of the individual's problem(s). This part focuses on two aspects of rehabilitation:

- ensuring that the persons' situation is considered as a whole, and not piecemeal, and
- making recommendations about specific ways of treating activities that are limited.

The processes involved in rehabilitation are often described as being a 'black box', although in fact they are better considered as a 'Russian doll'. This is because they can be described at many levels, from the global (assess, plan, intervene, review) to the very specific (for example, 'This person will benefit most from 20mg baclofen at night, botulinum toxin injection into the right gastrocnemius muscle, a resting splint at night and a daily stand in a standing frame ...'). Given the large number of impairments that may arise secondary to multiple sclerosis, the large variety of contexts that will apply to people with MS, and therefore the almost infinite number of particular situations, each being unique, it is not practical for these guidelines to give specific

detailed recommendations to cover each potential limitation of activities. Therefore the recommendations made in this section are necessarily only at a relatively high level, covering only more general principles.

There are only a few studies on the general effectiveness of rehabilitation in MS[49,250,251] but the effectiveness of rehabilitation from a specialist multidisciplinary team has been demonstrated beyond all reasonable doubt in other situations, notably stroke.[15] The effectiveness of multidisciplinary rehabilitation has also been shown in other disabling conditions such as head injury[43,44] and back pain.[252] In these studies the patients have had complex problems with many interrelated factors and the rehabilitation process of multifocal interventions by a team has been the intervention investigated and found to be effective. People with MS also have similar features, and it is reasonable to generalise from this evidence. The evidence suggests that in this circumstance an expert (specialist) multidisciplinary team that involves the patient and family actively will achieve a better patient outcome, often at no extra cost.

▷ Evidence statements

Three RCTs, two CCTs and two uncontrolled studies assessed the effectiveness of multidisciplinary rehabilitation programs. The first RCT examined an inpatient rehabilitation program, comprising medical, nursing, occupational therapy and physiotherapy input. The results indicated beneficial effects on the functional independence measure (FIM), London Handicap Scale score, improvements in functional abilities and levels of handicap. The second RCT focused upon physical rehabilitation. Results showed significant positive changes on two of the five outcomes assessed, FIM and self-care abilities.[251] The third RCT examined the effectiveness of an outpatient rehabilitation treatment programme. This study reported significant beneficial effects on various outcome measures including the SF-36 (all subscales, fatigue, social experience and depression). No significant effect was found on the EDSS score[253] (**Ib**). One CCT assessed the efficacy of an occupational and physiotherapy program for MS patients who suffered from moderate to severe ataxia of the upper limbs and trunk. The results indicated significant improvement on half of the outcome measures assessed, which included ADL indices.[254] The second CCT assessed the effectiveness of an outpatients rehabilitation programme. This reported beneficial effects on two of the three outcomes assessed[49] (**IIa**). Both uncontrolled studies assessed multidisciplinary inpatient rehabilitation programmes. The results of the first study showed beneficial effects on four out of seven subscales of the Nottingham Health Profile Part 1 (NHP-1) assessed, including pain, physical mobility and emotional reactions.[255] The results of the second study indicated beneficial changes on five out of the six RIC-FAS subscales assessed, including transfers, toileting, grooming and dressing[256] (**IIb**).

▷ Economic evidence

There is very little economic evidence relating to rehabilitation in MS. The establishment of a multidisciplinary rehabilitation programme can result in significant benefits to people with MS and their families and carers. An effective programme may also result in future savings to the NHS and social services by reducing subsequent dependency, and in particular by reducing the need for hospitalisation at certain stages during disease progression.

The establishment of a multidisciplinary community MS team in Newcastle increased contacts with many health professionals following team referral, among the 38 people with MS whose

data was analysed. However, these additional referrals were offset by a decrease in GP contacts, hospital consultant contacts and occupied bed days. Over the six-month period of the evaluation total costs for these people were lower than in the six months prior to the establishment of the team. No firm conclusions could be drawn about the effectiveness of the team but survey evidence showed a high degree of patient satisfaction with the team.[257]

An older study from the US considered the costs and benefits of a multidisciplinary, inpatient rehabilitation program designed along the same lines as similar programs that had been shown to be effective in stroke patients.[258] Only 20 people were assessed in this study, but it did suggest that active, intensive multidisciplinary rehabilitation can improve functional outcomes and may result in cost savings in the long term.

▷ From evidence to recommendations

The GDG considered the evidence available here in the light of other evidence concerning MS reviewed elsewhere in this document and also in the light of strong evidence supporting specialist rehabilitation in other fields. It also noted that people with MS might present with new onset activity limitations needing medical diagnosis of the cause. Next, it noted that some readers might need explicit guidance on the components of the rehabilitation process. Finally, it was aware of emerging evidence in stroke that task-centered therapy may be more effective. The GDG agreed the recommendations made by unanimous consensus where direct evidence was lacking.

RECOMMENDATIONS

R61 If a person with MS starts to experience a new limitation on his or her activities, the cause should be identified medically, and the following considered: **D**

- is it due to an unrelated disease?
- is it due to an incidental infection?
- is it due to a relapse of the MS?
- is it part of a gradual progression?

R62 If the limitation persists, despite treatment of any identified cause, the person with MS should be seen and assessed by a multidisciplinary service, specialised in neurologically based disability. **D**

This service should implement a rehabilitation programme. **A**

R63 The components of the rehabilitation programme should include the following: **D**

- establishing the wishes and expectations of the person with MS
- assessing and, if necessary, measuring relevant factors, in order to identify and agree goals with the person; these might include one or more of the following:
  - identifying and treating any treatable underlying impairments
  - giving task-related practice of a specific activity or activities
  - providing suitable equipment (with training in its use)
  - altering the environment as needed
  - teaching others how to assist with (or take over) tasks
- monitoring progress against set goals; the goals should be reviewed and reset, until no further goals exist and no further interventions are needed.

R64 Where possible, both assessment and task-related practice should take place in the environment most appropriate to the task (for example, home, work or leisure). **D**

LOCAL IMPLEMENTATION POINTS

Local services will need to:

- identify how people with MS access neurological rehabilitation services at any stage in the course of their disease
- ensure that people working within neurological rehabilitation services work with appropriate statutory and voluntary organisations, both health and non-health.

5.3 Vocational activities: employment and education

Many people who develop or have MS will be finishing education or training, or will be in employment. In some people the MS will have little impact, but for most people MS will have some impact. It is important to minimise the impact if possible because being in employment has many health benefits and among other things enables an individual to retain self-esteem, social contacts, financial independence and a valued place in society. The importance of vocational rehabilitation services for people with MS at all stages but especially in the early stages was emphasised many years ago,[17] and has been reiterated recently.[259]

The Department of Employment has some schemes available for people with disability, but generally specialised vocational rehabilitation services are not available. MS is relatively rare and usually poses very specific problems. For example cognitive losses and fatigue are probably the major impairments affecting employment, yet both are outside the normal scope of employment services. Therefore health service personnel have a vital role to play in providing people with MS and their employers with accurate, impartial information and advice, recognising both the abilities and limitations of the person with MS. Sometimes they may need to offer advice about alternative appropriate work.

▷ Evidence statement

Two studies were identified that examined interventions for limitations in undertaking employment in persons with MS. One RCT examined the effectiveness of a job retention programme combined with standard medical care compared to standard medical care alone.[260] The results indicated no beneficial effect of the programme (**Ib**). One CCT[261] assessed the utility of an accommodation team planning approach compared to traditional job seeking skills for people who were unemployed.[261] Again the results indicated no benefit for the programme (**IIb**).

▷ From evidence to recommendations

The very little evidence on vocational rehabilitation available does not allow any conclusion to be drawn. However the Department for Work and Pensions, the British Society of Rehabilitation Medicine, and the Department of Health all recognise the potentially important role of the NHS in vocational rehabilitation. The GDG therefore thought it important to make recommendations to support this approach, and a consensus was easily reached.

RECOMMENDATIONS

R65 Any person with MS who is in work or education should be asked specifically whether they have any problems, for example motor, fatigue or cognitive difficulties. **D**

R66 Any individual who has problems that affect their work or education should be seen for further assessment of their difficulties, preferably by a specialist vocational rehabilitation service, or specialist neurorehabilitation service. **D**

R67 The results of the assessment should be used:

- to advise the person with MS on strategies, equipment, adaptations and services available to assist with vocational difficulties; and/or **D**
- to advise the employer or others, with permission from the person with MS, on strategies, equipment and adaptations to assist; and/or **D**
- to give information to the disability employment advisor, if involved (see R68).

R68 The person should always be informed about available vocational support services (currently including Disability Employment Advisers and the Access to Work Scheme), and that there may be adjustments at work to which they are entitled under the Disability Discrimination Act. **D**

R69 Any individual who cannot stay in or find alternative employment should be advised about other options such as voluntary work and where to find information about these options. **D**

LOCAL IMPLEMENTATION POINTS

Local health, social and employment services will need to:

- agree an integrated approach to vocational rehabilitation, including defined referral criteria for relevant services, and methods for exchanging relevant information
- disseminate information on the location of and means of referral to the Disability Employment Officer at the local job centre and other employment services (including those in the voluntary sector)
- collect, collate and disseminate information about educational and retraining opportunities, and work within the voluntary sector.

5.4 Leisure and social interaction

All people, those in and out of employment, will have a range of key leisure activities. Leisure gives balance to life, as well as giving opportunities for social interaction. The impairments and disabilities that may affect work will usually also affect leisure, but the person with MS can have more control over their leisure pursuits. Loss of independent social activity is very common in people with MS; one survey in the USA found that 62% of people with MS were either socially inactive or depended upon the initiative of others.[262] The importance of leisure as a valid focus for specialist rehabilitation services is being increasingly recognised, but specific services are rare and are often run by social services or voluntary agencies. While the NHS does not have a responsibility to provide specific ongoing opportunities to undertake leisure (eg day centres), the NHS does have a clear responsibility to all patients, including people with MS, to assess their needs in relation to leisure activities and then to give, where possible, the skills and techniques

needed to pursue chosen leisure pursuits and then to identify local resources and put the person with MS in touch with them.

▷ Evidence statements

No studies were identified that met the inclusion criteria.

▷ From evidence to recommendations

Although no research on leisure rehabilitation specific to MS has been undertaken, there is evidence that quality of life (in patients with stroke) is related to leisure activities and the GDG agreed that recommendations were needed and agreed those made by consensus.

RECOMMENDATION

R70 Any person with MS whose participation in or enjoyment of a leisure or social activity becomes limited should be referred to a specialist neurological rehabilitation service which should: **D**

- identify whether previous activities are still achievable and, if not, help the person consider new activities
- assess for, and then teach, the skills and techniques that could help achieve these activities
- if necessary refer the person to local services that might help them establish and continue leisure and social activities.

LOCAL IMPLEMENTATION POINTS

The local services should:

- maintain an up-to-date list of local organisations that can provide information on social activities for people with disabilities
- maintain an up-to-date list of local community transport providers
- have procedures to enable easy cross-agency working to optimise leisure activities for people with MS.

5.5 Mobility

The ability to negotiate the environment independently is fundamental to all aspects of daily life and almost all aspects of social participation are dependent upon adequate mobility. Limitation in mobility is one of the prime determinants of the amount (time and number of people) of 'care needs', whether given by family or paid carers. Limitation in mobility is common in people with MS. For example in one study 58% of people could not climb stairs unaided and 42% needed mobility aids including wheelchairs.[262]

The construct of mobility is or can be much broader than simply walking. It includes moving in bed, getting out of bed, moving into and out of chairs, going up and down stairs and slopes, getting to and from shops, using special mobility equipment such as walking aids and wheelchairs, and using public transport. It may also include endurance.

Reduced mobility is a common disability in many neurological and non-neurological conditions, and many studies have investigated treatments focused on improving mobility, usually walking. Furthermore, improvements in (or reduction in loss of) mobility are a common outcome measure in many other studies, including almost all interferon beta trials (the EDSS is primarily a measure of mobility).

▷ Evidence statements

Two RCTs and one randomised crossover trial assessed different interventions for mobility problems (**Ib**). The first RCT examined the use of fully trained service dogs for wheelchair mobile people with MS.[263] The results showed significant beneficial effects on all of the eight outcome measures assessed including psychological, social, employment and care needs indices. The second RCT assessed the intervention of awareness through movement classes compared to just educational sessions. The results showed no difference in the number of falls or functional balance performance or self-efficacy between the groups.[264] The randomised crossover trial compared hospital outpatient physiotherapy to home-based physiotherapy and no treatment. The results showed beneficial effects for the majority of outcomes assessed for physiotherapy interventions. There were no overall differences observed between the different physiotherapy interventions.[265]

▷ Economic evidence

There are no formal economic evaluations of any interventions for mobility problems in MS. However the randomised crossover trial of physiotherapy described above[265] did consider the costs of providing home- and hospital-based therapy alongside the outcomes. No significant difference was found between the outcomes of home-based against hospital-based physiotherapy. Home therapy was more expensive than hospital outpatient sessions, even when patient travel costs to hospital (including time) were taken into account. Patient travel costs were approximately 40% of total hospital session costs.

▷ From evidence to recommendation

The evidence reviewed only considered one intervention (physiotherapy) and only in one group of patients (those able to walk, or likely to). The section refers to all aspects of mobility. Furthermore, many of the topics considered elsewhere in this guideline might improve mobility. The recommendations therefore approach all aspects of mobility, taking into account not only the specific evidence reviewed above but a) other evidence within this document, b) general principles of rehabilitation, and c) evidence in other conditions such as stroke.

RECOMMENDATIONS

R71 Any person with MS who experiences reduced mobility (and it affects or threatens his or her activities) should be seen and assessed by a specialist neurorehabilitation service. The assessment should determine which of the following interventions are needed: **D**

- identification and treatment of any underlying impairment, especially weakness, fatigue, spasticity, ataxia, sensory loss and loss of confidence

- task-related practice of a specific mobility activity or activities (for example, walking, transferring, using a wheelchair, climbing stairs)
- provision of suitable equipment, including wheelchairs, driving equipment and adaptive technology (with training in its use)
- alteration of the environment to increase independent mobility
- teaching of others how to safely assist with (or take over) tasks such as walking, climbing stairs, moving in bed or transferring.

R72 Physiotherapy treatments aimed at improving walking should be: **A**

- offered to a person with MS who is, or could be, walking
- given at home or on an outpatient basis, depending on the preference of the person with MS and local resources.

LOCAL IMPLEMENTATION POINTS

Local services will need to:

- identify how people with MS whose activities are affected or threatened by reduced mobility can easily access neurological rehabilitation services
- agree common measures of mobility to be used locally.

5.6 Activities of daily living

A significant proportion of people with MS may eventually experience limitations on their ability to undertake a variety of activities needed to live independently such as shopping, housework and undertaking personal care. Collectively these activities are referred to as activities of daily living (ADL), in contrast to vocational and leisure activities. Occupational therapists are usually the professional group with most expertise in, and who lead on the rehabilitation of, activities of daily living. The limitation may arise from many of the common impairments including cognitive losses. The amount of direct support from other people needed by a person is determined primarily by their need for support with personal activities and/or with their mobility. Various terms are used in this part.

'Community activities' are those that involve the person leaving their home and undertaking activities in public areas and buildings, such as shopping, using public transport, negotiating the environment safely (primarily avoiding traffic), and accessing other public amenities (eg leisure facilities). Parents may also need to accompany children to school. Community activities depend greatly upon adequate independent mobility and upon adequate cognitive skills.

'Domestic activities of daily living' are those activities needed around the house to maintain life and safety, and a reasonable standard of cleanliness. They include cooking, washing up, all aspects of managing clothing (eg washing, ironing) and keeping the house clean. They may also include in some people other activities such as caring for children, and responding to financial and other demands such as paying bills. In contrast to personal activities, domestic activities often make more demands on cognitive skills, and consequently may be influenced more by cognitive deficits.

'Personal activities of daily living' refers to basic daily activities such as dressing, washing and bathing, grooming, using the toilet, controlling continence and getting around the house.

▷ Evidence statements

No studies were identified that met the inclusion criteria.

▷ From evidence to recommendations

No studies explicitly studied rehabilitation of these activities, but measures of these activities, especially personal activities of daily living, were the primary outcome measure in the RCTs of specialist neurological rehabilitation already reviewed (see 5.2.1). The GDG agreed unanimously that the recommendations below were reasonably derived from evidence reviewed elsewhere in this document, and from the evidence in other neurological conditions such as stroke.

RECOMMENDATIONS

Activities of daily living are usually divided into personal, domestic and community activities.

R73 Any person with MS who experiences a limitation in personal, domestic or community activities should receive a comprehensive multidisciplinary assessment. This should be carried out by a team experienced in the treatment and management of MS, and should cover the person's previous and current functioning in the following areas: **D**

- personal activities such as dressing, eating, using the toilet and washing
- domestic activities such as cooking, washing and ironing clothes, keeping the house clean and dealing with household bills
- community activities such as shopping, using public transport, negotiating the environment safely (for example, avoiding traffic) and accessing other public amenities
- any caring or support activities within the home, including caring for children.

R74 A comprehensive assessment of this type should: **D**

- actively involve the person with MS, encouraging them to think about and define what they need to continue to achieve their goals and aspirations
- take place on more than one occasion and in different environments
- take into account the individual's priorities, interests, goals and potential
- consider environmental factors, and the support available from family and carers
- take into account both current and future needs.

R75 After the assessment, a programme of interventions should be developed for the person with MS, with the aim of increasing and maintaining independence wherever possible. The programme of interventions should be agreed by the individual. The interventions specified should be goal-directed, and designed to meet the individual's priorities, interests and potential. **D**

R76 If the individual agrees, the programme of interventions should be shared with social services, and this must occur if social services are to be responsible for maintenance interventions. **D**

R77 There should be regular monitoring to check how effective the interventions are, with a view to changing them if necessary. **D**

R78 At the end of the planned programme, the person should know how to obtain a re-assessment if their situation changes. **D**

5.7 Equipment, adaptations and personal support

The consequences of any disease are influenced greatly by the person's environment. This includes both peri-personal (within immediate reach, eg clothes, wheelchairs) and local (outside immediate reach, eg ramps, rails) environmental factors and extends to the general community. The importance of providing equipment has been stressed by the Audit Commission,[122] who also illustrated the enormous variability in current provision. The effectiveness of providing equipment has also been demonstrated in an RCT in the USA.[267] These guidelines do not consider the need to ensure that the public environment is made more appropriate for individuals with a variety of impairments, but this is important to people with MS.

The physical environment, as the term is used here, also includes the availability of other people in a supporting role (ie as assistants, not specifically as social contact). In most instances family members will undertake this role but it must be recognised that friends and neighbours also provide additional support, and that for a substantial number of people paid carers provide support. It should also be recognised that the support offered by the carer may extend (legitimately) well beyond hands-on support to include monitoring safety, providing prompts, and even providing the reassurance needed to allow the person to perform the activity independently.

Increasingly, services are being encouraged to have a joint approach to funding and providing equipment. However at present some equipment and adaptations may be provided by social services and they may seek advice from health professionals about the current health of the individual with MS and about the likely course of the illness. It may be important to stress that the course of MS is unpredictable in any individual and that appropriate equipment should be made available both for the current needs of the individual and for their needs at any predictable or likely worse state, such as when suffering an incidental infection.

Equipment and adaptations can be costly but they can also make an enormous difference to the quality of life of people with MS and their families and carers. The Audit Commission report argued that resources could be saved by better targeting of equipment to people's needs and better coordination of services to improve the efficiency of provision.[122] In addition if equipment and adaptive technology enable people to remain independent in the community, this is preferable to admitting them for treatment in other parts of the health care system. There is a clear need for research on the costs and benefits of equipment and adaptive technology for people with MS.

▷ Evidence statement

One two-phase study encompassing both an RCT and an uncontrolled pre-post phase examined the effects of tilting the wheelchair seating position for patients with MS.[268] The results of the uncontrolled phase showed beneficial effects on four of the five outcome measures assessed, namely measures of respiration and voice volume, with a tilt of the seating angle of 25 degrees. The results of the RCT phase indicated that there were no differences between the groups when the seating angle was tilted by either 25 or 45 degrees. This phase did not include a 'no tilt' control group (**Ib**).

▷ From evidence to recommendations

There are few randomised studies of the value of equipment, and the best (Mann *et al*, 1999) was the basis of the Audit Commission report.[122] Much equipment is so self-evidently effective (eg a wheelchair for someone whose legs are paralysed) that trials are probably unethical. The GDG drew on the Mann *et al* study and Audit Commission report, and easily reached consensus on the recommendations made.

RECOMMENDATIONS

R79 Every person with MS whose activities are persistently affected should be assessed by a specialist neurological rehabilitation service to determine how their environment might be improved, enabling for example: **D**

- an increase in the person's independence
- the impact on their activities to be minimised
- a reduction in risk to the person or their carers.

The environmental changes considered should include the following: **D**

- provision of (or changes in) equipment
- alterations in the structure of the building
- provision of (or change in) the personal support provided.

Equipment and adaptations

R80 If a person with MS depends on someone else for an activity (especially in mobility), an expert should assess whether an aid or adaptation, including an environmental control system, could be of benefit. For example, it may increase the independence of the person with MS, and/or minimise the stress on, or risk for, the person who assists them. The person with MS or, if necessary, their family and/or carers, should be taught how to use the equipment. Ability and safety in using the equipment should be checked at least once, after a suitable interval. **D**

R81 The service providing or recommending the equipment should ensure the equipment's continuing appropriateness and safety, at appropriate intervals. **D**

Personal support

R82 If a person with MS receives support or supervision from someone, for any particular activity, an assessment should be made to determine whether a greater level of independence could be achieved. **D**

R83 If personal support is provided by family, friends or paid carers, an expert should offer knowledge and skills to help the carer(s) provide assistance in ways that maintain the dignity and utmost independence of the person with MS, while also not threatening the health or well-being of the carers. **D**

R84 If support is given on a daily basis for more than one hour, then the level and appropriateness of the support offered should be monitored, at a minimum, on a yearly basis. It should also be reviewed after any significant event (for example, infection, relapse, complication, departure of family member). Any person involved in hands-on **D**

activities, especially physical moving and handling, should be taught appropriate, safe techniques for the individual situation, and should be able to seek further tuition or advice when they need it.

LOCAL IMPLEMENTATION POINTS

Local health and social services must have systems in place to provide an integrated approach to assessment and provision of a) non-specialist equipment, b) specialist equipment and c) personal support services. To this end they need to:

- identify who assesses people with MS for specialist and non-specialist equipment and home adaptations they may need
- identify funding mechanisms in collaboration with social care providers
- set up local audit mechanisms showing average delays and the proportion of equipment which is actually used
- specify how pieces of equipment are monitored and maintained, and changed as necessary in line with changing needs
- agree how carers, including family members, are taught necessary skills and are assessed for competence in all aspects of caring undertaken
- specify how family members and other carers can contact appropriate experts for further advice and tuition.

6 Diagnosis and treatment of specific impairments

Lesions within the CNS in MS may or may not cause the nervous system to function abnormally. There is evidence that most episodes of demyelination do not cause any specific symptoms or signs at the time.[110] Moreover, factors other than episodes of demyelination may cause change in or occurrence of symptoms and signs. Nonetheless most people with MS will experience some specific impairments from time to time, if not constantly.

This section covers the assessment and management of many of the specific impairments that people with MS may experience. It considers each impairment individually, although in reality they will rarely occur in isolation. It does not cover the more general aspects of management nor does it cover the disabilities or other consequences of impairment. The primary outcome in the studies that support this section will generally be a change in the level of the impairment rather than the level of activities.

Effective management of any impairment depends upon its initial identification and so the first recommendation in most sections covers the detection of the impairment. While it is not necessary to ask every person with MS about every possible impairment, it is important to remember that any person with MS might have any of these impairments. Therefore the professional person in contact with the person with MS will need at least a mental checklist similar to that set out in Table 3. They should always ask specific questions in an appropriate and sensitive manner.

When considering how to act in any particular situation it is vital to take into account not only the recommendation(s) appropriate to the specific impairment but also all other aspects of the person's situation such as other impairments that they may have. **Thus for each impairment there is an unwritten first recommendation – do not start or modify treatment until all aspects of the person's clinical situation have been established and understood, and the wishes and expectations of the person with MS have been established.**

6.1 Fatigue

Fatigue is probably one of the commonest, most disabling and frustrating symptoms experienced by people with MS, although they may not explicitly complain about it. It varies widely both between people with MS and within a person from time to time. In a tertiary centre in the USA, fatigue limited activity in 78% of 224 people with MS, compared with 17% of 93 controls[269] and in an epidemiologically sound sample of 124 people with MS in Norway, 39% reported frequent problems with fatigue limiting activity.[270] A study in South Wales found that 48% of people with MS had fatigue at any one time.[271] In the audit of Oxfordshire people with MS, nearly half had fatigue on entry although only 3% (7/226) complained of new fatigue over a ten month period.[6]

Fatigue is associated with both disability and depression, and management of fatigue should consider all aspects of a patient's situation, not simply the fatigue. Furthermore, it is in practice often difficult to distinguish complaints of fatigue from complaints about weakness, both in research studies and in clinical practice.

