

# **Drug Class Review on Disease-modifying drugs for Multiple Sclerosis**

**Final Report  
Executive Summary**

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**The Agency for Healthcare Research and  
Quality has not yet seen or approved this report**

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The logo for Oregon Health & Science University (OHSU), consisting of the letters 'OHSU' in a bold, black, sans-serif font.

## INTRODUCTION

Multiple Sclerosis (MS) is a chronic, autoimmune disease of the central nervous system (CNS) that affects about 250,000 people in the United States, although estimates are as high as 400,000 people. Most patients are diagnosed between the ages of 20 and 50 years. MS affects women to a greater degree than men in the nation by a ratio of 1.6 females:1 male. The highest prevalence of MS is found in Caucasian women, persons of Northern European descent, and those who live in northern latitudes. MS can cause physical, mental, and emotional disability in individuals, independent of age. From a societal perspective, MS costs are estimated at \$47,215 per patient per year, including \$16,050 (34%) spent on disease-modifying drugs (DMDs) used in the treatment of MS.

Progression of MS is measured by the disability caused by the disease. The Expanded Disability Status Scale (EDSS) is a common measure of MS disability and is the primary clinical outcome in many MS clinical trials. The scale ranges from 0, defined by a normal neurological examination, to 10, defined as death due to MS. An EDSS <6 indicates the patient can walk without aid for limited distances. An EDSS  $\geq$ 6 and <8 indicates the patient is severely restricted in movement with aids or assistance. An EDSS >8 indicates the person is restricted to a bed and use of arms and legs are severely restricted. Four main types of MS have been characterized: relapsing-remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS), and progressive relapsing (PRMS). About 85% of MS patients have RRMS at the onset of the disease, and about 10% have PPMS. RRMS is characterized by well-defined acute relapses (attacks) of neurological symptoms followed by full or partial recovery. RRMS rarely progresses between relapses, although the patient may never fully recover after a relapse. On the contrary, PPMS progresses from the onset without acute attacks. Most patients with RRMS will eventually develop SPMS, which is a progressive form of the disease that may or may not have superimposed relapses. PRMS occurs in about 5% of the MS population and progresses from the onset with superimposed relapses of neurological symptoms followed by full or partial recovery.

The treatment of MS involves acute relapse treatment with corticosteroids, symptom management with appropriate agents and disease modification with DMDs. For example, when acute exacerbations occur (i.e., vision loss or loss of coordination), they are commonly treated with a short duration of high dose oral or intravenous corticosteroid; if spasticity occurs, it can be addressed with muscle relaxants; however, therapy with DMDs is designed to prevent relapses and progression of disability rather than treat specific symptoms or exacerbations of the disease. These agents modify the immune response that occurs in MS through various immunomodulatory or immunosuppressive effects. Current DMD treatments options for MS are found in Table 1.

**Table 1. Pharmacology and dosing of included drugs**

Agent	Dosage and Administration	Indication	Clinical Pharmacology
Glatiramer Acetate Copaxone <sup>®</sup>	20 mg Subcutaneously daily	RRMS	Interferes with antigen presentation by mimicking and competing with MBP, a self-antigen, for binding to the MHC on the APC. The glatiramer-MHC complex competes with the MBP-MHC complex for binding to the TCR on T helper cells, which down-regulates Th1 activity and promotes a Th2 cell response, leading to increased anti-inflammatory cytokine production
Interferon $\beta$ 1a Avonex <sup>®</sup>	30 mcg Intramuscularly	RRMS	Modulates the immune system by reducing T cell migration from the periphery into the CNS by decreasing the

