

***Executive summary***

**Disease-modifying drugs for  
multiple sclerosis: a rapid and  
systematic review**

A Clegg\*

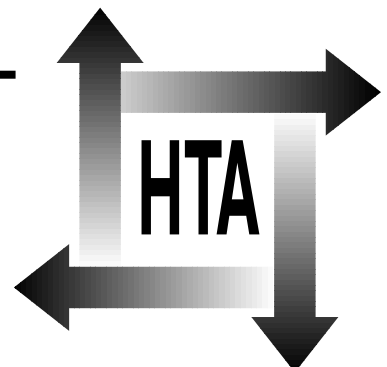
J Bryant

R Milne

Wessex Institute for Health Research and Development,  
University of Southampton, UK

\* Corresponding author

**Health Technology Assessment  
NHS R&D HTA Programme**





## Executive summary

### Background

Multiple sclerosis (MS) is a disease of the central nervous system (CNS) which affects the CNS myelin and axons. It is believed that MS is primarily an inflammatory condition in which autoimmune attack is associated with breakdown of the normal barrier separating blood from the brain.

There are three current approaches to the treatment of MS.

1. **Prevention of disease progression and relapse rates.** This is the aim of the disease modifying (or immunomodulatory) drugs. The drugs examined in this report are: azathioprine, beta interferon (IF $\beta$ ), cladribine, cyclophosphamide, glatiramer, intravenous immunoglobulin, methotrexate and mitoxantrone. Azathioprine is licensed for use in all forms of MS. IF $\beta$ -1a and 1b are licensed for use in relapsing–remitting MS and secondary progressive MS, and IF $\beta$ -1b is licensed for use in secondary progressive MS. Cladribine, cyclophosphamide, glatiramer, intravenous immunoglobulin, methotrexate and mitoxantrone are not licensed in the UK for use in MS.
2. **Treatment of acute exacerbations.** Steroids are the treatment for acute worsening of symptoms or new neurological disturbances that do not spontaneously resolve. Steroids reduce the severity of the exacerbation but do not affect consequent disability.
3. **Treatment of chronic symptoms** – such as spasticity by physiotherapy and antispasticity drugs, and fatigue by psychological and physiological treatments, and by neurorehabilitation.

### Objectives

The aim of the report is to provide a rapid review of the effectiveness and costs of disease-modifying drugs in MS.

### Methods

Methods involved searching electronic databases and bibliographies of related papers for randomised controlled trials (RCTs) and

systematic reviews, and contacting experts and pharmaceutical companies for further information. Inclusion and quality criteria were assessed, and data extraction undertaken by one reviewer and checked by a second reviewer, with any discrepancies being resolved through discussion.

### Results

#### Azathioprine

Evidence on the effectiveness of azathioprine comes from a good quality systematic review of the literature, as well as from one good and one poor quality RCT. Results suggest that azathioprine may reduce rates of relapse in patients with relapsing–remitting, relapsing–progressive and progressive MS. However, side-effects are common, particularly gastrointestinal disorders, and may affect compliance. Annual drug costs per patient are estimated to be between £50 and £1200.

#### Beta interferon

There is evidence from three large RCTs that IF $\beta$ -1a (two trials) and IF $\beta$ -1b (one trial) have limited benefit in relapsing–remitting and secondary progressive MS, respectively, although all the trials have methodological limitations. Benefits, in terms of reduced relapse rate and severity, are achieved at high cost with the annual cost per patient estimated to be between £10,000 and £20,000. Side-effects are common, particularly flu-like symptoms and injection site reactions.

#### Cladribine

Evidence on the effectiveness of cladribine comes from two small RCTs, one in chronic progressive MS patients and the other in relapsing–remitting MS patients. Results suggest that cladribine may be effective in delaying disease progression in chronic progressive MS but no significant treatment effect was found in disease progression or relapse rate in relapsing–remitting MS. The annual drug cost per patient is estimated to be £5800–8800.

#### Cyclophosphamide

The quality of evidence on the effectiveness of cyclophosphamide comes from five RCTs,

of variable design and quality, and in which different types and severity of MS and different treatment regimes are considered. One study in progressive MS suggests that cyclophosphamide combined with adenocorticotrophic hormone may be of some benefit, while another suggests that boosters of cyclophosphamide may slow progression. A wide range of side-effects is reported in all studies. The annual drug cost per patient is estimated to be less than £100.

### **Glatiramer**

Evidence for the effectiveness of glatiramer comes from one systematic review of two RCTs and a paper in which additional outcomes are reported from one of the RCTs included in the systematic review. The results suggest that relapse rate may be reduced by glatiramer treatment but the size of the benefit is not clear. The annual drug cost per patient is estimated to be about £10,000.

### **Intravenous immunoglobulin**

Evidence for the effectiveness of intravenous immunoglobulin comes from three good RCTs. The results suggest that relapse rate may be significantly reduced by intravenous immunoglobulin therapy at 3 years. A wide range of adverse effects is commonly reported. The annual drug cost per patient is estimated to be between £1600 and £10,000.

### **Methotrexate**

Evidence for the effectiveness for methotrexate comes from two RCTs, one for chronic progressive MS and the other including all forms of MS. The results suggest a treatment effect in chronic progressive MS only when using a composite outcome measure of treatment failure. Side-effects were similar to those reported for placebo. The annual drug cost per patient is £18–58.

### **Mitoxantrone**

Evidence for the effectiveness of mitoxantrone comes from two RCTs in relapsing–remitting MS. Results from both trials suggest that mitoxantrone may be of benefit in disability progression and relapse rate, although one study was of short duration and combined mitoxantrone with methylprednisolone. A range of side-effects is reported. The annual drug cost per patient is about £3600.

### **Conclusions**

Evidence for the effectiveness of immunomodulatory drugs in MS is problematic because:

- there are few good quality trials for each drug
- trials often have methodological limitations or poor reporting of data
- trials are often of small size and short duration
- there is no consistency in treatment regimes, patient groups and outcome measures
- the clinical significance of reported benefits is not clear.

### **Recommendations for research**

Well-conducted trials using outcome measures with clinical significance for different groups of MS patients and long-term follow-up are needed.

### **Publication**

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# NHS R&D HTA Programme

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The research reported in this monograph was commissioned by the HTA programme (project number 99/05/01) on behalf of the National Institute for Clinical Excellence (NICE). Rapid reviews are completed in a limited time to inform the appraisal and guideline development processes managed by NICE. The review brings together evidence on key aspects of the use of the technology concerned. However, appraisals and guidelines produced by NICE are informed by a wide range of sources. Any views expressed in this rapid review are therefore those of the authors and not necessarily those of the HTA programme, NICE or the Department of Health.

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The National Coordinating Centre for Health Technology Assessment,  
Mailpoint 728, Boldrewood,  
University of Southampton,  
Southampton, SO16 7PX, UK.  
Fax: +44 (0) 23 8059 5639 Email: [hta@soton.ac.uk](mailto:hta@soton.ac.uk)  
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