Clinically, recommendations are needed to ensure that fatigue:

- is recognised as being present
- is analysed to determine whether it is primary or symptomatic
- is managed as far as possible, to try and ameliorate its effects.

▷ Evidence statements

Interventions for fatigue were investigated in one systematic review (**Ia**), one RCT, two randomised crossover trials (**Ib**) and one CCT (**IIa**).

Amantadine – The review included four RCTs which compared the effects of amantadine to placebo, and in addition one randomised crossover trial and one CCT also met the inclusion criteria. The review reported that all four RCTs showed a pattern in favour of amantadine but as the effect size was small there is considerable uncertainty about the validity and clinical significance of the findings.[272] The CCT also reported positive findings on the two outcomes assessed, namely overall improvement and patient's selection of drug for continuing therapy. The incidence and type of side effects reported were similar between the intervention and the control group.[273] The randomised crossover trial[274] examined the effects of amantadine on cognitive functioning in patients with fatigue. There were no differences reported on two of the three outcome measures assessed, with the only positive measure being attained on a test of stimulus selection with event-related potentials (ERP) as the outcome measure.

Pemoline – Pemoline was investigated in two RCTs included in the review and also one RCT and one randomised crossover trial not included in the review. The review showed that there was no beneficial effect of pemoline over placebo and an excess number of reports of adverse effects were recorded in the intervention groups.[272] The RCT not included in the review supports these findings, with no difference between the groups being evident on four of the five outcomes measures assessed.[275] The final randomised crossover trial[276] reported beneficial effects on the two patient report outcomes assessed. Drop outs were similar between the two intervention periods.*

▷ Economic evidence

The HTA systematic review found no formal economic evaluations of amantadine or pemoline. The review then attempted to identify indirect data on potential costs and benefits 'that might allow tentative modelling of cost-effectiveness'. Unfortunately, no information about the reduction in quality of life in MS due to fatigue, or the costs of managing fatigue, was identified. The HTA report concludes that:

> if the interventions were of similar cost to amantadine [Amantadine costs £15.35 for 56 × 100mg tablets (BNF, 43) – therefore, a dose of 100mg twice a day costs approximately £200 per year] … and costs of administration were minimal, it seems likely that such interventions would be cost-neutral. Although the NHS bears only a small proportion of the total burden of cost for MS, such is the size of this burden, that any savings in hospital and other treatment services may well outweigh the extra drug costs. Undoubtedly however, the bulk of the benefit arising from an effective treatment for

* NB Pemoline is no longer available in the UK

fatigue in MS would be to the individual themselves, who might be able to remain in full-time paid employment for longer.[272]

▷ From evidence to recommendations

The clinical significance of the benefits shown in the studies reviewed was judged to be too low to allow any firm recommendations in favour of amantadine. The GDG was also aware that modafinil is being used on the basis of one published study,[277] but felt that until RCT evidence was available no recommendation should be made for this. The GDG therefore has recommended a simple approach, including traditionally used, though not researched approaches; this was agreed by consensus.

RECOMMENDATIONS

R85 Each professional in contact with a person with MS should consider whether fatigue is a significant problem or a contributing factor to their current clinical state. **D**

If fatigue is disrupting the individual's life, then the following recommendations apply.

R86 The presence of significant depression should be considered; if significant depression is present, it should be treated. **D**

R87 Other factors causing fatigue, such as disturbed sleep, chronic pain and poor nutrition, should be identified and treated if possible. **D**

R88 Some medicines may exaggerate fatigue, thus any medication being taken should be reviewed. **D**

R89 General advice and training on how to manage fatigue should be given, including encouragement to undertake aerobic exercise and to use energy conservation techniques. **D**

R90 At present, no medicines targeted at fatigue should be used routinely, although people with fatigue should be informed that a small clinical benefit might be gained from taking amantadine 200mg daily. **D** **A**

LOCAL IMPLEMENTATION POINTS

The local services should:

- identify which health workers have expertise in fatigue management for people with MS and how they are accessed
- decide whether a specific measurement tool is to be used, and if so which one.

6.2 Bladder problems

Urinary tract symptoms are common in people with MS. In a population-based sample in the USA, 25% of people with MS had intermittent or constant catheterisation for bladder dysfunction[262] and in a second American survey 59% had some bladder disturbance.[278] A study in South Wales suggested that 14% of all people with MS had an indwelling urethral catheter and 44% of the remainder had bladder dysfunction.[279] In the Southampton survey of

people with MS, 33% suffered urinary incontinence.[280] In the Oxfordshire audit[6] bladder problems were the most common presenting problem affecting 39/226 patients on 78 occasions over ten months, and they were the fifth most common problem in terms of prevalence.

Bladder dysfunction can be very disabling and may have many adverse consequences, including great emotional distress, curtailed social activities, and disturbed sleep. Incontinence also increases the risk of pressure ulcers. Its effects may be compounded by reduced mobility. Unfortunately matters are worsened by the reluctance of people with MS, their families and professional staff to discuss the problems.

While it is likely that disturbed bladder control is the commonest general cause of bladder symptoms, some bladder symptoms may be indicative of infection, and infection not only causes pyrexia (high temperature) and malaise but can also cause general exacerbation of all impairments, especially spasticity. Urinary tract infection (UTI) may also, rarely, cause pyelonephritis and septicaemia. The frequency of actual UTI is unknown and so, although the potential importance of urinary tract infection is great, its actual medical importance is unknown.

This section will first cover the assessment and management of disturbed bladder control leading to urinary frequency, nocturia, urgency of micturition, and incontinence. Then the specific issues of UTI will be covered. Many of the issues are not specific to people with MS, being similar to those faced by other people with neurogenic bladder disturbance and so some recommendations are based on generic evidence. The main issues to be covered are:

- detection and diagnosis of disturbed bladder physiology
- management of disruptive bladder function
- diagnosis and treatment of UTIs
- management of intractable incontinence.

6.2.1 *Bladder dysfunction*

This part considers disturbances in the control of bladder emptying. The use of catheters is mentioned, but 6.2 should also be consulted for further recommendations concerning the use and management of long-term catheters.

▷ Evidence statements

Ten systematic reviews were identified that assessed the efficacy of a number of different interventions for urinary incontinence, though some of these contained data from the same trials (**IIa**). Four reviews examined the effectiveness of different behavioural bladder training programmes for urge, mixed and stress incontinence. The first review compared bladder training to no intervention, drug therapy (oxybutynin and flavoxate hydrochloride plus imipramine), pelvic floor muscle training and electrical stimulation. The results showed that there was weak evidence to suggest that bladder training is more effective than no treatment, and that bladder training is better than drug therapy. There was insufficient evidence that electrical stimulation is more effective than sham electrical stimulation.[281] The second review assessed the efficacy of prompted voiding either alone or in combination with oxybutynin. The results indicated that prompted voiding was beneficial compared to no intervention, and that prompted voiding combined with oxybutynin was superior to prompted voiding alone.[282] The

third review compared the effectiveness of pelvic floor muscle training against placebo, electrical stimulation, vaginal cones and bladder training either alone or in combination. The results indicated that pelvic floor muscle training was superior to either no treatment or placebo, and that 'intensive' appeared to be better than 'standard' training. The effect of adding adjunctive treatments to pelvic floor training was unclear due to the limited amount of evidence.[283] The last review compared bladder training to flavoxate hydrochloride and imipramine, electric prompting devices and combinations of training plus terodoline or oxybutynin. The results from the review tended to favour bladder training but data was only available for a limited number of prespecified outcomes.[284]

Four reviews were included that examined the use of different devices or surgical interventions as management options for incontinence. The first review compared suburethral slings to abdominal retropubic suspension and needle suspension. The results showed no differences between suburethral slings and abdominal retropubic suspension or needle suspension. However sling operations had a significantly higher complication rate.[285] The second review compared the effect of weighted vaginal cones to control, electro stimulation, pelvic floor muscle training and these interventions in combination. The results showed that cones were better than no active treatment, but that there were no differences between cones and pelvic floor muscle training or electrostimulation. There was not enough evidence to show that cones plus pelvic floor muscle training was different to either cones alone or pelvic floor muscle training alone.[286] The third review compared anterior vaginal repair to pelvic floor muscle training, open abdominal retropubic suspension and bladder neck needle suspension. The results indicated that anterior vaginal repair was less effective than open abdominal retropubic suspension both in the short and long term. There were no differences between anterior vaginal repair and bladder neck needle suspension.[287] The last review assessed the efficacy of a number of different surgical procedures for stress incontinence. Overall, the results indicated that colposuspension may be more effective and the effect more long-lasting than that for anterior colporrhaphy and needle suspension. It was also found that second and subsequent operations to correct stress incontinence are less successful than first procedures.[288]

One small review compared the effectiveness of tolterodine to oxybutynin. The results showed that both drugs had similar effects on the number of micturitions in a 24-hour period, but that oxybutynin was marginally superior in decreasing incontinence and increasing the mean voided volume per micturation.[289]

The last review assessed the effects of different types of absorbent product for the containment of urinary and/or faecal incontinence. The results indicated favourable outcomes in terms of skin problems, the number of changes, ease of disposal and cost for disposable *vs* non-disposable body worns.[290]

Five RCTs and nine randomised crossover trials examined different interventions for bladder impairment (**Ib**).

Six placebo-controlled randomised crossover trials assessed the effect of desmopressin on voiding frequency and incontinence. Three of the trials specifically examined nocturia, whilst the other three assessed daytime voiding frequency. The three trials that reviewed nocturia all reported beneficial effects on the frequency of voiding, night-time urine volumes and sleep duration.[291–293] No significant differences were reported in the number of episodes of incontinence. All three trials report a number of side effects of a minor nature. The trials that

examined daytime voiding frequency reported significant effects upon both frequency and volume up to six hours after drug intake.[294–296] However, no benefit was observed on the frequency of night-time voiding; the 24-hour urine volume was unaffected. None of the trials reported side effects of a significant nature.

Four placebo-controlled trials assessed the efficacy of different drug interventions. One RCT examined the effect of synthetic capsaicin solution in patients with hyperreflexic bladder.[297] The results showed an overall significant benefit in terms of voiding patterns, leakage, bladder pressure and the need to use pads. There were no differences in the incidence of side effects between the groups. The second RCT reviewed the use of indoramin in male patients with symptoms of urinary tract dysfunction.[298] The study reported significant effects upon two of the five outcome measures assessed (flow rates) but not upon the overall symptoms score. Two randomised crossover trials assessed the efficacy of different drugs in patients with detrusor hyperreflexia. The first trial examining the use of atropine reported significant differences in bladder capacity.[299] The second trial assessed the intervention of flurbiprofen.[300] The study reported beneficial effects on five of the seven outcomes assessed. However, side effects were more common during the intervention phases although all of these were minor.

Two further placebo-controlled RCTs addressed the effectiveness of biofeedback and electrical stimulation of the pelvic floor muscles. The first RCT addressed biofeedback in combination with behaviour modification, pharmacological adjustment and pelvic floor training.[301] The results showed no significant differences between the groups on any of the outcome measures assessed. The other RCT examined the use of electrical stimulation of the pelvic floor muscles followed by pelvic floor exercises.[302] Significant beneficial effects were observed on all but one of the outcomes measures assessed.

Two studies, one RCT and one randomised crossover trial, compared different interventions against active comparators. One RCT compared oxybutynin to propantheline and reported no significant differences between the groups either in terms of benefits or the side effects observed.[303] The randomised crossover trial examined the three interventions; methantheline bromide, meladrazine tartrate and flavoxate chloride in patients with detrusor hyperreflexia.[304] The results showed that methantheline bromide was superior to the other two interventions on the outcomes measures of patient preference, entire cystometric pattern and micturition reduction. No significant differences were observed on measures of incontinence or residual urine volumes between the interventions. Meladrazine tartrate caused side effects so severe that the drug was discontinued. No serious adverse events were reported for the other two interventions.

At the time of writing there is insufficient evidence to comment on the use of cannabinoids in MS. However, we are aware that further evidence is likely to be published and that NICE intend to conduct a technology appraisal on cannabinoids in MS with a projected publication date of April 2004.

▷ Economic evidence

There are no formal economic evaluations of interventions for bladder impairment in MS. A study of the use of sacral rhizotomies and electrical bladder stimulation in people with spinal cord injury, showed this to be a cost-effective strategy in comparison to standard care, with

considerable savings on health care costs possible in the long run.[305] This group of patients may be similar to the population of people with MS. However, this is a before-and-after study with a relatively small sample ($n = 52$), so the results should be treated with caution. A study of all people with MS in Hordaland County, Norway, between 1976 and 1986 ($n = 194$), showed that bladder impairment was a significant cause of reduced quality of life (as measured by the generic SF-36), underlying the need for identifying and treating this problem.[306]

▷ From evidence to recommendations

When considering the available evidence, the guideline developers recognised that the evidence was often primarily related to other causes of bladder disturbance, and lacking for many widely practiced procedures. They also recognised the need to suggest simple and safe interventions before more complex, more expensive or more risky interventions. However good consensus was achieved on the recommendations made.

RECOMMENDATIONS

R91 Each professional in contact with a person with MS should consider whether the person has any problems controlling bladder function. Problems may include frequency or urgency of micturition, sleep disturbance from nocturia (awaking with need to empty bladder), difficulty in passing urine or incontinence of urine. **D**

R92 Any person with MS who has bladder symptoms should:

- have their post-micturition residual bladder volume measured using a simple measure such as ultra-sonography of the bladder **D**
- be assessed for the presence of a urinary tract infection clinically and, if necessary, using an appropriate dipstick for nitrites and leucocyte esterase. Treatment should be provided, if necessary. **D**

Urgency or urge incontinence sufficient to be bothersome or cause incontinence should be treated in the first instance using:

- advice on changes to clothing and/or toilet arrangements (for example, provision of a commode downstairs) **D**
- intermittent self-catheterisation if there is a high residual volume, and the person is able and willing **D**
- anticholinergic medicines such as:
  - oxybutynin, or **A**
  - tolterodine **D**
- checking for an increased post-voiding residual volume if symptoms recur. **D**

R93 Any person who has nocturia should be offered desmopressin (100–400µg orally or 10–40µg intranasally) at night, to control the symptom. **A**

R94 Any person who wishes to control urinary frequency during the day (for example, when travelling), and who has failed with other measures, should be offered desmopressin (100–400µg orally or 10–40µg intranasally) but **desmopressin should never be used more than once in 24 hours.** **A**

R95 Any person with MS who, despite treatment, has incontinence more than once a week should:

- be referred to a specialist continence service for further assessment and advice **D**
- be considered for a course of pelvic floor exercises, **A**
  preceded by a course of electrical stimulation of the pelvic floor muscles (if such a course is available). **B**

R96 Any person with MS who experiences persistent incontinence should be offered a convene drain (for men) or pads (for women). **D**

R97 Any person who has continued bladder symptoms despite pharmacological and other treatments should be considered: **D**

- for intermittent self-catheterisation taught by a suitably trained specialist, or
- for longer-term urethral catheterisation as a means of control, with suprapubic catheterisation being considered especially when active sexual function is still wanted. **See R99 to R102.**

R98 Intravesical botulinum toxin should only be used by suitably trained doctors in the context of clinical research. **D**

LOCAL IMPLEMENTATION POINTS

The local health system should identify:

- which community health workers have a particular expertise in managing incontinence and how they are accessed
- who can measure post-micturition bladder volume locally and how they are contacted
- the local urology service responsible for all managing aspects of neurologically-based bladder problems and incontinence and how it is contacted.

6.2.2 *Urinary tract infections*

This part discusses the prevention, identification and management of urinary tract infections (UTIs). It also specifically covers all aspects of long-term catheter use and management, drawing upon guidelines for preventing health care associated infections during long-term urinary catheterisation in primary and community care.[307]

▷ Evidence statements

All evidence statements for UTIs are level **Ia.**

Prevention of UTI – Five SRs were identified which assessed interventions for the prevention of UTI.[308–311] A review of five studies looking at the effects of cranberry extract in elderly patients, patients needing intermittent catheterisation, and women with recurrent UTI, found no reliable evidence of the effectiveness of cranberry juice and other cranberry products.[309] A review of eight RCTs comparing the effectiveness of indwelling silver coated urinary catheters and uncoated indwelling urinary catheters found that silver alloy catheters were significantly more effective in preventing UTIs as measured by the presence of bacteriuria than uncoated catheters but these studies were confined to relatively short-term use of catheters (2–10 days).[311] The results from three of the eight trials indicated that women benefited from the silver-coated

urinary catheters more than men. The third review looked at risk factors for UTI and the effects of antibiotic prophylaxis in patients with neurogenic bladder due to spinal cord dysfunction.[310] This review found that indwelling catheterisation was associated with more frequent infections than intermittent catheterisation, which in turn is associated with more frequent infection than methods not involving a catheter. The literature did not support firm conclusions regarding most other risk factors. It also reported that antibiotic prophylaxis significantly reduces bacteriuria among acute spinal cord injury patients. However, antibiotic prophylaxis was not associated with a reduced number of symptomatic infections in the populations studied. Antibiotic prophylaxis resulted in a twofold increase in the occurrence of antibiotic-resistant bacteria. A second review assessing the effectiveness of antibiotic prophylaxis reported similar findings. However, this review only found reduced bacteriuria among patients with acute spinal cord injury, not in those with non-acute spinal cord injury.[308] A final review of 11 studies assessed the efficacy of methenamine hippurate in patients at risk of developing a UTI. Four of the trials studied symptomatic bacteriuria and six studied bacteriuria as an outcome measure. The direction of six of the seven pooled trials was towards a favourable treatment effect for methenamine hippurate. However, due to heterogeneity interpretation of the pooled estimates could not be undertaken.[312]

Health economic analysis of interventions to reduce the risk of UTIs – Only one economic study was identified with any relevance to the population of people with MS.[313] This was a decision analytic model to compare the cost-effectiveness of silver alloy-coated urinary catheters with standard (uncoated) catheters. Coated catheters are more expensive (per unit) than uncoated catheters but are more effective; hence the relevant decision is whether the improved efficacy is worth the additional per unit cost?

The base case simulation showed silver-coated catheters to be a *dominant strategy*, ie more effective and less costly, due to savings in costs of treating symptomatic UTIs and bacteraemia. One-way sensitivity analysis revealed that the strategy remained dominant throughout the ranges evaluated. In the multivariate sensitivity analysis the strategy provided clinical benefits over standard catheters in all cases and cost savings in 84% of cases.

Interventions to treat UTI – Two reviews which assessed the effectiveness of interventions for the treatment of UTI met inclusion criteria. The first review assessed the effectiveness of cranberry juice or cranberry products for the treatment of UTI, but did not find any RCTs which met inclusion criteria and so was unable to draw any conclusions.[314] The second review compared the effectiveness of single dose and multi-dose antibiotic treatment in female adult patients with UTI.[315] This review found no significant differences between women treated with single dose and multi-dose antibiotic therapy (**1a**). One further RCT comparing cranberry concentrate supplements to placebo found no significant difference between the groups in terms of the number of patients developing a UTI[316] (**1b**).

Areas where evidence was not found – No evidence was found to allow recommendations on several important clinical issues including altering fluid intake, the frequency of changing long-term catheters, the use of bladder wash-outs, the appropriate use of suprapubic catheters, and the best policy concerning routine monitoring of renal tract structure and function.

▷ From evidence to recommendations

The recommendations made draw largely on the published NICE document,[307] which itself is largely based on consensus. However, where adequate evidence exists, grade A recommendations have been made

RECOMMENDATIONS

R99 Any person with MS at risk of urinary tract infections should not be recommended prophylactic use of antibiotics or cranberry juice. **A**

R100 If a person with MS experiences new urinary tract symptoms, or develops general malaise and/or worsening of existing symptoms with a raised temperature, they should:

- be given a urine dipstick test for infection, and culture, if necessary **D**
- be offered treatment with an appropriate antibiotic. **A**

R101 Any person with MS with more than three confirmed episodes of urinary tract infection in a period of one year should be assessed by a continence specialist for residual urine and other evidence of risk factors, and offered appropriate treatment and guidance. **D**

R102 The general principles of care for people with long-term urinary catheters, as described in the NICE guideline on prevention of health care associated infection in primary and community care (see Table 6) should be followed. Of particular note in treating a person with MS are that long-term indwelling catheters should: **D**

- be used only after all reasonable non-invasive methods have been tried
- be reviewed regularly, to check whether less invasive methods can be used

and that drainage systems from the catheter should:

- be emptied regularly, before the bag is overfull **D**
- bladder installations and wash outs should not be routinely used. **A**

LOCAL IMPLEMENTATION POINTS

The local health system should identify:

- specific guidance on choice of antibiotics for suspected or confirmed urinary tract infection
- the local urology service responsible for all aspects of managing neurologically-based bladder problems and incontinence.

Table 6 The general principles of bladder management

Long-term indwelling bladder catheters should:

- only be used after all reasonable non-invasive methods have been tried (**D**)
- be inserted by fully trained and competent personnel using aseptic procedures with cleaning of the meatus and the use of an appropriate lubricant (**D**)
- be reviewed regularly, to check whether alternative less invasive methods can be used (**D**)
- be clearly documented, including insertion, changes and routine care (**D**)
- only be changed when clinically necessary or according to the manufacturer's recommendations (**D**).

Drainage systems from the catheter should:

- be attached to a catheter valve outlet when the patient wishes and the system can be used (**D**)
- be kept sterile and continuously closed through ensuring clean handling whenever changes are required (**D**)
- be kept below the bladder but off the floor at all times to prevent stagnation or reflux of urine (**D**)
- emptied regularly, before the bag is over-full (**D**)
- have any samples taken using an aseptic technique through a sampling port (**D**).

Bladder instillations and wash-outs should not routinely be used (**A**).

From NICE's *Infection control: prevention of health care associated infection in primary and secondary care*.[307]

6.3 Bowel problems

People with MS may suffer bowel problems in two ways: reduced gut mobility may follow from immobility and the drugs used to treat various impairments; and neurological control of defecation may be directly impaired. One survey of 280 people found 43% to be suffering constipation.[317] More importantly the same survey found that 25% had been incontinent of faeces once a week or more frequently and 51% had been incontinent in a three month period. The total prevalence of bowel problems was 68%. In the South Wales survey, 29% of those with MS suffered faecal incontinence, and 54% suffered constipation.[279] In another American study 39% had bowel problems.[278] In the Oxfordshire audit, 19% of patients were experiencing problems with their bowels at any one time, and 26/226 presented with gastrointestinal problems over a ten month period, with 16 of these being specific problems with bowel control.[6]

Although constipation is probably clinically recognised in most instances, it is likely that health care professional staff are woefully unaware of how much faecal incontinence affects their patients with MS. The consequences of faecal incontinence are great: social embarrassment, risk of pressure ulcer, curtailing of activities etc.

Recommendations are needed to ensure that disturbed bowel control, both constipation and incontinence, is detected early, is evaluated to determine its aetiology, and is managed actively.

▷ Evidence statements

One systematic review of seven RCTs that assessed the effects of different management strategies for faecal incontinence and constipation in people with neurological diseases was identified. The results showed that psyllium was superior to placebo in terms of bowel movements and stool weight. A comparison of different suppositories indicated that

polyethylene glycol-based bisacodyl suppositories initiated defecation faster than hydrogenated vegetable oil-based bisacodyl suppositories. A comparison of bowel programmes indicated participants assigned to morning schedules were more likely to established successful bowel regimes than those assigned to evening schedules. No differences between the use of mandatory or optional suppositories was noted[318] (**Ia**).

▷ Economic evidence

No relevant economic evidence relating to bowel impairment was identified.

▷ From evidence to recommendations

The guideline developers noted the general lack of evidence concerning this important question and although a systematic review was found, the studies were small and of low quality and it was difficult to draw any firm conclusions. The recommendations made are largely on the basis of consensus, considering the experience of geriatric services that are faced with similar problems.

RECOMMENDATIONS

R103 Each professional in contact with a person with MS should consider whether the person has any problems controlling bowel function. Potential problems include urgency, difficulty, pain, constipation or incontinence. **D**

R104 Any person with MS who has apparent constipation (pain on or difficulty with defecation, bowels open less than twice a week) should be offered advice on fluid intake and dietary changes that might help, and then be considered for oral laxatives. **D**

R105 Any person with faecal incontinence should be assessed for constipation with overflow, possibly exacerbated by laxative use. **D**

R106 If a person with MS has apparent constipation (pain on or difficulty with defecation, bowels open less than twice a week) despite treatment with oral laxatives he or she should be considered for the routine use of suppositories or enemas. **D**

LOCAL IMPLEMENTATION POINT

Local guidelines need to consider which local specialist (medical or surgical) services should be approached for advice in cases of difficulty.