	1x/week		production of adhesion molecules and increasing the production of metalloproteases on the vascular endothelium that constitutes the blood brain barrier.[Billiau, 2004 #478] These agents may also inhibit the proliferation of pro-inflammatory cytokines from Th1 cells (TNF $\alpha$ , IFN $\gamma$ , IL-12).
Interferon $\beta$ 1a Rebif <sup>®</sup>	22 or 44 mcg Subcutaneously 3x/week	RRMS	
Interferon $\beta$ 1b Betaseron <sup>®</sup>	0.25 mg Subcutaneously Every other day	RRMS, SPMS	
Mitoxantrone Novantrone <sup>®</sup>	12 mg/m <sup>2</sup> Intravenously Every 3 mos (Max cumulative dose 140 mg/m <sup>2</sup> )	SPMS, PRMS, or Worsening RRMS	Inhibits cell division and impairs the proliferation of T cells, B cells and macrophages by intercalating and crosslinking DNA, thus inhibiting DNA replication and RNA synthesis of these cells. Impairs antigen presentation by causing apoptosis of APCs and other cells that associate with APCs.
Natalizumab Tysabri <sup>®</sup>	300 mg Intravenously Every 4 weeks	RRMS	Binds to $\alpha_4$ integrins expressed on leukocytes, which prevents binding to adhesion cells VCAM-1 and MAdCAM-1 on the vascular endothelium and prevents migration of leukocytes from the periphery into the CNS.

APC = antigen-presenting cell, CNS = central nervous system, IL = interleukin, IFN = interferon, MAdCAM-1 = mucosal vascular addressin cell adhesion molecule-1, MBP = myelin basic protein, MHC = major histocompatibility complex, PRMS = progressive relapsing multiple sclerosis, RRMS = relapsing-remitting multiple sclerosis, SPMS = secondary progressive multiple sclerosis, TCR = T cell receptor, Th = T-helper, TNF = Tumor Necrosis Factor, VCAM-1 = vascular cell adhesion molecule-1, CIS = clinically isolated syndrome

Natalizumab (Tysabri<sup>®</sup>) was approved by the FDA in November 2004 but withdrawn by the manufacturer in February 2005 following reports of small numbers of patients who had been exposed to natalizumab in clinical trials developing progressive multifocal leukoencephalopathy (PML). In June 2006, the drug was reintroduced to the market for use in appropriate patients, with a required risk-minimization program (TOUCH; <http://www.fda.gov/cder/drug/infopage/natalizumab/default.htm>).

## Scope and Key Questions

The purpose of this review is to compare the effectiveness and safety of different disease-modifying drugs for the treatment of Multiple Sclerosis (MS). The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of disease-modifying treatments for multiple sclerosis, including use of differing routes and schedules of administration?
2. What is the comparative tolerability and safety of disease-modifying treatments for multiple sclerosis?
3. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?
4. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), other medications, or co-morbidities for which one disease-modifying treatment is more effective or associated with fewer adverse events?

## METHODS

### Review inclusion criteria

#### Population(s)

- Adults with Multiple Sclerosis: Relapsing Remitting MS (RRMS), Secondary Progressive MS (SPMS), Primary Progressive MS (PPMS), or Progressive Relapsing MS (PRMS)
- Adults with a clinically isolated syndrome (also known as ‘first demyelinating event’, first clinical attack suggestive of MS, or monosymptomatic presentation)

#### Interventions

Glatiramer acetate (Copaxone<sup>®</sup>), Interferon  $\beta$ 1a (Avonex<sup>®</sup>, Rebif<sup>®</sup>), Interferon  $\beta$ 1b (Betaseron<sup>®</sup>), Mitoxantrone (Novantrone<sup>®</sup>), Natalizumab (Tysabri<sup>®</sup>),

#### Outcomes

- Multiple Sclerosis or Clinically isolated syndrome
  - Disability
  - Clinical exacerbation/relapse
  - Quality of life
  - Functional outcomes (e.g., wheel-chair use, time lost from work)
  - Persistence (discontinuation rates)
  - Interferon  $\beta$  neutralizing antibodies
    - Rates of occurrence
    - Persistence with continued use
    - Impact on clinical outcomes
  - Adverse Events and Long Term Safety (e.g., cardiovascular, hepatotoxicity, progressive multifocal leukoencephalopathy (PML), secondary cancers, etc.)
- Clinically isolated syndrome:
  - Progression to MS diagnosis

*Note: MRI findings are not included, as they are intermediate or surrogate outcomes.*

#### Study designs

- For effectiveness, controlled clinical trials and good-quality systematic reviews. Observational studies with two concurrent arms of at least 100 patients each and duration  $\geq 1$  year will be included (e.g. cohort, case-control).
- For safety, in addition to controlled clinical trials, observational studies

We searched Ovid MEDLINE<sup>®</sup> (1966-week 4, Sept. 2006), the Cochrane Database of Systematic Reviews<sup>®</sup> (through Sept. 2006), and the Cochrane Central Register of Controlled Trials<sup>®</sup> (through Sept. 2006) using terms for included drugs, indications, and study designs. We also hand searched reference lists of included studies and reviews, the FDA’s Center for Drug Evaluation and Research (CDER) web site for medical and statistical reviews and dossiers submitted by pharmaceutical companies.