6.4 Weakness and cardiorespiratory fitness

Many people with MS will experience 'weakness'. In a survey of 656 people with MS in the USA, 63% had 'weakness or paralysis' which affected 45% of those with limitations on personal ADL.[278] In the same survey, 77% had fatigue and 74% had 'balance problems'. In South Wales weakness was the commonest single symptom experienced (89% at any time, 80% at any one time).[271] However, the term weakness may include many different phenomena and have many different contributing factors. This part specifically considers both actual or perceived weakness of voluntary muscle contraction and also more general lack of cardiorespiratory fitness.

Reduced strength of voluntary muscle contraction (weakness) is a common consequence of damage to 'upper motor neurone' tracts within the CNS, but it may be associated with several other impairments of motor function including clumsiness, spasms and spasticity. In people with MS muscle weakness may occasionally be a side effect of medication such as steroids or anti-spastic agents. Complaints of weakness may also be referring to or caused by: fatigue, the development of weakness only after some muscular exercise, reduced cardiorespiratory endurance, and depression. Consequently it is vital to establish exactly what the person with MS means when complaining of weakness.

In this guideline weakness and alterations in tone are considered separately as they may occur separately. Balance problems are not considered separately because they are also difficult to define, and will usually be associated with, if not caused, by weakness, spasticity, sensory loss or ataxia and all these are discussed. This section of the guideline needs to cover:

- detection and diagnosis of weakness and its associated phenomena
- management of and advice about weakness, especially relating to exercise
- management of secondary consequences.

▷ Evidence statements

No RCTs or CCTs in patients with MS were identified which assessed interventions to treat weakness. Four RCTs assessed interventions for cardiovascular dysfunction. Two trials examined the efficacy of expiratory muscle training *vs* sham training in patients who were bedridden or wheelchair bound (EDSS score 6.5–9.5). The first trial reported no overall significant improvement in the intervention group, whilst the second trial showed mixed results. Significant beneficial effects were reported for expiratory muscle strength, but not for inspiratory strength.[319,320] The third study examined the effectiveness of an aerobic exercise training program. The results indicated positive effects on four out of eleven of the outcome measures assessed, namely aerobic capacity, physical work capacity, isometric strength and skinfold thickness. No effect however was seen on any of the general health indices measured.[321] The last trial assessed the use of music therapy with relaxation and diaphragmatic breathing in patients who were wheelchair bound. The results showed no significant effect[322] (**Ib**).

▷ Economic evidence

No relevant economic evidence relating to weakness in MS was identified.

▷ From evidence to recommendations

In the absence of any specific MS-related evidence the guideline developers drew on general principles often derived from research in patients with other neurological conditions such as stroke.

RECOMMENDATIONS

R107 Each professional in contact with a person with MS should consider whether muscular weakness is a significant problem, or contributing factor, to the person's current clinical state. If so, the person should be assessed to determine the nature and cause of the weakness. **D**

R108 People with a limitation of their activities should be assessed for weakness of voluntary motor control using a valid technique. **D**

R109 People with motor weakness should be shown and advised to undertake exercises and techniques to maximise strength and endurance appropriate to their circumstances (**D**), including aerobic training (**B**). Usually, specific exercises should be selected and explained by a neuro-physiotherapist, or other members of the neurological rehabilitation team (**D**).

R110 People with motor weakness should be taught techniques and given equipment, such as orthoses, needed to optimise performance of activities appropriate to their circumstances. **D**

R111 People with weakness sufficient to cause postural abnormalities should be assessed for specialist supportive equipment, including but not limited to seating. **D**

LOCAL IMPLEMENTATION POINTS

These should include:

- advice on measures and assessment techniques to be used locally
- list of gyms, health centres and other places where people with health conditions and/or disability can take exercise, with systems for collaboration and discussion between the NHS (likely to be physiotherapists) and gym instructors being developed. The Department of Health exercise referral national quality assessment framework provides more detail (**www.doh.gov.uk/exercisereferrals/**).

6.5 Spasticity, spasms and contractures at joints

6.5.1 *Spasticity and spasms*

Many patients with upper motor neurone weakness from any cause have altered tone in their limbs, and when increased this may be referred to as hypertonia or, most commonly, spasticity. There are continuing debates as to the meaning of the terms. However in practice it is characterised by increased stiffness and slowness in limb movement, the development of certain postures, an association with weakness of voluntary muscle power, and with involuntary and sometimes painful spasms of limbs. Spasticity and spasms are common in people with MS, and may be the dominant disabling impairment in some people. Spasms were present in 21% of the people surveyed in Oxfordshire, and new problems with spasms were the commonest single specific complaint relating to reduced mobility.[6] Painful leg spasms were reported in 21% of 159 community patients with MS in Ontario, Canada[323] and spasticity was reported in 49% of 656 people surveyed in the USA.[278] The underlying neurophysiology in MS is likely to be similar to that seen in most other diseases associated with spasms and spasticity such as stroke, head injury and spinal cord injury. Consequently evidence from and recommendations for spasms and spasticity in these conditions will be applicable to people with MS.

It must be emphasised that treatment for spasticity and spasms may be necessary or justified simply to reduce the spasticity and/or spasms without expecting any other functional benefit for the patient. These impairments can cause pain and distress by their very presence. Furthermore it must be emphasised that amelioration of spasticity and spasms may be an integral part of a wider plan of management, for example through reducing the burden of care,

through enabling appropriate seating to be provided and used, or through reducing the risk of pressure ulcer. Lastly and of great importance, control of spasticity is vital in the prevention and management of joint contractures (fixed limitations on the range of movement available at a joint). Given the close connection between spasticity and contractures, contractures are also covered in this section (6.5.2).

The guideline recommendations need to ensure:

- identification of spasticity and spasms
- diagnosis and management of any treatable causes
- a stepped approach to management, tailoring interventions to each person's needs and wishes
- a cautious but appropriate use of more risky or expensive interventions
- prevention of complications of spasticity.

▷ Evidence statements

Two systematic reviews that examined interventions for spasticity were identified. In addition 46 studies that looked at a number of different interventions for spasticity and spasms in patients with MS met the inclusion criteria. These consisted of 16 RCTs, 27 randomised crossover trials, (**Ib**) two CCTs and three non randomised crossover trials (**IIa**).

Baclofen – One RCT and six randomised crossover trials compared baclofen to placebo (**Ib**). Overall three of the trials[324–326] showed significant beneficial effects on the outcome measures assessed. All these measures were directly related to the number and intensity of spasms. Two further randomised crossover trials reported mixed results with significant differences being reported on direct measures of spasticity, but no benefit being evident on outcomes measures of ambulation or transfer activity.[327,328] The last two small crossover trials reported no overall significant differences between the intervention groups.[329,330] Six out of the seven trials that reported adverse events, stated that minor side effects were more common in the intervention phase than in the placebo phase. None of the trials reported serious adverse events.

Four RCTs, two randomised crossover trials and one CCT also examined the effect of baclofen against an active comparator. Three RCTs and one randomised crossover trial compared the efficacy of baclofen to tizanidine[331–334] (**Ib**). All four of these trials reported no significant differences between the groups on any of the outcomes measured or in terms of side effects reported. A further RCT that compared baclofen to tetrazepam and tizanidine also reported no significant differences between any of the group.[335] One randomised crossover trial examined the effects of baclofen alone against baclofen combined with stretching exercises, stretching exercises alone and placebo alone.[336] The results showed significant differences upon a measure of spasticity for baclofen alone and baclofen combined with stretching exercises, but no differences were observed between the groups on the Ashworth scale score or a measure of functional abilities. A last CCT assessed baclofen against clonazepam and placebo[337] (**Ia**). No differences were reported between the groups upon either the measure of spasticity or the number of side effects reported.

Baclofen pump – One systematic review of 27 studies conducted in patients with MS and other neurological conditions and one randomised crossover trial reviewed the efficacy of intrathecal baclofen via pump delivery. The review reported a beneficial effect with both the Ashworth scale score and Penn spasm score significantly reduced[338] (**Ia**). The results of the crossover trial also indicated significant beneficial effects on all the outcome measures assessed.[339]

Tizanidine – Three RCTs and two randomised crossover trials compared the effect of tizanidine to placebo. One of the RCTs reported beneficial effects on four of eight of the outcomes measures assessed, including a reduction in muscle-tone score.[340] One of the randomised crossover trials also reported beneficial effects on the number of patients in whom spasticity improved.[334]

However, none of the other three trials reported any overall effect on any of the outcome measures assessed.[341–343] One further RCT compared tizanidine to the active comparator diazepam. The results indicated no difference in the clinical symptoms between the groups, and that diazepam was better tolerated.[334]

Dantrolene sodium – One non-randomised and two randomised crossover trials compared dantrolene sodium against placebo[344–346] (**Ib**). Two of the trials reported no differences between the groups, whilst data from the third trial was not reported adequately. No serious adverse events were reported in any of the trials. One further randomised crossover trial compared dantrolene sodium to diazepam and placebo.[347] The results showed that both dantrolene sodium and diazepam were superior to placebo on measures on spasticity, reflexes and clonus. However, dantrolene sodium was reported to have a negative effect relative to diazepam and placebo on both hip flexor strength and deltoid strength.

Gabapentin – Two placebo-controlled randomised crossover trials investigated the efficacy of gabapentin. The first trial reported significant differences between the groups on all of the eight outcomes measures assessed, with no minor or severe adverse effects being reported from the trial.[348] The second trial reported significant effects on three of the seven outcomes measures, including the Ashworth scale score and the EDSS. Again no major side effects were reported in the trial.[349]

Progabide – One randomised and one non-randomised crossover trial compared progabide to placebo.[350,351] Both of the trials reported no overall significant effects on either measures of spasticity or functional tests. The non-randomised trial reported eight cases of serious adverse events (**IIa**).

Progabide is not available in the UK.

Diazepam – Two randomised crossover trials compared diazepam to different active comparators. The first compared diazepam to ketazolam and placebo, with no significant differences between the groups being reported.[352] The second trial compared diazepam to dimethothiazine. However, the significances of the results for the trial was not reported[353] (**IIb**).

Other pharmacological interventions – One systematic review and a further nine studies examined the efficacy of a variety of pharmacological interventions for spasticity. The systematic review of three RCTs, and one additional RCT assessed the efficacy of botulinum toxin. The review compared botulinum toxin to placebo and plaster casts for the treatment of lower limb spasticity in children with cerebral palsy. The results reported no significant differences between those treated with botulinum toxin and those treated with either placebo or plaster casts[354] (**Ia**). The RCT compared three different doses of botulinum toxin to placebo.[355] No overall significant differences were reported between the groups with a number of side effects reported for all three of the intervention groups, with these being proportional to the intervention dosage.

Two randomised crossover trials that assessed L-threonine and threonine respectively compared to placebo both reported no significant effects.[356,357] Neither of the trials reported any major adverse events (**Ib**). Likewise a further non-randomised crossover trial examining brolitene and placebo reported no effect[358] (**IIa**). One placebo-controlled randomised crossover trial that assessed 3,4 diaminopyridine reported significant differences on five of the six outcomes measures examined, including the ambulation index (AI). However side effects were reported by a high proportion of patients in the intervention group.[359]

Four placebo-controlled crossover trials examined the efficacy of different cannabis derivatives for spasticity. The first randomised crossover trial compared Delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), and a combination of THC and CBD to placebo. The results indicated that THC and the combination of THC and CBD showed beneficial effects on four of the seven outcome measures assessed, whilst CBD alone showed positive effects on three when compared to placebo.[360] The second trial assessing Delta-9-THC reported no overall significant effects at lower doses, with a significant reduction in symptoms being noted only at high doses of the drug which was intolerable due to the number of side effects reported.[361] The third trial assessed the effect of active smoked marijuana on postural stability and reported negative effects on both outcome measures recorded.[362] The last randomised crossover trial compared THC and cannabis sativa plant extract to placebo. The results showed no overall beneficial effects for either of the interventions compared to placebo.[363]

Although four studies on the use of cannabinoids are reviewed, the totality of evidence is small with few patients included, so it was felt inappropriate to make any recommendations.

However, we are aware that further evidence is likely to be published and that NICE intend to conduct a technology appraisal on cannabinoids in MS with a projected publication date of April 2004.

Other non-pharmacological interventions – Seven RCTs investigated the efficacy of a number of different non-pharmacological interventions for spasticity (**Ib**). The first RCT assessed the utility of the interadductor *vs* the traditional approach to obturator nerve blockade for bilateral adductor muscle spasms. The results reported positive effects on four of the six outcomes examined, including discomfort, spasms and hygiene scores. No complications were reported with either approach.[364] Two RCTs assessed different physiotherapy approaches. The first examined whether an inpatient physiotherapy rehabilitation program would lead to functional gains in mobility in the home.[365] The trial reported no overall significant differences between the intervention group and the waiting list control group. The second RCT examined the utility of impairment-based physiotherapy approaches compared to disability-orientated approaches.[366] Again no significant effects were observed on any outcome measures between the groups. Four further RCTs examined different interventions. The first assessed the use of muscle passive shortening with traction stress for patients with hip abductor hyposthenia.[367] The results showed a positive benefit on the range of motion against gravity for the intervention, but other outcome measures assessed were not interpretable. The second RCT examined electrical neuromuscular stimulation (ENS) against sham stimulation.[368] No significant benefits were seen for the intervention. The third examined the effects of magnetic stimulation. This RCT reported beneficial short-term effects on the stretch reflex but these did persist at longer term follow-up, it also found no significant effect on ADL.[369] The last RCT assessed the use of weighted leg extension exercises for strengthening the quadriceps against a standard prescribed exercise program.[370] Again, no significant benefits were observed for the intervention.

▷ Economic evidence

The forthcoming HTA review of treatment for pain and spasticity in MS could identify no formal review of current clinical practice regarding the treatment of spasticity. Anecdotal evidence suggests that it may be variable, with an MS society survey reporting that 32% of people did not see a hospital specialist for treatment.[371] In the systematic review of economic evidence the forthcoming HTA report identified no formal economic evaluations. The only existing economic analysis considers the effect of continuous intrathecal baclofen infusion (CIBI) on hospitalisation rates. At present CIBI is not commonly used in Britain; in 1998 only around 200 people were implanted with a pump for intrathecal baclofen of which only around 60 had MS.[371a]

None of the identified studies are based in the UK, they only include small numbers of patients, and they include people with spinal cord injury as well as MS. The studies all show significant savings in terms of hospitalisation, implying significant potential cost offsets and patient benefits.

A working group on acute purchasing report in 2000 attempted to model the costs and benefits of intrathecal baclofen in the management of people with severe spasticity (not only from MS).[372] The estimated cost per quality-adjusted life year (QALY) was around £20,000, which is relatively high but is within the acceptable range identified in historical NICE appraisal decisions. However, the report commented on the poor clinical evidence for CIBI, hence there is a large amount of uncertainty surrounding the cost per QALY estimate.

In general, though, the initial high cost of CIBI implantation could be offset by reductions in pressure ulcer and other admissions related to spasticity, orthopaedic procedures and reductions in requirements for aids. On the basis of the advice provided in this report, the Trent Development and Evaluation Committee recommended that CIBI be made available to those patient groups for which there is evidence of greatest benefit; that is 'patients who are bedbound due to severe spasticity, patients who cannot be seated in a wheelchair due to severe extensor spasms, and other wheelchair-bound patients in whom spasm-related pain or skin breakdown is a severe problem'.

▷ From evidence to recommendations

In formulating its recommendations, the guideline developers noted the relatively low level of evidence available for most of the commonly used drugs, that comparative studies were very rare, the absence of evidence for most of the commonly used physical therapies, and the difficulty in defining and measuring the benefits of treating spasticity in formal trials. Further, we recognise that cannabis derivative and extracts are currently being researched with several large studies to be published and that NICE is undertaking a review of cannabis drugs. It also recognized that the management of spasticity was an important topic, and hence derived a series of recommendations that drew on clinical consensus as well as the limited evidence.

RECOMMENDATIONS

R112 Each professional in contact with a person with MS who has any muscle weakness should consider whether spasticity or spasms are a significant problem, or a contributing factor, to the person's current clinical state. **D**

R113 If spasticity or spasms are present, then simple causative or aggravating factors such as pain and infection should be sought and treated. **D**

R114 Every person with MS who has persistent spasticity and/or spasms should be seen by a neurophysiotherapist to assess and advise on physical techniques, such as passive stretching and other physical techniques, to reduce spasticity and especially to avoid the development of contractures. Families and carers should be taught how to prevent problems worsening, and a monitoring system should be put in place. **D**

R115 More active specific measures should be considered only if the spasms or spasticity are causing pain or distress, or are limiting (further) the individual's dependence and activities. In this case, both benefits and risks should be considered carefully. A specific goal (or goals) should be set, but will rarely include improved performance in activities. **D**

R116 Initial specific pharmacological treatment for bothersome regional or global spasticity or spasms should be with: baclofen or gabapentin. **A**

The following should be given only if treatment with baclofen or gabapentin is unsuccessful or side effects are intolerable:

- tizanidine **A**
- diazepam **D**
- clonazepam or **D**
- dantrolene. **D**

Combinations of medicines, and other medicines such as anticonvulsants, should only be used after seeking further specialist advice. **D**

R117 People with MS who have troublesome spasticity and spasms unresponsive to simpler treatments should be seen by a team specialising in the assessment and management of spasticity. **D**

The team should consider using one or more of the following:

- standing and weight-bearing through legs **D**
- splints **D**
- serial casting **C**
- special or customised seating, such as tilt-in-space chairs **D**
- intrathecal baclofen **A**
- phenol injections to motor points or intrathecally. **D**

R118 Intramuscular botulinum toxin should not be used routinely, but can be considered for relatively localised hypertonia or spasticity that is not responding to other treatments. It should be used when specific goals can be identified, and: **B**

- in the context of a specialist service that can consider all aspects of rehabilitation (for example, seating)
- by someone with appropriate experience and expertise
- followed by active input from a neurophysiotherapist.

LOCAL IMPLEMENTATION POINTS

These will need to:

- identify who within local neurological rehabilitations services will deal with difficult problems of spasticity and how they are accessed
- identify who may assess and give botulinum toxin injections and how they are accessed
- identify how preventative stretching and handling are delivered to people with MS in the community
- identify what assessment protocols and measures for spasticity should be used locally
- ensure collaborative working with those providing services such as specialized seating to give a comprehensive service to people with MS affected by spasticity
- agree funding arrangements (and prioritising mechanisms if any) for botulinum toxin, baclofen pumps and other specific treatments.

6.5.2 *Contractures at joints*

A contracture is a shortening in the soft tissues (ie tendons, muscles or ligaments) around a joint that limits the passive (and active) range of movement at that joint. Contractures generally arise when a joint is not moved through a full range of movement on a regular basis, for whatever reason. In people with MS the common reasons are spasticity and weakness. The prevalence of contractures in people with MS is not known, nor is it known how frequently they start to develop, but they are seen commonly in daily clinical practice, and much effort is devoted to their prevention and treatment. Contractures may cause pain, and may sometimes be the primary impairment limiting activities such as walking, feeding or dressing. Contractures frequently make caring for, and positioning, seating, walking, dressing and feeding people with MS extremely difficult, requiring expensive care packages to be set up and specialist seats to be made. Prevention and treatment of contractures always involves attempts to ameliorate underlying impairments or other causes.

The main aim of management is to prevent contractures, but some are inevitable and then specific treatments may be needed.

▷ Evidence statements

All evidence statements for contractures at joints are level **Ib**.

No SRs or primary studies in patients with MS were identified which assessed interventions to prevent contractures at joints. An ongoing study was identified on the national research register, which aims to investigate whether a daily muscle stretch regime prevents the development of contractures and muscle stiffness in stroke patients. However, this study is not due to be completed until December 2003.[373]

Five RCTs were identified which looked at interventions for the treatment of contractures (**Ib**). Three RCTs looked at various stretching programmes,[374–376] one looked at a topical cream[377] and the last looked at a bed positioning programme.[376] Two of the studies, which assessed the effectiveness of a stretching programme, found a beneficial effect of treatment compared to the control group. The first of these studies evaluated the effectiveness of a low-load prolonged stretch in geriatric patients with bilateral knee flexion contractures and found a significant improvement in the passive range of motion in legs treated with the low-load prolonged stretch compared to those receiving a traditional high-load brief stretching programme. The other, a

crossover RCT, evaluated a below-the-knee cast and stretch in patients with traumatic head injury who had ankle contractures. This study reported a significant improvement in passive ankle dorsiflexion motion during the intervention period compared to the control period.[376] The third study evaluated the 'Dynasplint', which applies a prolonged stretch unilaterally, in geriatric patients, and found no beneficial effect of treatment.[374] An RCT, in people with joint disease, of a cream containing chlorproethazine, a muscle relaxant (not available in the UK), found significant improvements in a range of outcomes including pain intensity, tender point palpitation, patients evaluation of treatment, and contracture severity in patients receiving the active cream compared to those receiving a placebo cream. No effects were found for one of the outcomes investigated (limitation of movement).[377] No beneficial effect was found for a bed-positioning treatment programme in older patients.[378]

▷ Health economics

No relevant economic evidence relating to contractures was identified.

▷ From evidence to recommendations

In the absence of much specific evidence the guideline developers drew upon consensus when developing recommendations in this area.

RECOMMENDATIONS

R119 Any person with MS who has weakness and/or spasticity sufficient to limit the regular daily range of movement around a joint should be considered at risk of developing a contracture at that joint, and should be considered for preventative measures. **D**

R120 Any person with MS at risk of developing contractures should have the underlying impairments assessed and ameliorated if possible (see sections on weakness (6.4) and spasticity (6.5)). **D**

R121 Any person with MS at risk of developing contractures should be informed; the individual, and/or carer(s) should be taught how to undertake preventative measures, such as regular passive stretching of the joint(s) at risk and appropriate positioning of limbs at rest. In more severe instances, specialist advice should be obtained on seating and positioning, including positioning in bed. **D**

R122 Any person with MS who develops a contracture should be assessed by a suitable specialist for specific treatment; the assessment should take into account the problems caused by the contracture, the discomfort and risk of any treatment and the wishes of the person. At the same time, renewed efforts should be made to reduce the underlying causes and to prevent further contracture. **D**

R123 Specific treatment modalities to be considered should include prolonged stretching using:

- serial plaster casts **A**
- other similar methods, such as standing in a standing frame and removable splints. **D**

These are usually combined with:

- local botulinum toxin injection, and **D**
- surgery when necessary. **D**

6.6 Ataxia and tremor

Ataxia refers to uncoordinated voluntary movement usually attributed to disturbed function of the cerebellum or associated pathways and not attributable to direct motor weakness or sensory loss. When present it may be extremely disabling. Ataxia may also arise from loss of adequate sensory feedback. Tremor is a broader term referring to any regular or rhythmic alternating movement affecting a joint or group of joints, and in practice it is difficult to distinguish the precise nature or cause of uncoordinated tremulous movements. The presence of ataxia often indicates lesions in areas that also control bulbar functions (articulation and swallowing) and eye movement control.

Although some people feel that ataxia and tremor are quite distinct,[379] in practice there are great difficulties in describing and classifying tremor and ataxia in people with MS.[380] Both will be considered at once because it is unlikely that most studies have made unequivocal distinctions. Generally the word 'tremor' will be used to include ataxia, but ataxia will be used primarily to refer to uncoordinated intentional movement thought to arise from cerebellar disturbance.

Tremor of some sort was a newly presenting symptom in 6 of 226 patients followed up over nine months in Oxfordshire.[6] In a randomly selected group of 100 people with MS in London, tremor was reported by 37 but detected in 58: 15 had 'severe tremor' and 27 had disability attributable to the tremor.[380] In another sample, 27% had shaking (tremor).[278] In a South Wales survey, ataxia was experienced by 82% of people with MS, and had a point prevalence of 82%.[271]

Although there are no proven treatments, the clinician will need guidance that describes possible managements, and also that alert them to possible complications that arise in people with tremor.

▷ Evidence statements

One RCT compared the use of Johnstone pressure splints as an addition to standard PNF physiotherapy approaches for ataxia. The results showed that the use of Johnstone pressure splints plus exercise using the proprioceptive neuromuscular facilitation technique was only beneficial on two of the eight outcome measures assessed, single limb stance time (right and left), compared to exercise alone[381] (**Ib**).

One RCT, two randomised crossover trials and one CCT assessed different interventions for tremor. The RCT examining thalamotomy compared to thalamic stimulation (implanting of electrodes) reported that thalamic stimulations was more beneficial. A large number of relatively serious adverse events were also reported in both groups in the six month period post surgery.[382] The first randomised crossover trial compared a single intravenous infusion of ondansetron to placebo, with positive results being reported on all three outcome measures at 60 minutes follow-up. The incidence of side effects was low and these were of a minor nature.[383] The second crossover trial examined the efficacy of isoniazid with no effect being reported on either of the two outcome measures[384] (**Ib**). The CCT which assessed the utility of unilateral stereotactic surgery also reported no overall effect, although beneficial results were reported for two out of the five outcomes examined.[385] The trial also reported a number of adverse events both at the time of surgery and post-operatively (**IIa**).

▷ Economic evidence

No relevant economic evidence relating to ataxia or tremor was identified.

▷ From evidence to recommendations

The guideline development group recognises that many drugs are tried for this distressing and disabling impairment, although there is no evidence. It also noted that the only 'positive' drug trial was insufficient to make any recommendation, and that the evidence supporting neurosurgery was limited for such a risky and expensive procedure. The recommendations made reflect the lack of strong evidence or even consensus on specific interventions.

RECOMMENDATION

R124 Any person with MS who experiences a limitation of activities due to tremor should be assessed: **D**

- by a specialist rehabilitation team for medicines, treatment techniques and equipment (using the general principles of goal setting and evaluation recommended)

and, if problems remain severe and intractable, the person should be assessed:

- by a neurosurgical team from a specialist centre, for suitability for an operation to reduce ataxia (after being given a full explanation of its major risks and possible benefits).

LOCAL IMPLEMENTATION POINTS

These should identify:

- the local specialist rehabilitation service able to assess and advise on treatment and compensatory techniques and equipment
- the neurosurgical centre able to assess for and undertake neurosurgical interventions
- the preferred local measures and assessment techniques, if any.

6.7 Sensory losses

Altered sensation in the form of tingling, numbness, 'odd' feelings etc are common in people with MS. In one sample of 656 people, 63% with MS had 'numbness, tingling or other sensory disturbance'.[278] In one survey[271] sensory disturbance was the commonest first symptom (34%) and was the second most common symptom experienced (87%) and still existing at prevalence point (73%). Sensory losses may be associated with painful hypersensitivity and spontaneous neuralgic pain. The treatment of neurogenic pain is covered separately. Sensory disturbance can directly limit activities; for example numbness in a hand can make fine dextrous activities impossible and people may drop items or injure themselves. Abnormal sensation was present in 49/150 people surveyed at one point, and was a new problem in 6/226 people followed up over nine months in Oxfordshire.[6]

Although there are no proven treatments, the clinician will need guidance about possible managements, and also to alert them to possible complications that arise in people with sensory loss.

▷ Evidence statements

No RCTs or CCTs in patients with MS were identified which assessed interventions for the treatment of sensory losses.

▷ Economic evidence

No relevant economic evidence relating to sensory losses was identified.

▷ From evidence to recommendations

In the absence of any evidence even from other conditions or situations, the GDG has limited itself to simple advice, emphasising the risk that may follow on from loss of sensation.

RECOMMENDATIONS

R125 Any person with MS who experiences a limitation of activities not otherwise explained should be assessed for sensory losses. **D**

R126 Any person with sensory disturbance sufficient to limit activities should be seen and assessed by a specialist rehabilitation team; the individual should be given advice on techniques and equipment to ameliorate their limitations, and advice on personal safety. **D**

6.8 Visual problems

Demyelination within the optic nerve is a common if not universal occurrence in MS. Surprisingly, most people with MS do not have significant symptoms from this demyelination, though on formal testing visual acuity and colour vision are often impaired. Some people do suffer direct visual loss from optic nerve damage but more people suffer significant, sometimes severe visual problems from disturbed oculo-motor control (ie abnormalities in the control of eye movements) that may lead to double vision and movement of images. Reading is difficult for many people with MS. There are few studies on the frequency of significant limitations of visual function in people with MS but one survey did note that 30% had significant disturbance of visual function.[278] In Southampton 10% had seriously impaired vision,[280] and in South Wales 51% had experienced double vision and the prevalence of visual disturbance was 33%.[271] In Oxfordshire, 18 of 150 people mentioned problems with their eyes and eyesight at one point, and 3 of 266 developed new problems with their eyes and/or eyesight over nine months, with one having an episode of optic neuritis.[6]

This part aims to ensure that difficulties in this under-recognised area are identified and diagnosed accurately, and that people reach the services most equipped to help, and that the few specific treatments available are tried.

▷ Evidence statements

No RCTs or CCTs in patients with MS were identified which assessed interventions for the treatment of visual problems.

▷ Economic evidence

No relevant economic evidence relating to visual problems in MS was identified.

▷ From evidence to recommendations

Although there was no MS-specific evidence, the GDG has made several recommendations for two reasons. First, there was a strong view that visual impairments are often overlooked and that people with MS and visual impairment did not benefit from any specialist advice, which often may improve their abilities. Second, there is reasonable (RCT) evidence supporting the use of gabapentin for nystagmus, and it is widely used.[386,387]

RECOMMENDATIONS

R127 Each professional in contact with a person with MS should consider whether the individual's vision is disturbed, by considering, for example, the individual's ability to read the text of a newspaper, book or other written material and to see the television. **D**

R128 Any person with MS who is unable to read normal print or to see the television should be assessed for glasses by an optometrist. **D**

R129 Any individual who experiences reduced visual acuity, despite using suitable glasses, should be assessed in a specialist ophthalmology clinic. **D**

R130 Any person with MS who has nystagmus that causes reduced visual acuity or other visual symptoms, should be offered a time-limited trial of treatment with oral gabapentin. This should be initiated and monitored by a suitable specialist. **D**

R131 Any person with MS who is unable to read (due to low visual acuity) or to see television, despite all available treatment, should be: **D**

- assessed for low-vision equipment and adaptive technology
- referred to the appropriate specialist social services team
- registered as partially sighted.

LOCAL IMPLEMENTATION POINTS

These should identify:

- which local ophthalmologist has an interest in neuro-ophthalmology
- the nearest specialist low-vision service
- the social service team responsible for people with visual impairment.

6.9 Pain

People with MS may suffer pain in at least three ways: specific 'neuropathic' pain arising from areas of demyelination (trigeminal neuralgia is the most well known but not the most common); musculoskeletal pain secondary to postural and other consequences of the disease; and pain from an incidental medical problem unrelated to their MS. Unfortunately, anecdotal experience suggests that much pain is incorrectly diagnosed and poorly managed. A survey of 159 people with MS in Ontario found that 88 had had either an acute or chronic pain syndrome, and that

78 were experiencing chronic pain of one or more types: 46 had neuropathic pain, 22 had back pain, 21 had painful leg spasms.[323] Pain was present in 42 of 150 people with MS surveyed in Oxfordshire, and 24 of 226 people with MS followed up for nine months developed new pain requiring diagnosis and management.[6] Fifteen had neurogenic and eight had musculoskeletal pain (six more presented specifically with secondary musculoskeletal pain) and one had headaches (no specific cause). In another survey, pain was the second most frequent 'worst symptom' at 12% (fatigue achieved 17%).[269] In a third survey, 36% of 656 people with MS had pain.[278] One may conclude that pain is common, and anecdotal experience suggests that pain is often misdiagnosed and mistreated such that patients may suffer unnecessarily.

This section covers all aspects of pain management in people with MS. However the evidence relating to the management of non-neuropathic pain has not been reviewed, and only the evidence that concerns pain that is specific to neurological disease is included. The recommendations are intended to ensure that pain is adequately detected and correctly diagnosed so that the most specific and appropriate treatments available are used.

▷ Evidence statements*

A relatively large number of reviews were identified which assessed the effectiveness of a wide variety of interventions for the treatment of secondary pain. In total, 17 reviews met inclusion criteria. These can be grouped into three main categories: behavioural interventions (n = 4 SRs), pharmacological interventions (n = 7 SRs) and other therapies (n = 6 SRs).

Behavioural interventions showed mixed results in terms of effectiveness. A fairly poor review of cognitive coping strategies found that cognitive strategies were generally effective in enhancing pain tolerance, and that imagery methods were the most effective.[388] A review of cognitive behavioural therapy also reported a beneficial effect of treatment on chronic pain.[389] A review of multidisciplinary rehabilitation in patients with musculoskeletal pain reported no overall beneficial effects of treatment,[390] and a review of non-pharmacological intervention for the treatment of chronic pain reported that studies were too heterogeneous to detect an effect of treatment.[391]

The reviews of pharmacological interventions also reported mixed effects of the interventions evaluated. Two reviews assessed the effectiveness of antidepressants for the treatment of neuropathic pain,[392,393] one of these also included patients with chronic pain.[393] Both reviews found that antidepressants were more effective than placebo in the treatment of neuropathic pain.[392,393] One of the reviews reported no difference between the different tricyclic anti-depressants in terms of efficacy but that these were more effective than the benzodiazepines.[392] Three reviews looked at the effectiveness of anticonvulsant drugs in the treatment of chronic pain. Two looked at these drugs in general[394,395] and one only looked at gabapentin.[396] These reviews reported conflicting results. The first found that generally anticonvulsants were effective for trigeminal neuralgia, diabetic neuropathy, and migraine prophylaxis, but that minor adverse events occurred as often as benefit.[395] The second reported that few trials

* Beard S, Hunn A, Wight J. Treatment for spasticity and pain in multiple sclerosis: a systematic review. *Health Technology Assessment* 2003;7:40, was published in December 2003, after the cut-off date for evidence in this guideline. It can be obtained at **www.ncchta.org/fullmono/mon740.pdf**

showed analgesic effectiveness and concluded that these drugs should be withheld until other interventions have been tried for patients with chronic pain, with the exception of trigeminal neuralgia.[394] The review which only considered gabapentin reported positive effects in diabetic neuropathy and post herpetic neuralgia compared to placebo, and found it similar in effectiveness to amitriptyline. However, intolerable side effects occurred in up to 10% of recipients.[396] A poor quality systematic review found that chemical sympathectomy was effective in relieving pain in around half those receiving treatment.[397] However, these results came mainly from uncontrolled studies, and the results of controlled studies were not reported separately. It is therefore difficult to draw conclusions from these results.

The remaining reviews looked at transcutaneous electrical nerve stimulation (TENS), phytodolor (a herbal preparation), acupuncture, ultrasound and low-level laser therapy (LLLT). TENS was reported to be better than inactive control but high frequency TENS (HFTENS) and low frequency TENS (LFTENS) were found to be similar.[398] The effectiveness of phytodolor in treating osteoarthritis, chronic epicondylitis and rheumatic diseases was found to be superior to placebo and similar to synthetic drugs.[399] There was limited evidence that acupuncture was more effective than no treatment in treating chronic pain, but the evidence was inconclusive as to whether it was more effective than placebo, sham acupuncture or standard care.[400] Two reviews of ultrasound therapy and a review of LLLT for musculoskeletal pain reported no beneficial effects of treatment.[401–403]

A review of cannabinoids for the treatment of cancer pain, post-operative pain and non-malignant pain found that cannabinoids were more effective than placebo in relieving pain but similar to codeine.[404]

At the time of writing there is insufficient evidence to comment on the use of cannabinoids in MS. Further evidence on the use of cannabinoids in MS is likely to be published and NICE intend to conduct a technology appraisal on cannabinoids in MS with a projected publication date of April 2004.

▷ Health economics

The forthcoming HTA review of treatment for pain and spasticity in MS found no studies that looked explicitly at the impact of pain on the quality of life of people with MS and no studies that considered the health economics of treatment for pain in MS. In addition, no formal review of current clinical practice was identified. However, there is some evidence that despite the high prevalence of pain as a symptom in MS, few patients are referred to pain specialists – fewer than 2% in an MS Society survey.[371]

▷ From evidence to recommendations

When drawing up recommendations, the guideline developers was aware that although there were few MS-specific studies on pain and its treatment, much of the more generic evidence should be applicable. Consensus was achieved easily on the recommendations made.

RECOMMENDATIONS

R132 Each professional in contact with a person with MS should ask whether pain is a significant problem for the person, or a contributing factor to their current clinical state. **D**

R133 All pain, including hypersensitivity and spontaneous sharp pain, suffered by a person with MS should be subject to full clinical diagnosis, including a referral to an appropriate specialist service if needed. **D**

Musculoskeletal pain

R134 Every person with MS who has musculoskeletal pain secondary to reduced or abnormal movement should be assessed by specialist therapists to see whether exercise, passive movement, better seating or other procedures might be of benefit. **D**

R135 If non-pharmacological means are proving unsuccessful in managing the musculoskeletal pain (arising from reduced movement and/or abnormal posture), the individual should be offered appropriate analgesic medicines. **D**

R136 Any person with MS who has continuing unresolved secondary musculoskeletal pain, should be considered for transcutaneous nerve stimulation or antidepressant medication. **A**

R137 Treatments that should not be used routinely for musculoskeletal pain include ultrasound, low-grade laser treatment, and anticonvulsant medicines. **A**

R138 Cognitive behavioural and imagery treatment methods should be considered in a person with MS who has musculoskeletal pain only if the person has sufficiently well-preserved cognition to participate actively. **A**

Neuropathic pain

R139 Neuropathic pain, characterised by its sharp and often shooting nature, and any painful hypersensitivity, should be treated using anticonvulsants such as carbamazepine or gabapentin, or using antidepressants such as amitriptyline. **A**

R140 If the neuropathic pain remains uncontrolled after initial treatments have been tried, the individual should be referred to a specialist pain service. **D**

LOCAL IMPLEMENTATION POINTS

These need to specify which specialist services can assess and advise on pain associated with MS, especially:

- musculoskeletal pain and the use of equipment and exercises
- neuropathic pain (neurology, neurorehabilitation or pain service).

6.10 Cognitive losses

About half of all people with MS experience cognitive losses. Indeed, MS is probably the commonest single cause of acquired severe cognitive loss in adults aged under 65 years. For example in the Oxfordshire audit, 12 of 150 individuals felt they had problems with concentration and 10 of 150 with thinking, and only 2 of 226 people present new cognitive problems over a nine month period of follow-up.[6] In another community-based survey, 43 of

100 individuals had measurable cognitive losses[405] and in a third community study of 200 people, 46% had measurable cognitive deficits with 34% having impaired memory and 33% impaired planning and other 'frontal lobe functions'.[406] Other studies have shown similar findings.[278]

The main implication is that all people, professional and otherwise, who interact with the person with MS should be aware at all times that cognitive loss may be present. It is also important for the person with MS to be aware and to know how to minimise any problems. In practical terms cognitive losses will influence almost all aspects of life, but may be most important in their effects on more complex activities such as community and domestic ADL, making judgements and taking part in legally important decisions, work, and in communication. Other impairments such as disinhibition may also affect control of behaviour and social interaction.

Cognitive impairments in people with MS may have several causes and associated factors. They may be exacerbated by or associated with depression, drugs taken for other impairments, and fatigue. Relapses may cause cognitive impairment, in which case it may well improve. Cognitive loss may occasionally be the presenting or main feature of the disease. Its presence should always be considered but never assumed; formal assessment is usually necessary to clarify the situation. Although the severity of cognitive losses is generally associated with the severity of dependence, this is often not the case and the possible presence of cognitive impairment should always be considered.

The recommendations below should ensure that:

- cognitive impairments are always considered
- any factors that worsen cognitive impairment are identified and treated
- the effects of cognitive impairment are minimised
- any risks associated with cognitive impairment are identified and prevented if possible.

▷ Evidence statements

Four RCTs examined the efficacy of cognitive remediation programs for cognitive dysfunction. The first trial assessed the effectiveness of cognitive training and neuropsychotherapy in comparison to non-specific mental stimulation. The results showed no overall beneficial effect for the intervention at six month follow-up.[407] The second trial examined the use of cognitive assessment plus remediation, compared to assessment alone, or no treatment. The results indicated no significant differences between the groups on any of the outcomes measures.[408] The third study assessed the use of cognitive remediation strategies in patients who were resident in long-term nursing facilities. The results showed no beneficial effect for the intervention as compared to the no treatment control group.[409] The last study compared the use of the story memory technique to no intervention. The results showed positive effects on three out of five of the outcomes assessed, including patients self report of memory functioning[410] (**Ib**).

▷ Economic evidence

No relevant economic evidence on treatment for cognitive losses was identified.

▷ From evidence to recommendations

The GDG noted that cognitive impairments affected at least half of all people with MS, and that cognitive impairments were often not recognised even though they have pervasive effects. The evidence does not currently support any specific intervention, but nonetheless it was felt important to ensure that cognitive impairments were identified, and that simple advice and actions were undertaken. The recommendations made were agreed by consensus.

RECOMMENDATIONS

R141 Health care staff should always consider whether the person with MS has any impairment of attention, memory and executive functions sufficient to be a problem, or to be a contributing factor to their current clinical status. **D**

R142 When a person with MS is being involved in making a complex medical decision, or is starting a course of complex treatment that requires their active participation, they should have their cognition sensitively assessed to ascertain their ability to understand and participate adequately, and to determine what support they may need. **D**

R143 Any person with MS experiencing problems due to cognitive impairment should:

- have their medication reviewed, to minimise iatrogenic cognitive losses **D**
- be assessed for depression, and treated if appropriate. **D**

R144 Any person with MS complaining of cognitive problems, and any person where this is suspected clinically, should be: **D**

- offered a formal cognitive assessment, coupled with specialist advice on the implications of the results
- advised, if necessary, about any vulnerability to financial or other abuse that may arise, and how to reduce the risk
- asked whether the results can be communicated to other people.

R145 Any person with MS whose level of dependence or whose social behaviour cannot be easily understood in terms of other known impairments or factors should be offered a formal neuropsychological assessment by a specialist clinical psychologist (and speech and language therapist if appropriate); it should be investigated whether cognitive or communicative losses are a contributing factor and, if so, appropriate management should be recommended. **D**

LOCAL IMPLEMENTATION POINTS

These need to:

- agree simple assessments of cognition for use by staff interacting with people with MS
- identify which specialist psychology service (usually that within the neurological rehabilitation service) should be approached for assessment and treatment, and how they are accessed.

6.11 Emotionalism

People with MS can suffer several disturbances in their emotions and emotional control. Emotionalism refers to a tendency to cry, or more rarely laugh, when this is not the felt emotion and often without any ability to control the behaviour. It is associated with depression, in stroke patients. It has also been referred to as pathological crying and laughing, pathological emotionalism, and one aspect of pseudobulbar palsy. There are no clear-cut, agreed definitions. It can be extremely distressing to the person with MS but fortunately rarely causes severe or prolonged problems.

The frequency of emotionalism is not known. One study suggests that 10% of people with MS experience 'pathological laughing and crying,[411] and another that 32% found that they laughed or cried easily.[278]

▷ Evidence statements

One randomised crossover trial compared the effect of amitriptyline to placebo. The results showed a beneficial effect on both clinical improvement and the number of episodes of lability. No adverse events were reported[412] (**Ib**).

▷ Economic evidence

No relevant economic evidence on treatment for emotionalism was identified.

▷ From evidence to recommendations

Although there is little MS-specific evidence; there is some evidence from other neurological conditions. Because emotionalism can be so distressing, the GDG drew on all this evidence to reach the consensus recommendations made.

RECOMMENDATIONS

R146 A person with MS may comment (or it may be noticed) that they may cry or laugh with minimal provocation and with little control; the individual should be offered a full assessment of their emotional state by someone with suitable expertise. **D**

R147 If the emotionalism is sufficient to cause concern or distress to the person with MS, or their family, then treatment with an antidepressant should be offered:

- usually a tricyclic antidepressant, or **B**
- a selective serotonin re-uptake inhibitor. **D**

R148 If the person with MS still has uncontrolled emotionalism, is unwilling or unable to take antidepressants, or is not responsive to antidepressants, then advice on behavioural management strategies should be offered by a suitable expert. **D**

LOCAL IMPLEMENTATION POINTS

These need to specify:

- which local specialist(s) (neurorehabilitationalist, psychiatrist or clinical psychologist) has/have appropriate expertise to assess and manage emotional impairments
- whether one particular antidepressant is preferred.

6.12 Depression

Depression is a common emotional consequence in MS. For example, it was found in 36% of one sample.[278] Depression may arise as a specific impairment secondary to neurological lesions and it may be secondary to disability, altered life circumstances, pain, or loss of employment.[413] It is also likely that depression in turn may cause or worsen some impairments and disabilities. There is some evidence that people with MS have a higher rate of suicide than people with most other chronic disabling conditions, and this risk may be highest within the first five years of diagnosis. In the Oxfordshire audit, 13 of 150 individuals complained of disturbed emotions or emotional control at one time, and 11 of 226 presented with depression or low mood over a nine month period.[6] In the Southampton survey every person with MS was assessed formally using the Hospital Anxiety and Depression (HAD) scale and 7% were rated depressed and 9% borderline depressed.[280]

Consequently guidance needs to ensure that all professionals involved are aware of depression, and that it is identified and treated appropriately, not only by drugs but also through ameliorating some of the other causative factors. However it is also important that the important associations between depression, fatigue, social circumstances and other factors are always considered.

In the absence of strong evidence that depression in MS is different from depression in other people, the forthcoming NICE guideline on depression should be used once available.

▷ Evidence statements

Three RCTs examined the effect of cognitive behavioural therapy (CBT) compared to placebo or other active treatments. The first study compared weekly CBT, supportive expressive group (SEG) therapy and sertraline. The results showed that on all three of the outcome measures CBT was significantly superior to SEG; and that there were no differences in the results between CBT and sertraline. No adverse events were reported in the trial.[414] The other two trials both compared CBT to a waiting list control. The first trial reported positive effects on four of six outcome measures assessed, whilst the second that examined the use of individual telephone therapy also reported significant beneficial effects. Neither of the trials reported any adverse effects[415,416] (**Ib**).

▷ Economic evidence

No relevant economic evidence on treatment for depression in MS was identified.

▷ From evidence to recommendations

The GDG felt that this was an important topic and in the absence of much evidence used consensus to develop the recommendations made.

RECOMMENDATIONS

R149 If depression is suspected, the person with MS should be assessed:
- by asking 'Do you feel depressed?', or using a similar screening method **DS**
- clinically if necessary **D**
- by a liaison psychiatrist if severe depression is present. **D**

R150 In any person with MS who is depressed, a list of possible contributing factors (such as chronic pain and social isolation) should be drawn up. **D**

R151 Assessment and interventions should be undertaken to ameliorate those contributing factors, where possible. **D**

R152 Specific antidepressant medication, **D**
or psychological treatments such as cognitive behavioural therapy **A**
should be considered but only as part of an overall programme of depression management. **D**

R153 Other concurrent psychological diagnoses, especially anxiety, should be considered. **D**

LOCAL IMPLEMENTATION POINTS

These should consider:
- which screening question or questionnaire is recommended locally
- which formal depression questionnaire is recommended locally
- which psychiatrist and/or clinical psychologist should be approached when more specialist advice or treatment is required
- what antidepressants are preferred locally.

6.13 Anxiety

Although poorly studied, this is probably the commonest emotional impairment associated with MS. In one study the rate of anxiety at 25% (of 252 consecutive patients with MS) was three times the rate for depression in the same group.[417] In the Southampton survey using the HAD scale, 16% were anxious and 20% borderline anxious, over twice the rate of depression.[280] The precise aetiology is not known, although it is probably not due to any specific lesions.[413] Nevertheless it can significantly increase dependence and distress. In the Oxfordshire audit only one patient (from 226) presented with anxiety over nine months.[6]

▷ Evidence statement

No RCTs or CCTs in patients with MS which assessed intervention for the treatment of anxiety were identified.

Three systematic reviews assessed different interventions for anxiety in patient populations other than MS (**Ia**). The first review examined the utility of self-help treatments for patients with anxiety presenting in primary care settings. The results showed advantages associated with self-help on at least one measure, although most studies reported multiple comparisons. There were no data available concerning the long term clinical benefits.[418] The second review of seven

trials compared the efficacy of kava extract (a herbal treatment) to placebo. All the trials showed superiority of kava extract, with any adverse effects being mild and transient.[419] However, it should be noted that kava extract has been voluntarily withdrawn from the market because of fears of liver toxicity. A more permanent ban of kava extract is currently being considered by the MCA. The last review compared the effectiveness of group therapy, individual therapy, couple therapy and relaxation therapy in patients with a diagnosis of cancer who were at risk of developing anxiety. The results indicated that all the four treatments were superior to placebo, with psycho-education and group therapy being the most effective.*[420]

Readers should note that there is a NICE guideline on anxiety in development.

▷ Economic evidence

No relevant economic evidence on treatment for anxiety in MS was identified.

▷ From evidence to recommendations

The recommendations made by the guideline developers depend largely on consensus because the limited evidence available was difficult to translate into useful guidance.

RECOMMENDATIONS

R154	Any person with MS whose function or happiness is being adversely affected by anxiety should be offered specialist assessment and management.	**D**
R155	In people with MS with marked anxiety, psychologically-based treatment should be offered.	**A**
R156	Pharmacological treatment of anxiety should be through using antidepressants or benzodiazepines. The Committee on Safety of Medicines (CSM) guidelines on the use of benzodiazepines (reproduced in the British National Formulary) should be used.	**D**

LOCAL IMPLEMENTATION POINTS

These need to specify:

- how to access specialist psychological advice
- how to access specialist psychiatric advice.