Two reviewers independently assessed titles and/or abstracts of citations identified from literature searches for inclusion, using the criteria described below. Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the inclusion criteria. Data were abstracted by one reviewer and checked by a second. The following data (study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results) were abstracted from included trials: for each outcome.

We assessed the internal validity (quality) of trials using predefined criteria (methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis) based on the U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (U.K.) criteria. Trials that had fatal flaws were rated “poor-quality”; trials that met all criteria were rated “good-quality”; the remainder were rated “fair-quality.” Included systematic reviews and observational studies were also rated for quality (see full report methods).

Trials that evaluated one disease-modifying drug for MS against another provided direct evidence of comparative effectiveness and adverse event rates. In theory, trials that compare a disease-modifying drug for MS to placebos can also provide evidence about effectiveness. This is known as an indirect comparison.. Data from indirect comparisons are used to support direct comparisons, where they exist, and are also used as the primary comparison where no direct comparisons exist. Such indirect comparisons should be interpreted with caution.

In addition to discussion of the findings of the studies overall, meta-analyses were conducted where possible. For each meta-analysis, we conducted a test of heterogeneity and applied both a random and a fixed effects model. Unless the results of these two methods differ in terms of significance, we reported the random effects model results.

## RESULTS

**Key Questions 1 & 2. What is the comparative effectiveness of disease-modifying treatments for multiple sclerosis, including use of differing routes and schedules of administration? What is the comparative tolerability and safety of disease-modifying treatments for multiple sclerosis?**

### RRMS

#### *β Interferons*

In the placebo-controlled trials, the rates of progression in β interferon groups at two years ranged from 11.4 to 26.6% compared to 20.3% to 36.4% in placebo groups, while in the head-to-head trials the rates ranged from 13% to 57%. Annualized relapse rates for β interferon groups ranged from 0.61 to 1.83 in placebo-controlled trials compared to 0.9 to 2.56 in placebo groups, and 0.5 to 0.71 in head-to-head trials. The evidence supports a benefit of interferon β1b SC (Betaseron<sup>®</sup>) over interferon β1a IM (Avonex<sup>®</sup>) in both relapse (% relapse-free RR 1.51 95% CI 1.11 to 2.07; NNT 6) and disease progression outcomes (% progressed RR 0.44 95% CI 0.25-0.79; NNT 6), with no differences in adverse event profiles.. Two trials suggest a benefit of interferon β1a SC (Rebif<sup>®</sup>) over interferon β1a IM (Avonex<sup>®</sup>) in terms of relapse outcomes. No

differences in disease progression outcomes were found, although the larger trial followed patients for only 16 months such that differences may not yet have been seen. Adverse event profiles of the 2 drugs differ, with interferon  $\beta$ 1a IM (Avonex<sup>®</sup>) having a higher rate of flu-like syndrome and interferon  $\beta$ 1a SC (Rebif<sup>®</sup>) having higher rates of injection site reactions, elevated liver function tests, and white blood cell abnormalities. Current evidence is unable to identify differences between interferon  $\beta$ 1b SC (Betaseron<sup>®</sup>) and interferon  $\beta$ 1a SC (Rebif<sup>®</sup>) in terms of effectiveness, and comparative adverse events have been inadequately studied. While the placebo-controlled trial of interferon  $\beta$ 1b SC (Betaseron<sup>®</sup>) was unable to show a statistically significant benefit in disease progression, placebo-controlled trials of the interferon  $\beta$ 1a's did achieve a statistically significant benefit compared to placebo. However, the head-to-head trials contradict a conclusion of inferiority for interferon  $\beta$ 1b SC (Betaseron<sup>®</sup>) and the point estimates for all three  $\beta$  interferons are very similar. The largest difference between placebo-controlled and head-to-head trial results lies in the rates of relapse-free patients with interferon  $\beta$ 1a IM (Avonex<sup>®</sup>). The placebo-controlled trial rate was 66.5%, while the head-to-head trial rates were lower (20% and 36%), resulting in interferon  $\beta$ 1a IM (Avonex<sup>®</sup>) being inferior to the other  $\beta$  interferons.