6.14 Swallowing difficulties

Dysphagia is a difficulty with swallowing which may cause choking and aspiration of food or liquid into the lungs. There have been few studies on its actual prevalence, let alone its importance and treatment. One study found 49 of 143 consecutively identified people to have dysphagia, and that it was more common in more dependent people and in those with evidence of brainstem dysfunction such as dysarthria – compensatory treatment strategies were successful in 46.[421] In a second study, 43% of 79 people with MS had dysphagia and about half of these did

* Kapezinski F, Lima MS, Souza JS, Schmitt R. Antidepressants for generalized anxiety disorder. *Cochrane Database Syst Rev* 2003;(2):CD003592, has been withdrawn for updating and was therefore unavailable for inclusion.

not complain of swallowing difficulties.[422] Similar associations were found, and any complaint of difficulty swallowing, or coughing on swallowing, was a specific but insensitive marker. In the Oxfordshire audit 18 of 150 people had swallowing difficulties at one point in time, 5 of 226 people developed problems with swallowing over nine months.[6]

Dysphagia (choking, difficulty in swallowing, aspiration of food or fluid into the lungs) is not only distressing but it also may cause chest infections and death. Furthermore, inappropriate management may lead to malnutrition if the person fails to take an adequate diet. It is an important area of concern and the problem is quite common and probably underdiagnosed.

Fortunately, many patients will only have short-term difficulties with swallowing, usually associated with an acute relapse or an infection. Early detection is particularly important in these circumstances, but management is often only needed for a few days or weeks.

Guidance needs to consider various issues:

- early detection, before complications arise
- management that is appropriate to the nature and severity of the problem
- pro-active management to reduce complications
- clinical consideration of the ethical and resource implications of percutaneous endoscopic gastrostomy (PEG) feeding.

▷ Evidence statement

No RCTs or CCTs in patients with MS were identified which assessed interventions for the treatment of swallowing difficulties.

Two systematic reviews, both of good quality, investigated interventions for the treatment of dysphagia in patients with acute stroke or neurological disease[423,424] (**Ia**). Both reviews compared PEG to nasogastric (NGT) feeding; there was some overlap in the studies included in these reviews. Both reported that PEG was superior to NGT for the various outcomes assessed, including a reduction in mortality.[423,424] One of these reviews also investigated a variety of other interventions for the treatment of dysphagia. This review found that swallowing therapy, treatment with nifedipine, nutritional supplementation and fluid supplementation were not more effective than control in the treatment of dysphagia.[424]

▷ Economic evidence

No relevant economic evidence on treatment for swallowing difficulties was identified.

▷ From evidence to recommendations

The guideline developers recognized that the published evidence only covered a few of the important issues concerned with feeding, swallowing and nutrition and so used consensus to guide most of the recommendations in this important area.

RECOMMENDATIONS

R157 Any person with MS who is unable to transfer from bed to chair independently, or who has any symptoms or signs of bulbar dysfunction such as any abnormality of eye movements, slurring of speech or ataxia, should be asked whether they have difficulties with chewing, or swallowing food or fluids (for example, coughing), and also whether they have altered their diet because of previous problems. **D**

R158 Any person with MS with any bulbar symptoms or signs, and any person with MS who has a chest infection, should have their swallowing assessed by a competent person (using a standardised swallowing test). **DS**

R159 People with MS who, on formal assessment, have an abnormality of swallowing should be further assessed by a specialist speech and language therapist. Advice should be given on specific swallowing techniques, and on adapting food consistencies and dietary intake. Further diagnostic assessment (for example, by videofluoroscopy) should be undertaken if: **D**

- first-line therapy and advice are ineffective
- a specific objective of the investigation can be identified.

R160 Any person with MS who has difficulty swallowing for more than a few days should be assessed by a neurological rehabilitation team, to review the need for: **D**

- adjustments to or provision of seating that will increase ease and safety of swallowing and feeding
- chest physiotherapy
- short-term use of nasogastric tube, especially if recovery is anticipated.

R161 Any person with MS who has swallowing difficulties for more than one month should have his or her weight or nutritional status checked on a monthly basis (using a validated nutritional measure if needed). Dietary intake should be reviewed if there is continuing weight loss or evidence of malnutrition. **D**

R162 If PEG feeding is anticipated as being a likely future option, discussions with the person with MS should be commenced at an early stage and their wishes documented. **D**

R163 If swallowing difficulties persist, a PEG tube should be considered if any of the following occur:

- recurrent chest infections
- inadequate food and/or fluid intake
- prolonged or distressing feeding
- nasogastric tube *in situ* for over one month. **D**

R164 If PEG placement is indicated and agreed, the PEG tube should be inserted by a suitable specialist. Before the person with MS is discharged from hospital, full training should be given to any family members and carers who are going to be involved in feeding. **A**

LOCAL IMPLEMENTATION POINTS

These need to:

- produce brief guidance for health workers in contact with people with MS on warning signs of bulbar dysfunction and screening questions for swallowing problems
- agree which formal swallowing test should be used locally

- specify who may request and undertake additional investigative assessments
- specify how PEG tubes are requested, serviced and replaced
- agree who may train carers about PEG feeding
- specify funding arrangements for all equipment and feeds associated with PEG feeding.

6.15 Speech difficulties

Slurred speech (dysarthria) is another problem in people with MS where the prevalence and importance is little researched. In Oxfordshire the prevalence of speech difficulties was 11 of 150, but only one person of 226 developed a new speech difficulty over nine months.[6] A survey in Sweden found that 44% of people with MS experienced speech or voice difficulties,[425] and another study in Sweden found a prevalence of dysarthria of 51% in 77 people, and that a clinical dysarthria test was sensitive.[426] The survey in the USA found that 23% had speech or communication difficulties.[278] Undoubtedly a significant number of people have mild problems, and some people have problems so severe that communication is limited or prevented. This will usually be in people with severe disability, but sometimes it will be specifically associated with cerebellar disturbance and ataxia.

Other impairments may affect communication. Language disturbance (aphasia) is rare, although it can occur with a relapse leaving mild long-term word-finding difficulties. Cognitive losses can markedly affect communication. The voice can also be affected, causing changes in volume or pitch. Sometimes several impairments will combine to affect communication.

Guidance is needed to encourage recognition of the difficulty and its implications with appropriate management being followed.

▷ Evidence statements

No RCTs or CCTs in patients with MS were identified which assessed interventions for the treatment of speech difficulties.

Four systematic reviews assessed the effectiveness of various interventions for speech difficulties in patients with Parkinson's disease and/or stroke[427–430] (**Ia**). Three reviews investigated the effects of different forms of speech and language therapy. The first concluded that it was impossible for the review to determine whether formal speech and language therapy is more effective than informal support.[427] The second, which included only patients with Parkinson's disease, found that all trials reported a significant positive effect of speech and language therapy on dysarthria on a variety of outcome measures. However, this review concluded that it is unsafe to draw firm conclusions regarding the efficacy of speech and language therapy considering the small number of patients examined and the methodological flaws in the included studies.[429] The third review also found that the limitations of the studies in terms of methodological inadequacies and small numbers of participants meant that it was not possible to draw conclusions regarding the efficacy of one form of speech and language therapy over another.[430] The fourth review investigated the effectiveness of various forms of pharmacological therapy in the treatment of patients with aphasia due to stroke.[428] This review found that there was some evidence that piracetam was more effective than placebo in the treatment of aphasia. For other interventions investigated (bifemelan, pirbedil, bromocriptine and idenone) the data was not in an appropriate format for analysis. No significant beneficial effects of treatment with dextran 40 were found.

▷ Economic evidence

No relevant economic evidence on treatment for speech difficulties was identified.

▷ From evidence to recommendations

Although four systematic reviews met inclusion criteria these did not provide conclusive evidence on any of the interventions investigated; consensus was therefore used to agree the recommendations.

RECOMMENDATIONS

R165 Any person with MS who has dysarthria sufficient to affect communication with people outside the home or over the phone, and any person who is concerned about their speech sound or clarity, should be assessed and given advice by a specialist speech and language therapist. **B**

R166 Any person with MS whose ability to communicate is affected significantly by dysarthria should be taught techniques to improve and maintain speech production and clarity; tuition should be provided by a specialist speech and language therapist, working with any other members of the neurological rehabilitation service who are involved. **D**

R167 Any person who continues to have difficulties in communication should be considered for, and if appropriate taught the use of, alternative non-verbal means of assisting with or replacing speech. **D**

R168 Any person with MS who cannot communicate effectively should be assessed by a specialist speech and language therapist for an augmentative aid to communication, which should then be provided as soon as possible. The family members, carers and other frequent communicators with any person with MS who has significant communication difficulties should have discussions with the speech and language therapist on how best to help the person communicate. **D**

LOCAL IMPLEMENTATION POINTS

These need to specify:

- which speech and language therapist should see people with dysarthria
- who may assess for and recommend augmentative equipment and adaptive technology to communication
- funding arrangements for augmentative aids to communication (AACs).

6.16 Sexual dysfunction

MS almost always affects the spinal cord, and disturbance of sexual functions is a common concomitant of any spinal cord damage. The precise frequency of direct sexual dysfunction is unknown. In the Southampton study, 55% of people with MS reported a change for the worse in their sexual relationships, although only 77 (44%) reported a change in their emotional relationship with a partner and 19 of these changes were reported as improvements.[323] Another

study suggested that about 70% of people with MS had sexual dysfunction compared with 40% in non-neurological disabling conditions and 12% in the general population.[431] This study suggested that neurological damage was the single most common primary cause of sexual dysfunction. Nonetheless it must also be recognised that sexual behaviour will also be affected by many other impairments such as pain, sensory dysfunction, motor impairments, bladder dysfunction, bowel dysfunction, mood disturbance etc. Furthermore, physiological sexual dysfunction must always be considered in the much wider context of sexual behaviour and relationships. This section not only covers erectile dysfunction and disorders of sexual arousal mechanisms, but also covers wider aspects of sexual behaviour and social relationships that are probably of much greater importance.

Guidance needs to reflect the complexity of the problem, ensuring that problems are detected and then analysed fully so that targeted effective intervention is given where appropriate, while also ensuring that specific treatments are not given inappropriately.

▷ Evidence statements

No RCTs or CCTs in patients with MS were identified which assessed interventions for the treatment of sexual dysfunction.

Four systematic reviews which included men with erectile dysfunction were identified.[432–435] All were of good quality (**Ia**). Two reviews examined the effects of sildenafil (Viagra), one looked at yohimbine (a herbal preparation) and the fourth looked at a variety of interventions including both yohimbine and sildenafil. There was overlap in the trials included in these reviews. All three reviews which looked at the effectiveness of sildenafil reported that it was significantly better than placebo in the treatment of sexual dysfunction in men.[432,433,435] One review also reported that sildenafil was effective in all subgroups investigated.[433] Both the review which looked exclusively at yohimbine[434] and the review which also looked at a variety of other treatments[432] found that yohimbine was significantly better than placebo in the treatment of erectile dysfunction. The side effect profile of both drugs was reported to be good. The review which looked at a large variety of interventions for the treatment of erectile dysfunction found that inconsistent or lack of clinically relevant reported outcomes together with a lack of long-term follow-up or comparisons with active treatments and selection bias of enrolled patients limited study results.[432]

▷ Economic evidence

No relevant economic evidence on treatment for sexual dysfunction was identified.

▷ From evidence to recommendations

The only evidence available related to pharmacological treatments, but the GDG recognised that sexual activity and function depended upon far more than the neurophysiology of sexual structures.

The recommendations, agreed by consensus, therefore cover a much wider range of important issues.

RECOMMENDATIONS

R169 Men with MS:

- should be asked whether they experience erectile dysfunction (relative or absolute) and, if so, whether it is of concern **D**
- who have persisting erectile dysfunction and who do not have contraindications should be offered sildenafil 25–100mg **A**
- who do not respond to sildenafil should be assessed for the general and specific factors that might cause or worsen erectile dysfunction and that are amenable to treatment (such as depression, anxiety, vascular disease, diabetes and taking medicines that may cause erectile dysfunction). Other specific treatments such as alprostadil or intracavernosal papaverine should then be considered. **D**

R170 Women with MS should be asked whether they experience sexual dysfunction (such as failure of arousal or lubrication or anorgasmia) and, if so, whether it is of concern. **D**

R171 Women with sexual dysfunction should be assessed for the general and specific factors that might cause or worsen sexual dysfunction and that are amenable to treatment (such as depression, anxiety, vascular disease, diabetes and taking medicines that may cause sexual dysfunction). **D**

R172 Every person (or couple) with MS should be asked sensitively about, or given the opportunity to remark upon, any difficulties they may be having in establishing and/or maintaining wanted sexual and personal relationships; they should be offered information about locally available counselling and supportive services. **D**

R173 Every person (or couple) with persisting sexual dysfunction should be offered the opportunity to see a specialist (with particular expertise in sexual problems associated with neurological disease) and offered, as appropriate, advice on lubricants and the use of sexual aids, and other advice to ameliorate their sexual dysfunction. **D**

LOCAL IMPLEMENTATION POINTS

These need to specify:

- urologist or other doctor with expertise in male sexual dysfunction
- gynaecologist or other doctor with expertise in female sexual dysfunction
- all local services available to individuals and couples with difficulties in establishing and maintaining personal and sexual relationships for whatever reason, and especially any that have experience of neurological diseases.

6.17 Pressure ulcers

A pressure ulcer (pressure sore or decubitus ulcer) is an area of broken skin that is secondary to unrelieved pressure on the skin, often exacerbated by slight trauma, for example when being moved. A pressure ulcer may range from a minor break to very large deep areas of dead tissue extending over many square centimetres and down to bone. Once present they can be difficult to heal, and can cause general malaise and worsening of most impairments, and they carry a risk of generalised or localised infections. Many people with MS are at high risk of developing a pressure ulcer because they may have, for example, limited mobility, impairment of sensory

functioning, and reduced cognitive function or undernutrition. In an audit of 226 people followed over 10 months, 10 people experienced 14 pressure ulcers, three acquiring them during hospital admission.[6] Surveys and formal reports have repeatedly emphasised the costs of pressure ulcers both to the health service and to the patient with the ulcer.[436] Prevention must be a high priority yet they continue to occur with monotonous regularity. This section covers both prevention and treatment.

Readers should be aware that a NICE guideline on pressure ulcer management is currently in development.

▷ Evidence statement

All evidence statements for pressure ulcers are level **Ia**.

Monitoring for the development of pressure ulcers – Two reviews were identified which looked at the assessment of pressure ulcers.[437,438] The first review found great variation in the estimates of predictive validity both across scales and between assessment of the same scale, and that ultimately none of the scales appears to be unambiguously superior.[437] The second reported similar findings, concluding that no scale appears to be more accurate in identifying those patients at most risk from developing pressure sores although the Braden scale has been the most extensively tested.[438] This review also reported that there was no evidence that risk assessment scales are effective in reducing the incidence of pressure sores or that they improve preventive care.

Intervention to reduce the risk of pressure ulcers – Two reviews assessed the effectiveness of interventions to reduce the risk of pressure ulcers. Both reviews assessed the effectiveness of pressure-relieving interventions. Both reviews found that higher specification foam mattresses were more effective than ordinary foam mattresses in reducing pressure ulcer incidence in patients at risk of pressure ulcer.[437,439] The first review reported that the relative merits of higher-tech constant pressure and alternating pressure beds and mattresses were unclear.[439] However, the second found that these were more effective than standard hospital mattresses in preventing pressure ulcer. This review also reported that some types of large-cell alternating pressure devices (cell diameter 10cm or greater) may be more effective than simple, low-pressure mattresses, that low-air-loss beds are effective in preventing and treating pressure ulcer compared with foam mattresses and that there was no evidence to indicate the degree to which manual repositioning is effective, or what the optimum turning regime would be.[437]

Intervention for the treatment of pressure ulcers – Five reviews assessing the effectiveness of treatments for pressure ulcer met inclusion criteria.[437,439–442] Two reviews, both of which also looked at the prevention of pressure ulcers, looked at the effectiveness of pressure supports. The first review found that standard hospital mattresses are outperformed by a range of foam-based, low-pressure mattresses and overlays, and also by 'higher-tech' pressure-relieving beds and mattresses, in the treatment of pressure ulcer. It also found that some types of large-cell alternating pressure devices may be more effective than simple, low-pressure mattresses, that low-air-loss beds are more effective in treating pressure ulcer than foam mattresses, and that there is no evidence to indicate the degree to which manual repositioning is effective, or what the optimum turning regime would be.[437] The second review reported that air-fluidised supports and low-air-loss beds may improve pressure sore healing rates and that seat cushions have not been adequately evaluated.[439]

Two reviews looked at the effectiveness of topical agents for the treatment of pressure ulcers, one of these also looked at the effectiveness of various different dressings and compared dressings to topical agents. The first review found that there was not sufficient evidence to draw conclusions regarding the effectiveness of any topical agent. The second review reported that there was no significant difference in healing rates between topical agents and placebo. However, it found that topical hydrogel promoted healing more than hydrocolloid dressing, and that topical polysaccharide beads were less effective than calcium alginate dressings. It found good evidence (five RCTs) to suggest that hydrocolloid dressings were preferential to traditional therapies (saline gauze and antiseptics) for the treatment of pressure ulcer. Comparisons between dressings were unable to show any statistically significant difference in healing rates.

The fifth review looked at the effectiveness of therapeutic ultrasound, electrotherapy and electromagnetic therapy for the treatment of pressure ulcer.[441] This review found no evidence to support the use of ultrasound or electromagnetic therapy. It reported some evidence in favour of electrotherapy in the treatment of pressure ulcer, but highlighted that this evidence came from three small studies and so should be interpreted with caution.

One RCT assessed the effectiveness of providing personalized information and advice to patients with the aim of reducing the incidence of pressure ulcer and falls. This study found a negative effect of the intervention with an increase in the reports of pressure ulcer and falls in the group receiving information.[443]

▷ Health economic evidence on interventions to treat skins breaks and pressure ulcers

No formal economic evaluations of any interventions involving people with MS were identified. A systematic review in 1995 concluded that there was little evidence on the cost-effectiveness of methods of prevention or treatment (not MS specific).[437] The pre-NICE guideline on the risk assessment and prevention of pressure ulcers does not consider the cost-effectiveness of interventions.[444] A report by Touche Ross in 1993 estimated the costs of preventing and treating pressure ulcers in a 600-bed general hospital at between £600,000 and £3 million per year.[436] A recent pilot study has attempted to estimate the cost-effectiveness of a potential prevention programme *vs* standard care of geriatric inpatients with pressure ulcers. This study concluded that the prevention programme was the dominant strategy reducing both the incidence of pressure ulcers and the costs of care. This study was of poor quality and is of limited relevance to the population of people with MS so it is *not* included in the evidence tables.[436]

RECOMMENDATIONS

R174 Every person with MS who uses a wheelchair should be assessed for their risk of developing a pressure ulcer. The individual should be informed of the risk, and offered appropriate advice. **D**

R175 Every person with MS who uses a wheelchair daily should be assessed by a suitably trained person, whenever they are admitted to hospital (for whatever reason), for their need for pressure-relieving devices and procedures. The assessment should be clinical,

specifically taking into account the risk features associated with MS, and not simply the recording of a pressure ulcer risk score; it should lead to the development and documentation of an action plan to minimise risk, including:

- optimisation of nutritional status **D**
- provision of suitable equipment **B**
- documentation of agreed manual handling techniques. **D**

R176 Every person with MS who is provided with a wheelchair by a statutory organisation (NHS or social services), or whose wheelchair seating is being reassessed, should specifically be considered for pressure-relieving procedures and devices – not only in the wheelchair, but in all other activities, especially transfers and sleeping. **D**

R177 For every person with MS considered to be at risk on their bed (in hospital or in the community):

- an appropriate specialist mattress should be provided wherever they are lying down **A**
- regular turning should not be depended upon as a policy for preventing pressure ulcers **A**
- the skin areas at risk should be inspected to ensure adequate protection is being provided. **D**

R178 If a pressure ulcer occurs, it should be considered an adverse event worthy of investigation, and advice should be sought from a specialist service. **D**

R179 Any person with MS who develops a pressure ulcer should be nursed on a low-loss mattress (while in bed). **A**
The ulcer should be dressed according to appropriate local guidelines. **D**

(See also the NICE Clinical Guideline on prevention of pressure ulcers.[444,445])

LOCAL IMPLEMENTATION POINTS

The local services will need to consider:

- procedures and funding mechanisms to ensure that specialist pressure-relieving devices are made available promptly to people needing them wherever they are
- who has appropriate training to assess for risk of pressure ulcer
- which dressings are to be used locally
- which team specialises in prevention and management of pressure ulcer
- mechanisms for reporting the development of pressure sores and investigating why they occurred.

6.18 Other treatments including complementary therapies

Most people with MS take an active interest in managing their illness. This includes the use of unlicensed interventions that are not generally recognised by health professionals as influencing the disease process or ameliorating specific symptoms. A survey of 117 people in Cardiff showed that people with MS are high users of non-prescription medicines, and that these were usually purchased from sources where no health professional was available to give advice.[446] These interventions are often referred to as alternative or complementary therapies. The stated

or expected effect of these treatments may not be clear. Where a rationale does exist it should be recognised that there may be an overlap between alternative therapies taken in the belief that they affect the disease process, and those taken in the belief that they ameliorate the effects of the disease in some way. Some benefit may arise through placebo mechanisms but for the individual this may be an important effect.

Some of these treatments may cost the person with MS substantial sums of money, or expose them to risk. Further information on complementary and alternative medicines and other lifestyle recommendations are available from various MS support organisations. It should also be recognised that the boundaries between complementary/alternative and orthodox treatments varies between countries, cultures, over time and even between members of the health care professions. This section covers a variety of interventions that are used in non-specific ways, usually to ameliorate several symptoms. It includes both standard interventions and those that may be considered alternative.

The aims of the recommendations are similar to those concerning all treatments, namely to ensure that people with MS:

- are facilitated in pursuing any treatments that they wish to
- are given or directed to any information that may be available concerning any proposed treatment
- are specifically recommended to consider risks, cost and benefits for any treatment
- keep the health care professionals aware of all treatments being pursued.

▷ Evidence statement

One systematic review of 12 RCTs assessed the efficacy of a variety of complementary and alternative therapies used by people with MS[447] (**1b**). The specific therapies addressed in the review were nutritional therapy (n = 4), Feldenkrais bodywork (n = 1), reflexology (n = 1), magnetic field therapy (n = 2), neural therapy (n = 1) and psychological counselling (n = 2). It reported some evidence to suggest some benefit of nutrition therapy, linoleic acid (n = 3) and fish oils (n = 1) for the physical symptoms of MS. Likewise, magnetic field therapy and neural therapy also appeared to have a short-term beneficial effect on physical symptoms. The results also showed that massage/bodywork and psychological counselling appear to improve depression, anxiety and self-esteem. However, the strength of evidence for any of the therapies was limited as many of the trials suffered from significant methodological flaws. One further CCT that also examined reflexology reported no effect on a range of symptoms, and although symptoms scores improved slightly during treatment this was not maintained at follow-up[448] (**IIa**).

Two small randomised crossover trials examined the effectiveness of body cooling for heat sensitive patients[449,450] (**Ib**). The first placebo-controlled trial reported beneficial effects on three out of four of the indices tested, namely visual acuity, timed walk test and muscle strength, but no effect on coordination.[450] However, the length of follow-up was not reported and so it is impossible to determine whether these effects were transitory. The second trial reported no significant effects on either tympanic temperature decreases or on any of twelve performance tests.[449]

Three RCTs assessed the effectiveness of different exercise programmes for increasing the fitness and well-being of individuals with MS[451,452,453] (**Ib**). The first that examined the effectiveness of a water exercise training program found positive effects upon pain, energy, social and sexual

function as assessed by the MSQOL-54, and tension, fatigue and vigour, assessed by the POMS-SF.[452] However, the second RCT that examined an exercise programme using a leg cycle ergometer found no improvement in either the physical fitness indices assessed or grades of fatigue, as assessed by the Fatigue Severity Scale.[453] The last RCT examined the utility of lectures on exercise philosophy combined with nutrition, stress management and an individualised exercise programmes.[451] The results showed no effect on either graded exercise time or on EDSS scores.

Two RCTs (**Ib**) and one CCT (**IIa**) investigated the effects of antidepressants.[454,456] The antidepressants assessed included imipramine, lofepramine combined with phenylalanine, and tranylcypromine. None of these trials reported an overall beneficial effect of the intervention, although one of the RCTs reported some beneficial effect. This good quality RCT found a greater improvement on the Chalder fatigue scale score in those receiving lofepramine combined with phenylalanine compared to those receiving placebo, however, it found no effect of treatment for any of the other five outcomes investigated.[454] Side effects were relatively minor but occurred more frequently in the intervention group.

Two further RCTs (**Ib**) and two CCTs (**IIa**) examined the interventions of t'ai chi, Chinese medicine, relaxation training and a multimodal intervention program. The results of the CCT assessing t'ai chi reported significant changes in patients' assessment of their symptoms at three month follow-up.[457] One CCT of a multimodal intervention program reported significant effects on five of the eight areas assessed. These included two measures of list learning and memory, improved BDI scores, one measure of grip strength and one of tactile sensitivity[458] (**IIb**). One of the RCTs looked at relaxation training and biologically orientated imagery treatment.[459] The results showed a significant improvement on state anxiety, but not on trait anxiety or the other three tests examining mood or health states. The last RCT compared the efficacy of traditional Chinese medicine combined with Western medicine to treatment with Western medicine alone. The results indicated beneficial effects upon remittance of symptoms.[460]

▷ Economic evidence

There are no economic studies of complimentary therapies in MS.

▷ From evidence to recommendations

This section, and the evidence in it, covers a wide range of potential treatments that are considered or used by a large number of people. The evidence does not support any particular treatment, though conversely it does not show that any are specifically harmful. The GDG felt it was important to steer readers towards any available information, while also making it clear that it was insufficient to recommend use or non-use. The GDG was also especially concerned that people with MS were encouraged to inform professionals about any treatments being used so that potentially harmful interactions or effects could be avoided.

RECOMMENDATIONS

R180 People with MS should be informed that there is some evidence to suggest that the following items might be of benefit, although there is insufficient evidence to give more firm recommendations: **A**

- reflexology and massage **A**
- fish oils **A**
- magnetic field therapy **A**
- neural therapy **A**
- massage plus body work **A**
- t'ai chi **A**
- multi-modal therapy. **A**

R181 A person with MS who wishes to consider or try an alternative therapy should be recommended to evaluate any alternative therapy themselves, including the risks and the costs (financial and inconvenience). **D**

R182 A person with MS should be encouraged to discuss any alternative treatments they are considering, and to inform their doctors and other professionals if they decide to use any. **D**

LOCAL IMPLEMENTATION POINTS

These should cover:

- how and where people may find more information about, and access/purchase, most common alternative therapies
- which alternative therapies are going to be supported by health funds, if any.

7 Monitoring quality: audit and governance

Table 7 Suggested measures for auditing MS services in the NHS

Key priority for implementation	Criterion (data items needed)	Exceptions (interpreting the data)	Definitions (and other comments)
1. Specialist neurological and neurological rehabilitation services should be available to every person with MS, when they need them. This is usually when they develop any new symptom, sign, limitation on activities or other problem, or when their circumstances change.	The presence (or not) of a specific contract between the health commissioning organisation (primary care trust or local health board) and: • specialist neurology services • specialist neurological rehabilitation services and the quantity of service delivery with a currency to be agreed but probably for a defined population on a yearly basis: • number of new cases of MS seen by neurology service • number of confirmed cases seen by neurology (for disease diagnosis and treatment, including interferon beta) • number of people seen by neurology for methylprednisolone treatment • number of new cases seen by neurorehabilitation service • number of cases seen (excluding new) • equipment provided or maintained.	There are no exceptions. These data are not currently collected, and there are no data to predict a likely caseload and so initial data will be to establish a baseline that could be compared with known epidemiological figures on incidence and prevalence. The neurology rate of seeing confirmed cases is likely to be higher where neurorehabilitation services are limited. The effects on other services of the regular monitoring of patients in the risk-sharing scheme are unpredictable.	The neurology contract may be split to cover the specific work associated with the risk-sharing scheme, and the remaining work.

continued

Table 7 Suggested measures for auditing MS services in the NHS – *continued*

Key priority for implementation	Criterion (data items needed)	Exceptions (interpreting the data)	Definitions (and other comments)
2. An individual who is suspected of having multiple sclerosis should be referred to a specialist neurology service and be seen rapidly within an audited time. The individual should be seen again after all investigations necessary to confirm or refute the diagnosis have been completed (also rapidly* within an audited time).	The time in weeks • from referral with diagnosis of 'possible MS' to being seen in a specialist neurology clinic and, in those requiring further investigation, the time in weeks • from being seen in the neurology clinic to being seen again after any investigations organised.	There are no exceptions. These data are not currently collected, and so initial data will be needed to establish a baseline that could be compared to other timescales suggested in other conditions. Any standard set should recognise that: • some people with MS will need urgent investigation because serious alternative disease (for example, spinal cord compression in case of transverse myelitis) is possible, whereas • other people with MS may have had symptoms for years and may not be overly concerned, but • in general, uncertainty is itself stressful.	Some people will be diagnosed as definitely having MS, a small number will be diagnosed as definitely having some other condition (eg stroke), a large number will not achieve a diagnosis of any alternative condition and the majority of these will be experiencing somatisation (symptoms associated with no known disease, possibly related to emotional dysfunction).
3. Every health commissioning organisation should ensure that all organisations in a local health area agree and publish protocols for sharing and transferring responsibility for and information about people with MS, so as to make the service seamless from the individual's perspective.	The presence (or not) of agreed protocols for identifying and sharing responsibility • between different parts of health organisation, and • between health and social services. The time in weeks between initial contact about a problem with any service, including community NHS and social services, and contact with the 'final' service that can and does take responsibility for resolving the problem. The number of onward referrals made by services after initial contact before making contact with the final effective service.	There are no exceptions. These data are not currently collected, and so initial data will be needed to establish a baseline. have a protocol. Any standards set should: • focus on areas of concern locally (to people with MS and/or service providers and/or commissioners) initially • recognise that generic protocols (for example, for urinary incontinence) may be totally appropriate, and that not all protocols need to be MS-specific.	The presence or absence of protocols should be easily established, but it will be difficult to agree what protocols should exist as it would be unrealistic for every eventuality to Protocols could be given to every person with MS on making contact with the service to help them help themselves. It will be difficult to agree when the person has reached the final service. However, a method of people with MS collecting these data has been used and found to be effective, and so this is an achievable process.

Table 7 Suggested measures for auditing MS services in the NHS – *continued*

Key priority for implementation	Criterion (data items needed)	Exceptions (interpreting the data)	Definitions (and other comments)
4. All services and service personnel within the health care sector should recognise and respond to the varying and unique needs and expectations of each person with MS. The person with MS should be involved actively in all decisions and actions.	The number of complaints made to each service organisation that might reflect a failure to be responsive and to involve the person with MS actively.	There are no exceptions. These data are not currently collected, either specifically in relation to people with MS or specifically in relation to a service being responsive and patient-centred. It may not be appropriate to set a standard, and current NHS policies on complaints and the improvement of services should use the data.	As this standard should apply to all people making contact with NHS services (and other statutory services), it may not be necessary to separate out people with MS. A patient-centred audit of services would be able to monitor this without involving formal complaints.
5. Health service professionals in regular contact with people with MS should consider in a systematic way whether the person with MS has a 'hidden' problem contributing to their clinical situation, such as fatigue, depression, cognitive impairment, impaired sexual function or reduced bladder control.	No data can realistically be collected on a routine basis. However, many specialist services may wish to develop and use a formal structured assessment protocol (centres participating in the risk-sharing scheme will do so) and for these services the data to collect would be: • the number of people with MS who had a formal, documented (that is, able to be found in the notes) assessment on first contact in any episode.	These data are not currently collected by any service, and so initial data will be needed to establish a baseline for any service doing this. The data should only refer to an agreed initial 'screening' assessment aimed to detect major problems needing further attention An episode is a series of ongoing attendances, all of which concern a specified programme of care, and does not include monitoring visits.	Any specialist service that decides to use a formal structured approach to assessment should monitor its use.

continued

Table 7 Suggested measures for auditing MS services in the NHS – *continued*

Key priority for implementation	Criterion (data items needed)	Exceptions (interpreting the data)	Definitions (and other comments)
6. Every person with MS who has been seen by a specialist neurological or neurological rehabilitation service should be informed how to make contact with the service when no longer under regular treatment or review. The individual should be given guidance on when such contact is appropriate.	The presence (or not) of a formal procedure for responding to self-referral by someone with MS in the: • neurology service • neurorehabilitation service. The time taken between initial contact by person with MS, and initial clinical contact by the service.	There are no exceptions. These data are not currently collected, and so initial data will be needed to establish a baseline. It is important to recognise that 'initial clinical contact by the service' is: • more than a simple routine letter acknowledging the contact, but • not necessarily seeing the person in a clinic or their own home, and • implies a reasoned, personal response with action as necessary.	Often the response needed may be no more than reassurance or the provision of information. Some – perhaps many – centres already offer this level of service but probably in an intermittent and variable way.
7. The commissioning health organisation should require all health care services including community services: • to report every pressure ulcer that occurs in a person with MS, and • to undertake and report an investigation into what could have been done to avoid its occurrence, and • to agree actions that should reduce the risk of the same situation leading to a pressure ulcer.	Presence (or not) in all health service organisations of a procedure to identify and report every new (and existing) pressure ulcer. Presentation of reports on each pressure ulcer identified in a person with MS. Count of a) new and b) prevalent pressure ulcers in people with MS. Presentation of an action plan derived from the report.	There are no exceptions. Data on pressure ulcers are not currently collected in relation to people with MS, and so initial data will be needed to establish a baseline. Ideally none should occur, but in reality some will occur. Not every pressure ulcer represents a direct failure of the health care system. Some will reflect failures in other organisations (for example, social services), others will reflect the choices of the person with MS and a few may be 'inevitable'.	Properly executed, this audit could save huge resources but it requires continued vigilance by all staff to detect and report pressure ulcers, which will be inhibited by any suggestion that the inquiry will attribute blame to any individual or organisation. Pressure ulcers may be first recorded or detected in one organisation that was not responsible for the person at the time of occurrence, but once detected a full investigation should still be initiated.

*The Guideline Development Group debated the meaning of the word 'rapidly'. In this context, it is taken to mean that the exact time will vary according to clinical need but should, in the opinion of the development group, be no more than six weeks from referral to being seen by a neurologist, and a further six weeks until any necessary investigations are completed.

8 Research questions

As the tables of evidence and the list of references show, there is a large volume of research relevant to the guidelines available. Despite this, the great majority of recommendations are graded D – dependent on consensus – although this is partly a consequence of the system of grading evidence (which emphasises only one research method – RCTs) and translating this to the strength of the recommendation. Although a few might become more highly graded if evidence from other neurological conditions, notably stroke, were to be included, it is nonetheless obvious that there is a great lack of evidence relevant to day-to-day clinical practice, particularly relating to the long-term effects of treatments. This section of the document puts forward some research priorities that arise from the work undertaken to develop the national clinical guidelines on MS.

Choosing research priorities is not easy. Most people, when asked, will focus on relatively specific questions that are undoubtedly important for particular patients, but do not necessarily address questions that have a large general impact. This problem has been discussed in relation to rehabilitation research priorities.[6] Within the field of MS there are hundreds of potential specific research questions such as what dose of intramuscular botulinum toxin is effective in the biceps to control the development of contractures, do silver-coated catheters reduce morbidity if used long term, and is exercise specifically effective at reducing fatigue?

Those here have been chosen using the following criteria:

- the answer may benefit a large number of people with MS
- the process consumes significant resources.

The research priorities are given in no particular order.

8.1 Epidemiology of relapses, impairments and activity limitations

The epidemiology of multiple sclerosis has been well studied in relation to the aetiology of the disease. There are many studies on the incidence and prevalence of MS in different populations, in different parts of the world, in those who migrate, and in genetically related people. These studies have given some clues as to the cause of MS – as was the intention.

There have been some studies on the prevalence of the consequences of the disease, but these are relatively rare. They have used crude measures of impairment or disability, and they are often not fully representative. There have been no significant studies on the incidence of specific consequences of the disease, such as how many people in a given population will have a relapse each year. Indeed there is no agreed definition of a relapse, let alone studies on the reliability of its diagnosis. There are few studies investigating the mechanisms linking progressive impairments to limitations in activities and participation.

The lack of any firm data on the incidence, prevalence or severity of almost all impairments and activity limitations is one major problem in planning services, and in recommending service organisation. How many people have a relapse each year? How many people need a new wheelchair each year? How many people temporarily need a wheelchair? How many people have continuing faecal incontinence? How many people require more than four hours personal care each day?

Furthermore there is relatively little good information on the economic consequences of the disease. How many people have to stop work? How many family members have to stop work on account of the disease? How much money does the NHS spend on managing the consequences of MS?

The current cost-sharing scheme has highlighted the extreme poverty of useful information available to model the possible cost-effectiveness of expensive disease-modifying drugs. The scheme will not generate any information because it is not based on an epidemiologically sound sample.

This research recommendation does not relate specifically to any recommendation within the guidelines but without the information this recommendation should deliver, health commissioners will be unable to make estimates about the resources needed to enable any of the recommendations.

RECOMMENDATION

R183 There should be a prospective study on an epidemiologically sound defined population to establish reasonable estimates of:

- the frequency of relapses sufficient to cause increased limitation on activities
- the prevalence and yearly incidence of the most common impairments described in this guideline document
- the prevalence and yearly incidence of the most common limitations on activity including work described in this document
- the direct and indirect costs of the condition and how they relate to levels of limitation on activity, including not only NHS direct costs but all direct costs.

8.2 Diagnosing multiple sclerosis

There is much evidence that the MRI brain scan is abnormal in most people with MS. Further, it can indicate continuing disease activity in the absence of new impairments and this disease activity is dramatically reduced by disease-modifying drugs. There is also reasonable evidence that an MRI scan can predict reasonably the likelihood of MS developing in someone with an isolated first attack of optic neuritis.

However, the utility of MRI scans in clinical practice (as opposed to as part of research) is still not supported by much evidence, although major resources are involved in their use. Should MRI scans be offered to everyone, even if the diagnosis is clinically confirmed? Should second or subsequent MRI scans ever be undertaken?

Moreover the utility of other ancillary investigations is also unknown (given the predominance of MRI scanning). Is CSF examination ever helpful in confirming the diagnosis? When are visual evoked potentials useful?

This research recommendation relates primarily to recommendation R29 and may influence key recommendation 7 (Section 7).

RECOMMENDATION

R184 There should be a prospective study on an epidemiologically sound population to investigate the most cost-effective protocols for investigating people presenting with (potential) MS to establish:

- the sensitivity and specificity of MRI scanning in people with different levels of clinical diagnostic certainty
- the role of other investigations in confirming or positively excluding the diagnosis of MS
- the prognostic value of MRI scan information over five years.

8.3 Rehabilitation assessment protocols

In sections 5 and 6 there is great emphasis upon initial identification of specific impairments or activity limitations. This is emphasised because specific treatments can only be given if a specific difficulty is recognised. In addition, it is important to have as good an understanding of a situation as possible before initiating interventions, if only to avoid doing harm (and usually to guide one on the best course of action). Yet, as has also been emphasised, people with MS can have one or more of a large range of problems, and both the person with MS and the clinician will rapidly become fatigued and fed up by long, detailed assessments of each potential problem.

Consequently, research is needed on the best way to approach the identification (detection) of impairments and activity limitations. This research area is *not* concerned with developing measures; it concerns the development of short, simple protocols or 'data collection tools' for identifying possible areas of need, screening for referral on to other specialist/non-specialist staff. These protocols would be designed for use by any person making contact with the person with MS, with the priority being members of the neurology and neurological rehabilitation services. The protocols should also extend possibly to monitoring people in a non-threatening and efficient way when no longer in routine contact with any service.

RECOMMENDATION

R185 There should be a programme of research to develop and evaluate protocols, procedures or data collection tools that can be used by any profession to:

- identify the probable presence of most common impairments
- approximately quantify activity performance in personal and household activities of daily living
- identify areas of activity limitation that are present in people with MS.

8.4 Specialist neurological rehabilitation services

The guidelines recommend repeatedly that people with MS with any impairments or limitations on activities or social participation should be seen by a specialist neurological rehabilitation service. The recommendation is based upon some MS-specific evidence, but primarily draws upon evidence from stroke and other conditions. There are currently few specific neurological rehabilitation services in England and Wales, and certainly a completely inadequate level of services to meet even a small percentage of the needs of people with MS (let alone other neurological conditions).

Consequently this recommendation will have a major impact upon the allocation of health resources, partially through reorganisation of current resources but mainly through provision of new services. The evidence suggests that this may well be an effective and efficient use of resources – the evidence from stroke suggests that better outcomes may be achieved with similar or possibly less resources. Ultimately the cost of these services may well still be less than the cost of interferon beta. However it is notable that even strong evidence in favour of stroke units has not affected health commissioners much, and health commissioners may require more direct evidence.

Given the differing circumstances around England and Wales, with some areas being urban, others rural, and with some areas preferring outpatient and others inpatient services, it is probably best not only to investigate whether specialist services are effective but also whether one pattern of delivery is better than another. This research should certainly also investigate the health economic aspects of any service, and it would be important to consider whether there are any disbenefits for people with MS.

RECOMMENDATION

R186 A programme of research into the relative costs (direct and indirect) and benefits (direct and indirect) should be undertaken comparing:

- current rehabilitation practice with rehabilitation given by a specialist neurological rehabilitation service
- primarily inpatient with primarily outpatient or home-based neurological rehabilitation.

8.5 Acute relapse management: methylprednisolone and rehabilitation

Although some people with MS never have a relapse, having a progressive form from the onset (or a very benign form), it is likely that most people will have several relapses if not more. At present, treatment often involves hospital attendance if not admission, and the resources devoted simply to giving medical treatment are considerable. In addition many relapses are associated with a significant increase in activity limitation, often sufficient to require hospital admission.

Although there are many trials of many treatments for acute relapse it is still extremely difficult to give strong recommendations based on the evidence. Many questions remain unanswered, such as what dose of steroids, how long for, is oral as good as intravenous, are different types of steroids equivalent, how frequently can short courses be given, and what are the significant risks and side effects?

This lack of useful evidence needs to be set in a larger context. There is minimal evidence available on the diagnosis of a relapse and its distinction from minor progression, worsening associated with an intercurrent illness or simple normal fluctuations in a person's clinical status. In addition, the only way to access rehabilitation is often through hospital admission, and rarely can care needs be met quickly at home also often requiring hospital admission.

RECOMMENDATION

R187 A programme of research should investigate the management of acute relapse including comparing the costs and benefits associated with policies of:

- oral methylprednisilone against intravenous methylprednisolone
- hospital admission with early discharge once rehabilitation has started and support has been arranged against home care with rapid response care and rehabilitation input (with steroids if indicated).

8.6 Disease-modifying therapies

A recent publication has questioned the cost-effectiveness of interferon beta and glatiramer acetate and the current risk-sharing scheme.[461] The amount of money spent by the NHS on disease-modifying therapies (DMTs), including not only the drugs themselves but all the extra resources needed to run the scheme and to monitor the people on the scheme, is large. And this scheme only affects less than 15% of people with MS and many of those eligible withdraw due to side effects.

The guideline developers therefore agreed (by a large majority) that further well-designed research into DMT was a high priority, including impartial evaluation of their effectiveness in terms of reducing limitations on activities, the costs associated with any benefits at the level of activities, the type of side effects seen in both the short and long term, and the duration of any benefit.

RECOMMENDATION

R188 A programme of research into disease-modifying treatments sponsored and run by an organisation independent of either health purchasers or pharmaceutical companies should be set up to investigate interferon beta, glatiramer acetate, linoleic acid and azathiaprine (and any other newly licensed medicines) in terms of:

- benefits, specifically in terms of activity performance
- costs, including the medicines and all associated monitoring, etc
- disbenefits, both immediate side effects and longer-term rates of withdrawal and side effects
- effects of stopping treatment after two and four years.

8.7 Relationship between impairments and limitations in activities

The links between individual impairments and combinations of impairments and the resultant limitations on activities, and how these links may be affected by treatments including changing the environment, are unknown. If more were known, more effective interventions could be researched and undertaken. Investigations will require a prolonged programme of research based on epidemiologically sound populations of people, not only with MS but also with other neurological conditions.

RECOMMENDATIONS

R189 A programme of research extending over many years should be instigated to investigate the nature and extent of relationships between impairments and activities and how they change over time.

APPENDICES

Appendix A: Expanded model of illness (WHO ICF plus)[467,468]

A way of **describing** someone's situation

People with long-term conditions such as MS may face a large range of changes in, or effects on, their life. When considering their situation and how it might be analysed and improved, it is helpful to have a consistent framework or way of categorising the important factors that need consideration. The World Health Organisation developed their International Classification of Impairments, Disabilities and Handicaps (ICIDH) in 1980 as a way of classifying the consequences of disease. This was revised and expanded into the International Classification of Functioning (ICF) in 2001.[8]

Table A1 Expanded model of illness (WHO ICF plus)

'Location' of description	Subjective/internal (experience, attributions and beliefs of the patient)	Objective/external (observations made by, and implications drawn by, others)
Level of description (term used)		
Organ within person (pathology)	*Disease:* Label attached by person, usually on basis of belief and experience.	*Diagnosis:* Label attached by others, usually on basis of investigation.
Person (impairment)	*Symptoms:* Somatic sensation, experienced moods, thoughts etc.	*Signs:* Observable abnormalities (absence or change), often elicited explicitly; *and* deficits assumed from observations.
Person in environment (behaviour/'activities')	*Perceived ability:* What person feels they can do and cannot do, and opinion on quality of performance.	*Disability/activities:* What others note person does do, quantification of that performance (not what others think should do).
Person in society (roles/'participation')	*Life satisfaction:* Person's judgement or valuation of their own role performance (what and how well).	*Handicap/participation:* Judgement or valuation of important others (local culture) on role performance (what and how well).
Context of illness		
Personal	*'Personality':* Person's attitudes, expectations, beliefs, goals, outlook, reasoning style, etc.	*'Past history':* Observed/recorded behaviour prior to and early on in this illness.
Physical	*Personal importance:* Person's attitude towards specific people, locations.	*Resources:* Description of physical (buildings, equipment etc) and personal (carers etc), resources available.
Social	*Local culture:* The people and organisations important to person, and their culture; especially family and people in same accommodation.	*Society:* The society lived in and the laws, duties and responsibilities expected from and the rights of members of that society.
Totality of illness		
Quality of life –summation of effects	*Contentment:* Person's assessment of and reaction to achievement or failure of important goals; *or* sense of being a worthwhile person.	*Social involvement:* Extent of positive interaction with society, contributing to social networks.