Evidence for interferon  $\beta$ 1b SC (Betaseron<sup>®</sup>) and interferon  $\beta$ 1a SC (Rebif<sup>®</sup>) indicates that positive neutralizing antibody status adversely affects the impact of these drugs on relapse rates, by one-half to two-thirds, during longer periods of follow-up. This difference is not seen for any of the products in shorter follow-up (2 years or less). Interferon  $\beta$ 1a IM (Avonex<sup>®</sup>) appears to have the lowest immunogenicity, with rates of development of neutralizing antibodies of 2-8.5% reported, starting around 9 months of treatment, while evidence indicates that with interferon  $\beta$ 1a SC (Rebif<sup>®</sup>) antibodies occur somewhat later (9 months) with rates of immunogenicity as low as 12% and as high as 46%, and with interferon  $\beta$ 1b SC (Betaseron<sup>®</sup>) neutralizing antibodies appear as early as 3 months into treatment in 30-40% of patients.. Importantly, 40-50% of antibody positive patients will become antibody negative over time, while small numbers of patients will become antibody positive into the second year of treatment. While interferon  $\beta$ 1a IM (Avonex<sup>®</sup>) appears to have lower immunogenicity, clinical trial evidence indicates that the other 2  $\beta$  interferons may be superior in regards to clinical outcomes. Better quality trials are needed to resolve this apparent discrepancy.

### ***Glatiramer acetate***

The mean difference in relapse rate between glatiramer and placebo was statistically significant (-0.64 [-1.19, -0.09] p=0.02) when results from three trials were pooled. There was no statistically significant difference in the percentage of relapse-free patients between glatiramer acetate and placebo groups (RR 1.23; p=0.086). The effect of glatiramer acetate on disease progression is unclear. Mean change in EDSS was reported as a secondary outcome in one trial. Two-year data showed that while glatiramer acetate was associated with a statistically significant (p=0.023) change in EDSS (-0.05) when compared to placebo (0.21) the clinical significance of such a difference is likely minimal.

Adverse events rates were higher for glatiramer acetate when compared to placebo, most notably post-injection systemic reactions and injection-site reactions (both usually of limited duration; p<0.0001), as were withdrawals due to adverse events (3.7% vs. 1.1%, p=0.08). Withdrawal rates for glatiramer acetate were also consistently significantly higher in observational studies when compared to placebo.

### ***Natalizumab***

Natalizumab (Tysabri<sup>®</sup>) was consistently more effective than placebo for both relapse-related outcomes and disease progression in two trials. One of those trials included interferon  $\beta$ 1a IM (Avonex<sup>®</sup>) used concomitantly with the natalizumab and placebo arms; however this did not appear to impact the findings of that trial in terms of effectiveness outcomes. Adverse event rates were similar in both trials and there were no significant differences between the comparisons. Two cases of progressive multifocal leukoencephalopathy (PML) led to cessation of one trial although the link between PML and natalizumab use has not been firmly established.

### ***Mitoxantrone***

Limited evidence from one small trial showed that mitoxantrone (Novantrone<sup>®</sup>) was more effective than placebo for both disease progression and relapse rate. There was no adverse event data reported for the placebo arm in this trial, making it impossible to draw conclusions regarding the comparative safety of mitoxantrone relative to placebo.

## **SPMS**

### ***$\beta$ Interferons***

Based on 5 placebo-controlled trials there is evidence that interferon  $\beta$ 1b SC (Betaseron<sup>®</sup>) is effective in slowing progression in patients with SPMS, particularly those with more active disease. Evidence for the  $\beta$ 1a interferons (IM or SC; Avonex<sup>®</sup> or Rebif<sup>®</sup>) is less convincing for slowing progression based on the EDSS, although the newer measure, MSFC, allowed a benefit to be seen with interferon  $\beta$ 1a IM (Avonex<sup>®</sup>). Studies indicate that all of the  $\beta$  interferons do have an impact by reducing relapse rates. Again, those with more active disease appear to benefit more. No studies of glatiramer acetate, natalizumab, or mitoxantrone in patients with SPMS were found.