Appendix B: Issues for people with MS and their carers[14]

Table B1 Issues raised through focus groups and interviews

Issue	Links to recommendations
Diagnosis	
The time diagnosis takes – variation in services, from speedy to experiences of long delays.	Section 3.3.1 recommends the provision of ready access to a specialist neurological service for diagnosis. A local implementation point recommends that guidelines are set for how timescales for the confirmation of a diagnosis will be met locally. Diagnosis is primarily based on clinical history and examination – further tests to be carried out only if diagnosis in doubt (Section 4.1).
Misdiagnosis and the impact of this on peoples' lives.	Referral system recommended such that the diagnosis is made by a doctor with specialist neurological experience (Section 4.1).
Poor communication with or by medical staff at a devastating moment in your life.	General recommendations on communication are made in Table 2 (Section 3). Specific recommendations on communicating the diagnosis can be found in Section 4.2.
Support and information needs	
Access to support – the need for immediate access to someone knowledgeable to talk to at the time of diagnosis.	Recommendation in Section 3.1.2 to consider the provision of emotional support to the person with MS from the time of diagnosis onwards. Section 4.2 also deals with immediate needs for support and information – 'the person with MS should be put in touch with or introduced to a skilled nurse or other support worker, ideally with specialist knowledge of MS ... and counselling experience'.
Importance of a single contact point for people with MS, to provide ongoing information and support; provision of advice and sign-posting to other advice and support services. Could be an MS nurse, a GP, generic supporter or key worker knowledgeable about MS. Able to provide immediate advice and treatment in times of crisis.	Recommendation in Section 3.3.2 states that there should be someone within the MS-related services that ensures services are coordinated and collaborative. For the person with MS, they should have access to a person to assist in identifying and communicating local information sources and to facilitate access to resources and services needed.
Carers identified the need for someone to take responsibility for coordinating all aspects of care, eg organising annual review of drugs.	Recommendation to provide an annual review of support needs for people with MS who are 'severely impaired and markedly dependent', in Section 3.5.
To be in contact with people who look at physical disability in the context of the whole person, not as problems in isolation.	There are acknowledgements of the need to consider all aspects of a person with MS's situation in the introductions to sections 3, 5 and 6. It is a theme that the guideline developers have been committed to, and which runs through the whole document.
Importance of access to advice on how to stay in work, including the adaptation of the physical environment.	Recommendations in Section 5.3 includes this. Reference is made to accessing specialist advisers and services where necessary in order to stay at work.

continued

Table B1 Issues raised through focus groups and interviews – *continued*

Issue	Links to recommendations
Support and information needs – *continued*	
Important role of voluntary sector recognised, providing access to information.	Table 2 (Section 3) refers to the provision of information, including national sources, as does Section 4.2 – in particular recommendation R38.
GP role	
People with MS are positive about the general care provided by GPs, but acknowledge a GP isn't an expert in MS (and they need support and information themselves) – would like to see a person in each practice trained in the needs of people with MS.	This is covered by the two recommendations in Section 3.3.2.
Hospital services	
Patchy provision of neurologists – people with MS often fall through the net. Not enough emphasis on the social or practical side of having MS.	Section 3.3.1 recommends that every health commissioning authority should ensure its population has ready access to specialist neurological services for the initial diagnosis of MS and subsequent symptoms. Reference to the importance of considering leisure and social interaction is made in Section 5.4.
Problems with lack of access to case notes and full information at the time of a relapse – like starting again each time.	Importance of information sharing at the interfaces described in Section 3.3.2.
Physical problems mentioned specifically by people with MS	
There was very little discussion about specific physical problems associated with having MS. Participants recognised there is no 'cure' and were more interested in being able to get on with their lives. The following were mentioned, but not discussed: • bladder problems • mobility and balance • gait • speech • vision • hearing.	Sections 5 and 6 deal with these areas. Recommendations about bladder problems can be found in Section 6.2. Issues around mobility, balance and gait are dealt with in Sections 5.5 and 6.4. Section 6.15 makes recommendations about dealing with speech problems. Section 6.8 deals with the assessment, provision of equipment and referral to specialist ophthalmology clinic where necessary, for problems of vision.

continued

Table B1 Issues raised through focus groups and interviews – *continued*

Issue	Links to recommendations
Psychological problems mentioned specifically by people with MS	
Cognitive problems.	Section 6.10 includes offering a cognitive assessment and specialist advice when appropriate.
Frustration/lack of confidence.	
Psychological problems mentioned specifically by people with MS – *continued*	
Mood swings.	Section 6.11 deals with emotionalism and Section 6.12 depression, each of which could be factors associated with mood swings.
Depression.	This is discussed in Section 6.12.
Isolation. For people with mild-moderate MS this was about having someone to talk to, with counselling skills. For people with more severe MS it was isolation in the home and lack of mental stimulation.	The need for access to support and counselling is referred to in Section 4.2. Section 5.4 emphasises the need for people with MS to be supported in maintaining their chosen leisure and social activities.
Relationships	
Problems with relationships with partner – including breakdown or new relationships. Family carer feels they become a nurse, rather than a partner.	Sections 3, 5.7 and 6.16 all deal with different aspects of this. Support for carers is a recurring theme.
Impact on family life, children – young carers carrying out inappropriate tasks, including missing school to provide care.	A recommendation to consider the emotional and physical health of any children in the household of a person with MS is included in Section 3.1.4.
Recognition needed of the immensely difficult task of caring, both physically and emotionally.	Recommendation in Section 3.1.4 (also Section 5).
Anxiety within the family and the person with MS about possible hereditary influences.	This should be dealt with in the information given to people with MS about the disease (Section 4.2).
Support needs of partners and families must be recognised – should include advice and information, counselling and access to respite care.	Recommendations about the provision of support to family and informal carers are given in Section 3.1.4.

continued

Table B1 Issues raised through focus groups and interviews – *continued*

Issue	Links to recommendations
Respite care	
Better information needed on access to and availability of respite care – for person with MS and carer.	Reference to the provision of respite support can be found in Section 3.5 with a specific recommendation.
Variability in costs and quality of respite care highlighted – participants felt there was a need for a national benchmark.	
Need for a choice in styles and facilities of respite care, tailoring to the needs of an individual.	
Important factors for people with MS in respite care – care staff with time to talk to residents, treating the person with MS as a person.	
Treatment	
Physiotherapy – highly regarded, but strong feeling that continuous provision is needed rather than one-off sessions. Limited NHS provision criticised. Most provision currently in hospital settings – very little in the community – often stops once at home.	Section 5 (on rehabilitation) and Sections 6.4 and 6.6 (weakness and ataxia) relate to physiotherapy interventions.
Occupational therapy – long waits for assessment and provision of equipment criticised. Assessment usually only as a result of a hospital admission.	Section 5.7 deals specifically with the provision of equipment adaptations.
Speech and language therapy – regular treatment not available.	Recommendations about dealing with speech and swallowing difficulties can be found in sections 6.14 and 6.15.
Importance of adapting support and provision to individuals' needs stressed throughout.	Throughout the document/recommendations.
Need for more MS specialists (all professions) in hospital and the community – real anxiety about quality of care, particularly from carers.	Reference to the need for specific specialist members of a rehabilitation team in Section 3.3.1.

Source: Focus groups and interviews held with people with MS and their carers in July – September 2001

Appendix C: Literature searches

Table C1 Databases searched

Database	Date range searched
Cochrane Library	Pre Sept 2002
DARE	Pre Sept 2002
DARE (admin database)	Pre Sept 2002
Current Controlled Trials	Pre Sept 2002
National Research Register	Pre Sept 2002
Clinical Trials	Pre Sept 2002
Inside Conferences	1993 to September 2002
SIGLE	1976 to September 2002
Medline	1966 to September 2002
Embase	1980 to September 2002
Cinahl	1982 to September 2002
PsycINFO	1887 to September 2002
AMED	1985 to September 2002

Inclusion criteria

Studies identified by the searches were screened for relevance. Papers considered to be potentially relevant were ordered and screened for inclusion. Due to time constraints studies were assessed for relevance and inclusion by one reviewer only. Where any difficulties were encountered these were resolved by discussion between the two reviewers working on the project. All papers were assessed for inclusion using the same form and the reviewer made the decision on whether to include the study based on the criteria listed below.

Table C2 Inclusion criteria for 3.1.2 and 3.1.4

Study design	SRs and primary studies of any design
Intervention	Any intervention aimed at supporting people wih MS, family members or other socially important people
Condition	People with MS, stroke, TBI or spinal cord injuries
Outcomes	Any outcomes reported

Sections 3.1.1, 3.1.3, 3.2, 3.3, 3.4 and 3.5 were not included in the review process

Table C3 Inclusion criteria for 4.1 and 4.3	
Study design	SRs or diagnostic accuracy studies
Index test	Any test used for the initial diagnosis or diagnosis of a subsequent relapse, to monitor disease progression, or to determine the sub-type of MS
Reference standard	Any reported reference standard was considered acceptable (including patient follow-up)
Outcome	Studies must report at least sensitivity and specificity, the DOR or a ROC analysis
Population	Studies should aim to diagnose patients with MS

Table C4 Inclusion criteria for 4.2	
Study design	SRs or primary studies of any design
Intervention	Any intervention related to the provision of information regarding the condition or on how patients should be informed of their diagnosis
Condition	Only primary studies conducted with people with MS. SRs for any condition
Outcomes	Any outcomes reported

Table C5 Inclusion criteria for 4.4 and 4.6	
Study design	SRs, RCTs and CCTs
Intervention	Any intervention aimed at treating acute worsening, optic neuritis, transverse myelitis or reducing disease progression
Condition	People with MS
Outcomes	Studies must report at least one clinical outcome

Table C6 Inclusion criteria for 4.7.1, 4.7.2, 4.7.3, 5.2, 5.3, 5.4, 5.5, 5.6 and 5.7	
Study design	SRs and primary studies of any design
Intervention	Any intervention related to the assessment of rehabilitation or disability or which aim to alter the environment to maximise independence and safety
Condition	People with MS
Outcomes	Any outcomes reported by the studies will be considered

Table C7 Inclusion criteria for Section 6

Study design	*Assessment:* SRs and diagnostic accuracy studies *Intervention:* SRs, RCTs and CCTs
Intervention	Any intervention aimed at treating specific symptoms associated with MS
Condition	Only primary studies conducted with people with MS. SRs in relevant conditions for symptoms on which there is insufficient MS specific evidence available*
Outcomes	*Assessment:* studies must report at least a diagnostic outcome measure *Intervention:* studies must report at least one clinical outcome

*Insufficient MS evidence was available for the 6.2, 6.3, 6.5.2, 6.6, 6.9, 6.11, 6.13, 6.14, 6.15, 6.16, 6.17. Therefore SRs were included for the relevant conditions

Appendix D: Searching for health economics evidence

Searches and data sources

No study design criteria were imposed *a priori* as it was already known that little economic evidence was available, and it was thought best not to restrict the searches at this stage. The search strategies were designed and implemented by Catherine Beverley, Systematic Reviews Information Officer in the School for Health and Related Research at the University of Sheffield. All reviewing was carried out by the health economist. The following databases were searched: Medline, Embase, the Centre for Reviews and Dissemination (CRD) (including the Database of Abstracts of Review of Effectiveness (DARE), the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment Database (HTA)), the Office of Health Economics Health Economic Evaluations Database (OHE HEED) and Econlit.

▷ Inclusion assessment

The titles, and where available the abstracts, were screened to assess whether the study met the following inclusion criteria.

Patients – At least some of the patients had MS. After the initial searches, supplementary searches in relation to specific questions were carried out, without the requirement that some patients had MS.

Economic evidence – The study was an economic evaluation or included information on resources, costs or specific quality of life measures. Selected quality of life measures were SF-36, EQ-5D or HUI (in conjunction with EDSS). These measures are the most useful for economic analysis of outcomes since they can be used to generate utility values in a modelling framework, and since they are generic measures they are useful for comparative purposes.

Study design – No criteria for study design were imposed.

Summary results

The searches found 464 unique papers. The titles, abstracts and CRD/OHE HEED commentaries (where available) were reviewed, and 139 potentially useful papers were identified. The vast majority of these studies included only people with MS, but a small number make comparisons with other diseases. It was found that:

- 32 studies were solely concerned with quality of life (QoL) and contained no cost or resource information
- 38 studies were general resource use/cost studies, which consider the cost of MS to society and/or the individual with MS
- five studies were 'needs assessments'.

▷ Summary by type

Six systematic reviews (of which four were HTA reports) covered:

- one on treatments for pain and spasticity (HTA)
- one on treatments for fatigue (HTA)
- one on immunomodulatory drugs (HTA)
- one on role of specialist nurses (HTA)
- one on corticosteroids for acute exacerbations
- one on overview of azathioprine treatment.

Nine economic analyses based on RCTs included:

- three on intrathecal baclofen therapy for spasticity
- three on oral *vs* intravenous corticosteroids in acute relapses
- one on immunoglobulin in secondary progressive MS
- one on the effect of rehabilitation on disability
- one on reducing the period of immobilization following pressure sore surgery
- one on the effects of physiotherapy on mobility.

Thirty-eight studies considering the general costs and/or resource use of MS, all based in Europe, the US or Canada, included:

- 12 on cost of illness (COI) studies (eight using a bottom-up costing method)
- two reviews of COI studies
- a further three studies use bottom-up costing but do not consider a full COI
- 13 cost studies considering indirect costs, as well as direct costs*
- eight studies considering resource use but not including any cost information (of which five are patient surveys.

Five studies considered needs, specifically unmet needs, and included:

- three patient/carer surveys (from Europe, the UK and the US)
- one review
- one local study in Oxfordshire, which used a variety of data sources including observational data, audit and interviews.

Thirty-nine studies considered QoL as measured by the generic instruments outlined above, and included:

- 32 QoL studies containing no cost or resource data
- one study (a survey in Canada) considering QoL for carers of people with MS
- four studies making comparisons with QoL in other chronic conditions.

* 'Direct costs' are defined as all the goods, services and other resources that are consumed in the provision of an intervention, or dealing with side effects linked to the intervention. These costs can be medical and non-medical and can be incurred by the NHS, by patients and/or their carers and by wider society (eg social services). 'Indirect costs' are the lost productivity suffered by the economy as a result of an individual absence from work through illness, decreased efficiency or premature death.

Appendix E: Health economics of comparing different methods of administration of methylprednisolone in the treatment of acute relapses in multiple sclerosis

Introduction

The group were interested in finding out more about the potential costs and benefits of different methods of administering high-dose corticosteroids for the treatment of acute relapse. It is important to note that clinical practice varies widely and this document is based on 'usual' treatment, to the extent that it is possible to state what this is.

There is little clinical evidence available in this area. The evidence review (see Section 4.4) identified four trials comparing methylprednisolone with placebo and two trials comparing oral with intravenous methylprednisolone. The latter two trials are relevant to the current question and they were both carried out in the UK; unfortunately they are small and also difficult to compare given the different regimens used. Neither included any collection or analysis of resource use data. A further search for economic evidence in this area, which imposed no quality criteria on studies, found only one relevant paper. This is a survey of 212 consultant neurologists carried out in March 1997, which questioned them on their use of corticosteroids in the treatment of MS.

Formal economic modelling which attempts to systematically evaluate costs and benefits is not possible without relevant clinical data. Instead the costs and benefits of these three methods of administration were itemised in a way that facilitates comparisons.

While there are a number of choices of drugs and methods of administration, the focus here was on the use of methylprednisolone administered in three ways:

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

Background

Hospital administration of intravenous methylprednisolone is the most common treatment for relapse. In many cases the person with MS will need to be admitted to hospital as a result of the disability caused by the relapse and in these cases they will usually receive intravenous methylprednisolone during their hospital stay. Where admission for disability is not necessary, many people will still be admitted in order to administer intravenous corticosteroids.

The hospital intravenous category considered here largely refers to inpatient stays, as day case administration is rare. A recent survey suggested that only 7% of neurologists could offer administration as day case.[462] Admission to hospital is probably more common in those areas

where specialist neurology units are not available, as there are few alternatives for administering high dose corticosteroids in these cases. Day case administration (and home intravenous) will be more common in areas with specialist units.

It is important to note that the only efficacy information considered here comparing oral and intravenous methylprednisolone comes from trials where intravenous administration was offered as a day case by the pharmacy at hospitals with specialist centres. This may not be representative of the usual method of administration of intravenous methylprednisolone across England and Wales.

Home intravenous administration is included here as it was of interest to the group. However, it is not readily available in most parts of the country. The same survey suggested that only 5% of neurologists had the facilities to offer home intravenous treatment with methylprednisolone.[462] There is no information on the number of GPs who may be able to offer this service.

The survey of neurologists may be misleading as in many parts of the country people experiencing a relapse will be managed by their GP (who would usually take advice from a neurologist). Once GP contact is established the care pathway will depend on the GP's and patient's experience of MS and relapse, the GP's relationship with the patient and local access to neurology services.

Oral corticosteroids are used by some GPs and some neurologists to treat relapse.

The Tremlett survey found that 74% of neurologists would recommend oral administration instead of intravenous methylprednisolone at sometime, although the most popular response (48%) was for 'occasional use' (<25% of cases).[462] Oral prednisolone was the most common treatment, with only 23% recommending oral methylprednisolone. There is no evidence on the comparative efficacy of prednisolone against methylprednisolone.

Making comparisons

In the absence of appropriate clinical or economic evidence Table E1 is 'think piece' in an effort to encourage full consideration of potential costs and benefits when different methods of administration are being compared.

The potential costs and benefits have been classified under six headings.

▷ Effectiveness

The methods are compared in relation to their effect on relapse. The only formal comparative clinical evidence comes from two RCTs comparing oral methylprednisolone with intravenous administration as a hospital day case;[124,125,134] these show equal efficacy. There is no formal clinical evidence comparing home intravenous administration with either hospital intravenous or oral administration. Assuming comparable regimens there is probably no reason to expect a difference in efficacy between home and hospital intravenous administration. However, this does not take into account potential problems or side effects of treatments.

▷ NHS resources

There is no formal evidence on the NHS resource use involved in any of the methods of administration. In terms of the pure drug cost, an intravenous course of methylprednisolone costs just over twice as much as an oral course.[6] The costs of intravenous administration are much higher, especially if they involve an inpatient stay (although the stay may not always be solely for drug administration). Day case administration is likely to be cheaper than an inpatient stay, but this facility is probably only available at larger hospitals with specialist services.

Home intravenous administration requires equipment provision and involves staffing costs for home visits.

A study in a Toronto teaching hospital which followed 92 patients for 12 months showed that inpatient administration of methylprednisolone was more expensive than outpatient or home administration.[463] This finding was robust to all sensitivity analysis. However there was no clear finding on the comparative costs of home against outpatient treatment, and this depended on assumptions made about the relevant overheads and staff costs.

▷ Quality of life

There is no formal evidence on the effect of alternative methods of methylprednisolone delivery on quality of life. Positive effects on quality of life would be expected to result from alleviation of the symptoms associated with relapse. It is also probably reasonable to assume that intravenous procedures would have a greater adverse affect on QoL than oral administration. It is usually assumed that QoL is adversely affected by hospital admission, but it is also important to consider the substantial burden imposed by daily hospital visits.

Home treatment is likely to be preferred in terms of QoL. An Italian study by Pozzilli *et al* comparing a home-based management program with hospital care for MS found a significant benefit in favour of home-based care for four of the eight dimensions of the SF-36:* general health, bodily pain, emotional role and social functioning.[464]

▷ Patient and carer costs

There is no formal evidence on the patient burden associated with alternative methods of methylprednisolone delivery. The main costs will arise from absence from work which are due to the relapse itself and also from any costs of drugs or equipment borne by the patient. In addition day case administration will require travel to hospital which involves time and possibly direct financial burden.

▷ Side effects, tolerability etc

The trials of oral *vs* intravenous administration reported similar (minor) side effects in both arms. The risk of infection is greater from intravenous treatment, but it is not clear whether there may be a greater risk at home or in hospital.

* The SF-36 is a generic health-related quality of life instrument that has been used in many studies of multiple sclerosis treatments and has been shown to be a valid and sensitive measure of QoL in the population of people with MS. The SF-36 contains 36 items covering eight dimensions of health: general health, bodily pain, physical functioning, emotional role, physical role, mental health, social functioning and vitality.

It has been argued that oral therapy, being easier than intravenous, might be used more frequently or courses extended when clinical response is lacking. This increased 'routine' use would increase the chances of corticosteroid-induced side effects. It may also increase the chances of the therapy being used inappropriately.

▷ NHS delivery issues

There is geographical variation in the availability of home-based intravenous treatment and day case treatment at hospital. Home treatment requires equipment and the availability of appropriate staff, while day case treatment requires facilities that are unlikely to be available at DGHs.

Summary

Many factors should be considered when comparing alternative methods of methylprednisolone delivery and there is little formal evidence on any of these. There is no clearly dominant treatment in terms of clinical effectiveness or resource use.

Table E1 Comparing methods of administering methylprednisolone (compare row with column)

	Oral	Hospital IV	Home IV
Oral		**Effectiveness: equal (2 RCTs)** **NHS resources (no evidence)** • lower drug & admin costs* • no hospitalisation • Quality of Life (no evidence) • = relief of symptoms? • non-invasive *vs* invasive • higher than if in hospital? **Patient/carer costs (no evidence)** • absence from work • prescription charges? **Side effects etc (little evidence)** • equal ('minor') • increased routine use? **NHS delivery issues (no evidence)** • no major issues?	**Effectiveness: no evidence** **NHS resources (no evidence)** • lower drug & admin costs* • Quality of Life (no evidence) • = relief of symptoms? • non-invasive *vs* invasive. **Patient/carer costs (no evidence)** • absence from work? • prescription charges ? **Side effects etc (little evidence)** • increased routine use? **NHS delivery issues (no evidence)** • no major issues?
Hospital IV	**Effectiveness: equal (2 RCTs)** **NHS resources (no evidence)** • higher drug & admin costs* • hospitalisation (or day case) **Quality of life (no evidence)** • = relief of symptoms? • invasive *vs* non-invasive • hosp. (or daily visits) **Patient/carer costs (no evidence)** • absence from work • travel for day case **Side effects/tolerability** • equal ('minor') • risk of infection **NHS delivery issues (no evidence)** • Avail. of day case service • appropriateness of bed use		**Effectiveness: no evidence** **NHS resources (no evidence)** • = drug costs? • hospitalisation (unless day case) **Quality of life (no evidence)** • relief of symptoms • hospitalisation (or daily visits) **Patient/carer costs (no evidence)** • absence from work • travel for day case **Side effects/tolerability** • no evidence • risk of infection **NHS delivery issues (no evidence)** • availability of day case service • appropriateness of bed use
Home IV	**Effectiveness: no evidence** **NHS resources (no evidence)** • higher drug & admin costs* • costs of monitoring • home equipment costs **Quality of life (no evidence)** • = relief of symptoms? • invasive *vs* non-invasive **Patient/carer costs (no evidence)** • absence from work **Side effects/tolerability** • risk of infection • less tendency for routine use? **NHS delivery issues (no evidence)** • availability of equipment • staff for home visits	**Effectiveness: no evidence** **NHS resources (no evidence)** • = drug costs? • costs of monitoring • home equipment costs **Quality of life (no evidence)** • relief of symptoms • home *vs* hospital **Patient/carer costs (no evidence)** • absence from work **Side effects/tolerability** • risk of infection **NHS delivery issues (no evidence)** • availability of equipment • staff for home visits	

* Drug costs have been estimated using regimens from Barnes *et al*[134] and drug costs from BNF43 (September 2002). Intravenous methylprednisolone 1000mg daily for 3 days = £41.31. Oral methylprednisolone 48mg day for 7 days, 24mg day for 7 days, 12mg day for 7 days = £18.48.

Appendix F: Economic evidence for nuclear magnetic resonance imaging scans in the diagnosis of MS

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. While safety evaluations indicate that non-contrast MRI is safe for most people including pregnant women,[465] and the procedure is not painful or invasive, many people find it uncomfortable. 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, CSF examination and lumbar puncture has diminished in recent years.[466]

How might MRI affect care?

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. A review of evidence suggested that MRI has had little direct impact on therapeutics or patient outcomes.[465] However, it seem sensible to suggest that errors of diagnosis, delay in diagnosis and invasive tests will all occur more often if MRI is not carried out (expert opinion).

The availability of the disease-modifying therapies (DMTs) interferon beta and glatiramer acetate under the risk-sharing scheme may have implications for the use of MRI in diagnosing MS. DMTs are available to people with a diagnosis of relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS) in which relapses are the dominant feature, and who meet the Association of British Neurologists' criteria for treatment. It is estimated that between 7,500–9,000 people in England and Wales may be eligible for treatment (approximately 12.5% to 15% of the estimated total number of people with MS). The ABN criteria are not dependent on diagnosis via 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 MRIs.[466] The new international panel criteria which recommends MRI for diagnosis on people with clinically isolated symptoms is also likely to increase demand for MRI scans.[55]

Existing cost-effectiveness studies

Only two 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

* Cost estimates vary between £155 and £286 for an MRI within the NHS.

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, and they also allow identification of key areas of uncertainty around clinical utility and cost-effectiveness which can guide future research. Both 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 (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 (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 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 revealed that the key areas of uncertainty were the diagnostic accuracy of MRI and the value of the diagnostic information to patients (over and above the affect of the test result on disease management); both of these factors will have an important influence on the cost-effectiveness of the technology. 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.

Increasing the relevance of this information

In an effort to update these cost-effectiveness studies and improve their relevance to our recommendations, a further comprehensive search was carried out to find economic information on the use of MRI as a diagnostic technology in MS and other neurological diseases, ie to identify the potential costs and benefits of MRI. As well as updating the original search of standard bibliographic databases (and broadening this outside of MS) the new search also focused on a number of key websites and databases. In addition information was sought from a number of relevant professional and academic organisations.

This search (and the review of the clinical evidence) revealed that evidence on the diagnostic accuracy of MRI had improved very little since the US cost-effectiveness studies of the early 1990s. As a result it was not possible to construct a cost-effectiveness model within the required time. Furthermore, this model would probably be of little value since it would be characterised by the same key uncertainties as the earlier work.

As an alternative to cost-effectiveness modelling (and after taking further advice from some members of the GDG) the focus was on providing answers to some questions, which may help to inform our recommendations.

What proportion of people with (suspected) MS receive an MRI scan at present?

There is no formal data source containing this information. Expert opinion suggests that almost all people with MS will have had an MRI scan at some point, but it is not clear how many people

with suspected MS (ie some evidence from clinical tests) will get a scan, or how long they would have to wait (see below).

The number of MRI scans carried out for the purpose of diagnosing MS can only be estimated from incidence figures. There is uncertainty in estimating the current incidence and prevalence of MS. The HTA systematic review on the natural history and epidemiology of MS, produced to inform these guidelines,[4] cites prevalence of 100–109 per 100,000 and incidence of 3.5 to 3.8 per 100,000. Expert opinion from Alistair Compston and David Miller suggests an incidence of 7 per 100,000. This amounts to around 2,100 to 4,200 first diagnostic scans per year, depending on which incidence figure you take and assuming that all new cases receive an MRI scan. David Miller has suggested that as many again are probably done to exclude a diagnosis of MS.

Despite much concern over extremes in geographical variation there is little formal data on this. In relation to access to a neurologist, an ABN survey in 1999 and 2001 (**www.theabn.org/ukneuro/acuteneurology.html**) asked consultant neurologists how long was the wait until their next appointment for a routine referral from a general practitioner for any purpose. The results show waits varying from 13 weeks in North West Thames to 51 weeks in Wales. Some areas show improvement since 1999, but in others the situation has worsened.

MRI scanning facilities in the UK are heavily used and if scanners are not used for the purposes of diagnosing MS, the machinery and staff would almost certainly be involved in scans for other purposes, so any cost savings from fewer MS scans are unlikely to be realised. However, there is a true opportunity cost from using a scanner to aid in the diagnosis of MS.

What is the value of MRI in the diagnosis of relapse?

From the research point of view there appears to be much interest in MRI results as a potentially more objective outcome measure than EDSS in measuring disease progression. However, it is not clear how MRI results can be translated into patient-based outcomes (like quality of life) and evidence on the relationship between MRI and clinical progression is not conclusive. Any recommendations on the role of MRI in the continued management of MS (ie after diagnosis) must consider the effect on waiting times for initial diagnostic scans.

Other important questions for which it was not possible to find information

- Do patients have lower/higher subsequent treatment costs if they have had more MRIs?
- Do patients have different rates of disability/relapse/death if they have had more MRIs?
- Can the cost of an MRI be equated with any clinical gain?

Appendix G: The McDonald Criteria[55]

Table G1 Making the diagnosis

Clinical presentation	Additional data needed to make diagnosis	Comment
Two or more attacks; objective clinical evidence of two or more lesions.	None.	If tests (MRI scans or CSF analysis) are undertaken and are negative extreme caution must be taken before making a diagnosis of MS. Alternative diagnoses must be considered. There must be no better explanation for the clinical picture.
Two or more attacks; objective clinical evidence of one lesion.	Dissemination in space demonstrated by MRI.	MRI scan must fulfil criteria for brain abnormality (overleaf).
	Two or more MRI-detected lesions consistent with MS plus positive CSF.	Positive CSF: oligoclonal bands detected by established methods, preferably isoelectric focusing, different from any such bands in serum; or by a raised IgG index.
	Await further clinical attack implicating a different site.	
One attack; objective clinical evidence of two or more lesions.	Dissemination in time demonstrated by MRI.	MRI scan must fulfil criteria for dissemination of lesions in time (overleaf).
	Second clinical attack.	
One attack; objective clinical evidence of one lesion (mono-symptomatic presentation; clinically isolated syndrome).	Dissemination in space, demonstrated by MRI scan.	MRI scan must fulfil criteria for brain abnormality (overleaf).
	Two or more MRI-detected lesions consistent with MS plus positive CSF *and* dissemination in space, demonstrated by MRI scan *or* second clinical attack.	Positive CSF: oligoclonal bands detected by established methods, preferably isoelectric focusing, different from any such bands in serum; or by a raised IgG index. MRI scan must fulfil criteria in the second paragraph of the criteria for dissemination of lesions in time (overleaf).
Insidious neurological progression suggestive of MS.	Positive CSF *and* dissemination in space, demonstrated by nine or more T2 lesions in brain *or* two or more lesions in spinal cord, *or* four to eight brain plus one spinal cord lesion.	Positive CSF: oligoclonal bands detected by established methods, preferably isoelectric focusing, different from any such bands in serum; or by a raised IgG index.
	Abnormal VEP associated with four to eight brain lesions, *or* with fewer than four brain lesions plus one spinal cord lesion demonstrated by MRI *and* dissemination in time, demonstrated by MRI.	Abnormal visual evoked potential of the type seen in MS (delay with well preserved wave form).
	Continued progression for one year.	MRI scan must fulfil criteria shown in criteria for brain abnormality (overleaf).

Magnetic resonance imaging criteria

▷ Magnetic resonance imaging criteria for brain abnormality

Magnetic resonance imaging criteria for brain abnormality are based on **three of four** of the following:

- one gadolinium-enhancing lesion or nine T2-hyperintense lesions if there is no gadolinium enhancing lesion
- at least one infratentorial lesion
- at least one juxtacortical lesion
- at least three periventricular lesions.

Note that one spinal cord lesion can be substituted for one brain lesion. Data from Barkhof *et al* 1999 and Tintore *et al* 2000.

▷ Magnetic resonance imaging criteria for dissemination of lesions in time

If a first scan occurs three months or more after the onset of the clinical event, the presence of a gadolinium-enhancing lesion is sufficient to demonstrate dissemination in time, provided that it is not at the site implicated in the original clinical event. If there is no enhancing lesion at this time, a follow-up scan is required. The timing of this follow-up scan is not crucial, but three months is recommended. A new T2- or gadolinium-enhancing lesion at this time then fulfils the criterion for dissemination in time.

If the first scan is performed less than three months after the onset of the clinical event, a second scan done three months or more after the clinical event showing a new gadolinium-enhancing lesion provides sufficient evidence for dissemination in time. However, if no enhancing lesion is seen at this second scan, a further scan not less than three months after the first scan that shows a new T2 lesion or an enhancing lesion will suffice.

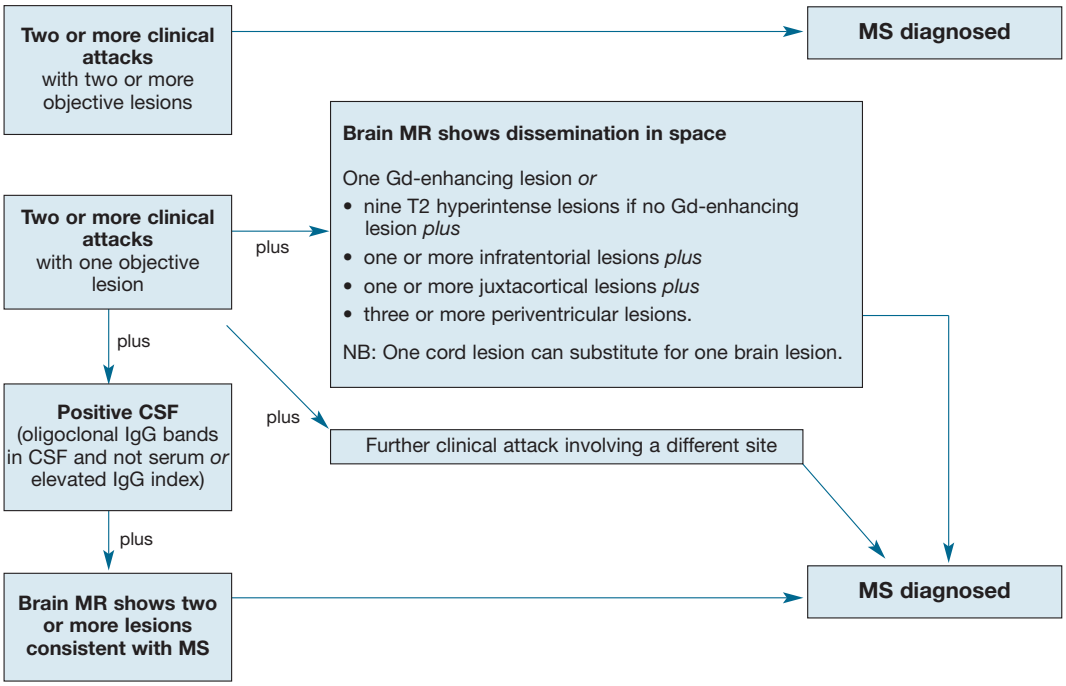
Guidelines for the accurate diagnosis of MS according to the McDonald criterias

1) The diagnosis should be made by an experienced clinician with expert knowledge of MS and similar neurological conditions.
2) The prior probability that the individual has MS depends on factors such as age, ethnicity and geographical location.
3) Objective evidence of dissemination in time and space of lesions typical of MS is mandatory, as is the exclusion of other, better explanations for the clinical features.
4) Historical reports of symptoms may suggest previous episodes of demyelination, but cannot be used without objective evidence to satisfy the requirement of lesions disseminated in time and space.
5) MS can be diagnosed on purely clinical evidence of lesions separated in time and space.
6) Radiological (MRI) and laboratory evidence is desirable and may be essential where clinical evidence is insufficient for a secure diagnosis.
7) The choice of investigation will be determined by the clinical situation; for example, a delayed visual evoked potential is of value in a person with a spinal cord lesion but is of little value in a person with optic neuritis.

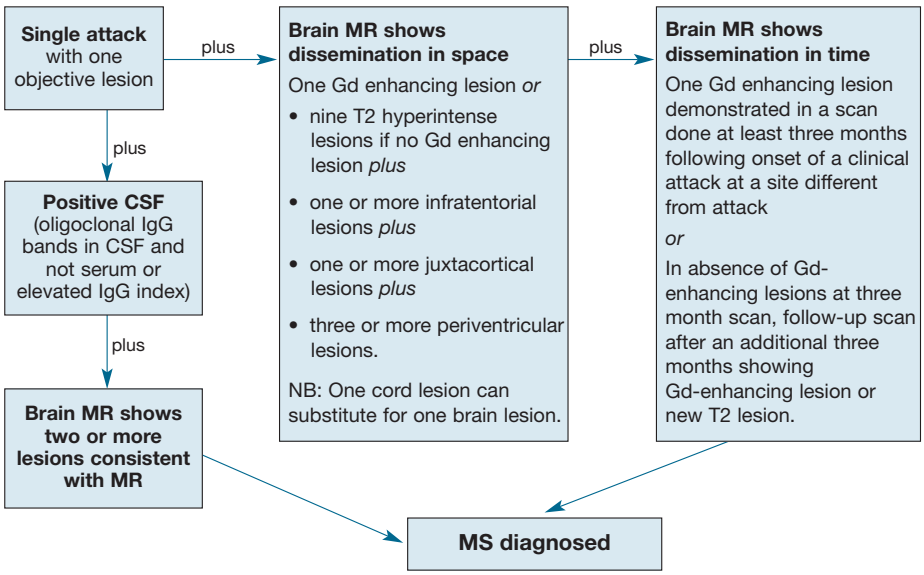
8) MRI is less useful in older people and in other inflammatory conditions such as acute encephalomyelitis where its specificity is lower. MRI is not applicable in people with metallic foreign bodies, pacemakers, etc or in those who cannot tolerate the procedure.

Flow charts for diagnosis of MS using McDonald criteria

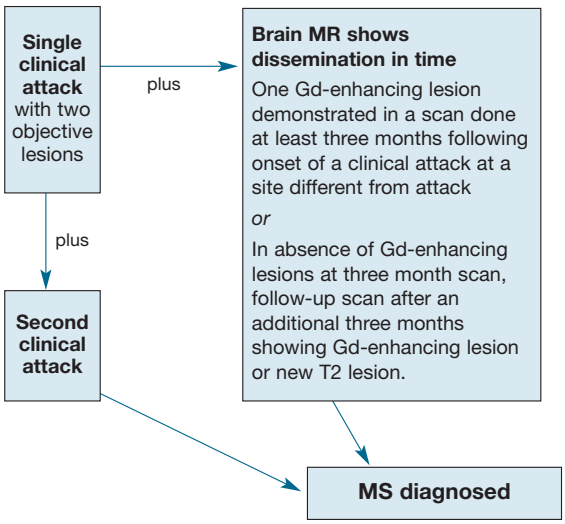
▷ Diagnostic criteria for suspected MS (two or more attacks)



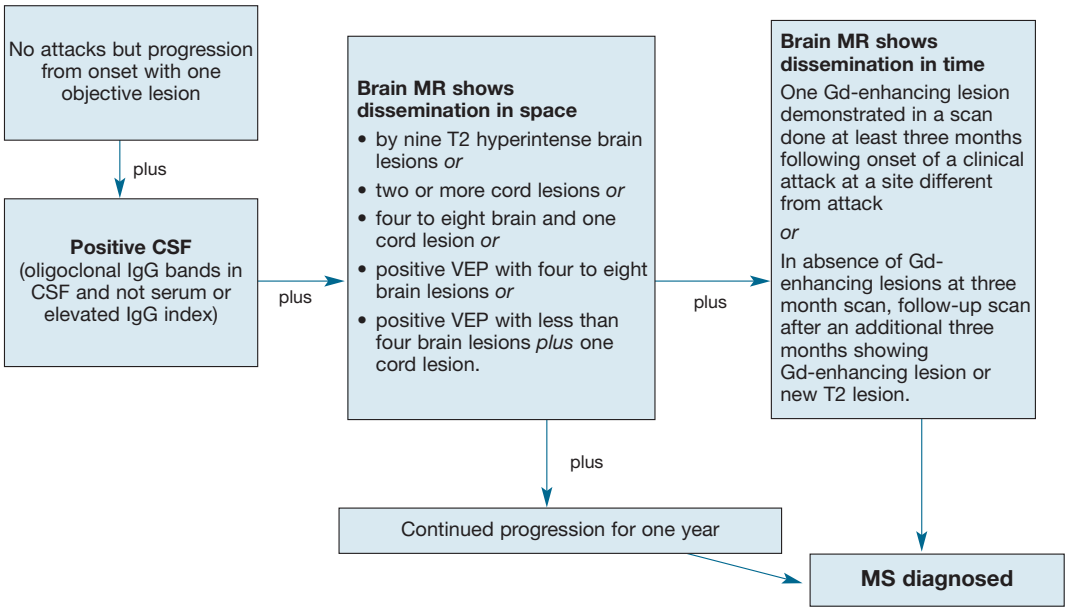
▷ Diagnostic criteria for suspected MS (monosymptomatic)



▷ Diagnostic criteria for suspected MS (single attack)



▷ Diagnostic criteria for suspected MS (progressive from onset)



Appendix H: Assessments and measures

These guidelines do not recommend or even mention specific measures or assessments. A brief explanation is given in the introduction. This appendix gives a little more information. However, it must be emphasised that the measures mentioned here are not being recommended in any way.

First, the reader is reminded of the second paragraph in section 3.2.1:

> The process of assessment refers both to the collection and to the interpretation of data needed to identify problems (screening) and to inform the solutions. The process of assessment may or may not include measurement, which is the quantification of data against some metric. In other words, an assessment procedure may be considered to have two purposes which may be distinct or combined:
> - the **detection** of a phenomenon (ie diagnosis); and,
> - the **measurement** of a phenomenon.

The questions faced are whether we are able to give recommendations that cover:

- how specific impairments or activity limitations should be detected
- how the severity of any impairment or activity limitation should be quantified, for example when measuring the outcome of an intervention
- what protocols should be used when first seeing a person with MS in order to detect most common or important difficulties.

In all three cases the first step is to collect data from or about the person with MS, and so the discussion is primarily concerned with whether or not the guidelines should mention or recommend specific data collection tools. These are referred to as 'measures' or 'assessments' interchangeably and loosely. A measure is a way of quantifying something; an assessment is a process of making a rehabilitation diagnosis through identifying and sometimes quantifying the presence of various abnormalities. The recommendations have emphasised the need for the process of assessment, and implied that measurement should be considered. The question is whether specific tools should be recommended.

The problems

There are several problems, especially in the context of a document that is emphasising the need to base recommendations on evidence.

The evidence searches undertaken have not been appropriate for making decisions on which data collection tools to recommend. To give reasonable evidence we would need to search for evidence on what purposes each tool might be suitable for, how reliable it is, how sensitive to change if used for that purpose, its diagnostic sensitivity and specificity if used for that purpose, its feasibility, and its comparative utility with other tools.

For almost all tools only minimal published data are available. Specifically there are very little comparative data to guide any choice between tools that collect data on the same problem.

However, the number of tools used in research is vast. This appendix includes a list of measures mentioned in the studies tabulated in the evidence tables. This list is only a small proportion of the measures used in the totality of MS research. Moreover, in clinical practice a different set of measures is used (in as far as measures are used at all). The utility, validity etc of most of these measures is unknown.

It also needs to be recognised that many people hold strong views on what to use and will anyway disagree with and probably ignore any recommendations. The comments by stakeholders illustrated the wide variety of opinions on appropriate measures vividly – there was no agreement by stakeholders on any single measure.

At the same time those without strong views might not use any tools, whatever is recommended.

In favour of making recommendations

In the guidelines we have suggested repeatedly that specific problems (such as swallowing difficulties) are identified, but not how. This omission lessens the likelihood of the recommendations being followed. Many stakeholders suggested that we should include recommendations, but usually recommended ones that others did not.

Against making recommendations

Although we have not searched systematically for evidence on measures, there is in fact little useful evidence available and we have not searched for or found the relatively limited available evidence. Consequently any recommendations made will be arbitrary and will not be agreed. Therefore it is unlikely that any specific recommendations will be followed, making it unwise to make them.

We do not have the time or resources to undertake a proper systematic search for evidence even in one domain, let alone for the whole of neurological rehabilitation. It is wiser to make no recommendations than to make recommendations that are personal preferences, rather than based on firm evidence, and likely to be disputed by more people than agree on them.

What is available?

In the process of formulating these guidelines and collating the evidence we have, however, produced some information.

First, there is a simple list of all the measures used in the research studies referred to in this document. Many of these measures are untested and few will be useful.

List of measures

The tabulated list of measures is simply set out in order of frequency, with a brief note on some measures where known. The names given are those abstracted from the original papers, and some of the measures may have no further data available. To find further details the reader should identify the study that used the test and read the original paper.

Conclusions

Several conclusions can be drawn from this appendix.

Firstly, future search strategies should focus on investigating:

- **validity:** what purposes the measure can fulfil (or what measures can fulfil a specific purpose)
- **reliability:** how consistent the tool is when used in different circumstances by different people or in different ways
- **sensitivity:** what change or difference can it detect
- **utility:** this is a review of such factors as the time and effort needed to use the measure, the amount of equipment needed, the training needed by the assessor, and how much the information gained alters clinical decisions.

Second, a large number of measures have been used, but many only once.

A research programme should be set up to investigate simple measures for routine use, preferably not limited to MS but covering all neurological conditions.

Table H1 Assessment tools used as outcome measures in multiple sclerosis RCTs and CCTs in evidence tables

Number of studies	Assessment tool	Number of studies	Assessment tool
84	EDSS	1	Fog scale
13	ADL otherwise unspecified	1	Global gait score
13	AI (Ambulation Index – Hauser)	1	Gottschalk and Gleser Scale
13	Ashworth scale	1	Gulick MS Specific Symptom Scale Score
12	SF-36	1	Health Attribution Test
11	FSS (Fatigue Severity Scale)	1	Hopkins Verbal Learning Test (HVLT)
10	BDI (Beck Depression Inventory)	1	HRSD
8	Alexander score	1	Imagery Assessment Tool
7	Nottingham health profile	1	Independence of activities of daily living (IADL)
6	9-HPT (Nine Hole Peg Test (manual dexterity))	1	Jebsen Test of Hand Function (JTHF)
6	Barthel Index ADL	1	Marital adjustment (Marital Adjustment Test – MAT)
6	Frenchay activities index – extended ADL		
6	Kurtske FSS (EDSS)	1	Memory concentration test
5	Rivermead mobility index	1	MFIS score
5	State Trait Anxiety Inventory (STAI)	1	MMPI D-30 scale
4	DSS (Disability Status Scale; precursor to EDSS)	1	MMSE (Mini-Mental State Examination)
4	General Health Questionnaire	1	MS self-efficacy function and control sub-scales
4	Incapacity Status Scale	1	MSIS
4	POMS (Profile of Mood States)	1	MSPSS (total social support)
4	RFSS	1	MSQOL-54
4	Scripps NRS (Neurological Rating Scale (impairments))	1	MSSE
		1	Nottingham Extended ADL index
4	FIM (Functional Independence Measure)	1	Oxford Handicap Scale Scores
4	HADS (Hospital Anxiety and Depression scale)	1	PASAT
3	GNDS (Guy's Neurological Disability Scale)	1	Personality change (NEO-PI, Hogan Empathy Scale)
3	NRS (Neurological Rating Scale Scripps)		
2	Berg Balance Test	1	Philadelphia Geriatric Center Morale Scale
2	ERP (Evoked Response Potential (EEG))	1	Prose Memory (MAS)
2	Hamilton Rating Scale	1	Rankin Scale
2	London handicap scale	1	Rehabilitation Institute of Chicago Functional Assessment Scale
2	MS Symptom Checklist		
2	Snellen test	1	RIC-FAS
1	Accomodation self-efficacy measure	1	Rivermead Behavioral Memory Test
1	Affect Balance Scale	1	Rivermead Motor Assessment (gross function, leg function, functional assessment)
1	AMB		
1	Anxiety Scale Score (ASQ)	1	Rosenberg Self-Esteem Scale
1	Arthritis impact measurement scale	1	SDDRE (how essential help with ADL is)
1	ASSS	1	SDDRO (help required in the last 24 hours with personal care, mobility, household tasks, leisure and employment)
1	Aulhorn Flicker Test		
1	Borg's post reading (perceived rate of exertion)	1	SDMT written (one of the attention/visuomotor search scales)
1	Boyarsky Scale		
1	Brief Assessment of Social Engagement and Life Satisfaction Index scores	1	SF-36
		1	SF-54
1	Bronx scale	1	Shiply Institute of Living Scales
1	CDQ	1	SOMC (Short Orientation Memory Concentration Test)
1	Cerebellar Functional System Score		
1	Chalder Fatigue Scale Score	1	Spiral copying
1	Community Integration Score	1	SSEP (Somato-sensory evoked potential (EEG))
1	COP Sway Centre of Pressure	1	Standardised neurological status
1	Cybex flexion score (quadriceps spasticity)	1	Symbol Digit Modalities Test (oral version)
1	Dartmouth Co-Op Chart	1	Symptom rating questionnaire (patient assessment)
1	DRS Disability Rating Scale		
1	Environmental status score	1	Symptom Trait Scale (physical symptoms)
1	EQUISCALE	1	Tempelaar Social Experience Checklist (SET)
1	Esteem (SES)	1	Visual Faces Scale Rating (patient rating of pain and spasticity)
1	Everyday memory problems (EMQ)		
1	FAMS symptoms (Functional Assessment in MS)	1	WAIS similarities and WAIS picture arranging
1	Fatigue Impact Scale (FIS)		
1	FDS (pyramidal functions and bladder and bowel functions)		

Appendix I: Evidence tables

These are available at **www.rcplondon.ac.uk/pubs/books/ms/**

The evidence tables provide full details of the studies identified and critically appraised as part of the formal systematic review. They are organised according to guideline section, clinical question and study design.

Appendix J: The scope of the clinical guideline

Preamble

The National Institute for Clinical Excellence is responsible for developing, disseminating and giving advice on the implementation of clinical guidelines to provide advice on best practice for patients and health professionals in the NHS in England and Wales.

Title

Multiple sclerosis: national clinical guidelines for diagnosis and management in primary and secondary care.

Summary

The guideline will be relevant to adults of all ages with MS and will cover the full range of care that should be routinely made available from the NHS, including appropriate use of mainstream pharmacological, physical therapy, rehabilitative and psychosocial treatments.

Status

This scoping statement has been subject to a period of consultation and discussed with stakeholders. It has been approved by the Guidelines Advisory Committee and the Institute's Guidance Executive and will be posted on the Institute's website along with details of the commission and the developers of the guidelines.

Issues and objectives

- Multiple sclerosis is a progressive neurological condition. It has a variable clinical course and patients present with a variety of problems. They can present with a relapsing-remitting disorder that, after a variable time course, may evolve to a secondary progressive disorder. They may also present with a primary progressive disorder particularly in older patients.
- The guideline will cover a very broad range of care services, and the developers will need to assess how best to approach this.
- This is an NHS guideline. Although it will comment on the interface with other services, such as those provided by social services and the voluntary sector, it will not include services exclusive to these sectors.
- The guideline will incorporate the Institute's guidance on the use of interferon beta and glatiramer acetate.

Inclusions and exclusions

▷ Disease or condition

The guideline will be relevant to adults of all ages with MS. The guideline should offer best practice advice on the diagnosis of MS and on the NHS care of patients diagnosed with various forms of MS. Diagnosis, early management, relapsing-remitting and progressive stages of the disease should be considered. Severe and advanced stages of the condition, and the management of rarer symptoms and treatment side effects will also be covered. Supportive and palliative care will be covered only to the extent that they relate specifically to MS.

▷ Health care setting and professions

The guideline will cover the care provided by clinicians who have direct contact with and make decisions concerning the care of patients with MS. It will address the needs of patients and carers in whatever setting NHS care is provided.

The guideline will need to comment on the way health care services need to interact with services provided by Social Services and the voluntary sector, but will not seek to guide the practice of social care or services provided by the voluntary sector.

▷ Interventions and treatment modalities

The guidelines will cover the full range of care that should be routinely made available from the NHS, including appropriate use of mainstream pharmacological, physical therapy, rehabilitative and psychosocial treatments.

These will include:

- **the diagnosis of the disease**
- **pharmacological treatments:** the guideline will consider the long established and widely used drugs such as steroids (various forms) and azathioprine but the brief specifically excludes evaluation of the interferon betas and glatiramer acetate which are being appraised by the Institute.
- **consideration of alternative treatments that might modify disease progress:** although the evidence base is much weaker for these therapies, many patients use them. By considering them, the developers will, amongst other observations, be able to point out where more data may be needed to enable a thorough appraisal of their value.
- **prevention of secondary disease processes:** including the prevention of pressure sores, contractures, and of incidental diseases that threaten life (eg 'flu vaccination) as these pertain to MS. The guideline will take account of the guideline on pressure ulcers.
- **management of impairments and disabilities:** the following will be considered as they apply to people with MS:
  - anti-spastic treatments
  - urinary and bowel problems
  - fatigue management
  - ataxia and other movement disorders
  - visual problems

  - mood/emotions
  - swallowing/feeding/diet
  - pair/sensory disturbance
  - mobility and function posture
- **models of care:** the guideline will consider evidence on the effectiveness of models of care required to deliver the recommendations in this guideline.

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