Pooled analysis suggests significantly higher rates of injection site reactions (2.51 95% CI 1.56- 4.04; NNH 3), abnormal liver function tests (3.38 95% CI 2.16- 5.27; NNH 8), and withdrawal due to adverse events (2.61 95% CI 1.23- 5.53; NNH 30) with interferon  $\beta$ 1a SC (Rebif<sup>®</sup>) and flu-like syndrome (1.37 95% CI 1.02- 1.85; NNH 7) and withdrawal due to adverse events (2.24 95% CI 1.26-4.00; NNH 32) with interferon  $\beta$ 1b SC (Betaseron<sup>®</sup>) compared to placebo.

## **Mixed populations: RRMS and SPMS**

### ***$\beta$ Interferons***

Quality of life is improved with interferon  $\beta$ 1b SC (Betaseron<sup>®</sup>) treated patients when compared to untreated controls; however the effect diminishes based on higher baseline disability scores.

### ***Natalizumab***

Based on limited data from two trials, there was no statistically significant difference between natalizumab (Tysabri<sup>®</sup>) and placebo in change in EDSS, although one of the trials did find that natalizumab significantly impacted relapse rate. These findings must be interpreted with extreme caution as these trials were of relatively short durations and this finding is markedly different from that of the two, larger natalizumab trials in RRMS patients alone. Adverse events

and withdrawal rates varied widely among the three studies reporting safety outcomes, however there were no overall differences between the natalizumab and placebo groups.

### **Mitoxantrone**

Pooled data from four trials provided evidence that mitoxantrone (Novantrone<sup>®</sup>) is superior to placebo for relapse-related outcomes and disease progression.

Mitoxantrone use is associated with more withdrawals due to adverse events than placebo.

Amenorrhea, nausea and vomiting, alopecia and urinary tract infections also affect significantly higher proportions of mitoxantrone patients relative to placebo.

### **PPMS**

Current evidence is limited to a small (n = 50) trial of interferon  $\beta$ 1a IM (Avonex<sup>®</sup>) which found no statistically significant differences in the time to sustained progression between the placebo and  $\beta$  interferon groups at doses of 30 or 60 mcg once weekly. The 60  $\mu$ g dose was not well tolerated, with 4 of 15 patients (27%) withdrawing due to flu-like reactions, and another third requiring dose reduction due to either flu-like reactions or elevations in liver function tests. No studies of glatiramer, natalizumab or mitoxantrone in patients with PPMS were found.

### **Mixed populations: PPMS and SPMS**

#### ***Glatiramer acetate***

Glatiramer acetate (Copaxone<sup>®</sup>) was found to be superior to placebo for disease progression and EDSS change at 24 months in a “chronic progressive” patient population; there were no other significant differences between the glatiramer acetate and placebo groups in effectiveness outcomes; glatiramer acetate patients also experienced more adverse effects compared to placebo patients. No studies of  $\beta$  interferons, natalizumab, or mitoxantrone in a mixed PPMS and SPMS population were found.

### **PRMS**

No studies were identified that assessed the use of one of the included drugs in patients with PRMS.

### **Adverse Events and Long-term Safety**

#### ***$\beta$ Interferons***

##### *Tolerability*

Tolerability adverse events were reported frequently with all 3  $\beta$  interferon products, although differences between the products are apparent:

**Table 2. Comparative tolerability of  $\beta$  interferons based on all trial evidence**

<b>Adverse Effect</b>	<b>Relative Frequencies Based on Pooled Trial Rates</b>
Injection Site Reaction	Interferon $\beta$ 1b SC (Betaseron <sup>®</sup> ) > Interferon $\beta$ 1a SC (Rebif <sup>®</sup> ) > Interferon $\beta$ 1a IM (Avonex <sup>®</sup> )
Flu-Like Syndrome	Interferon $\beta$ 1a IM (Avonex <sup>®</sup> ) > Interferon $\beta$ 1b SC (Betaseron <sup>®</sup> ) ~ Interferon $\beta$ 1a SC (Rebif <sup>®</sup> )
Fatigue	Interferon $\beta$ 1a SC (Rebif <sup>®</sup> ) > Interferon $\beta$ 1b SC (Betaseron <sup>®</sup> )
Fever	Interferon $\beta$ 1b SC (Betaseron <sup>®</sup> ) > Interferon $\beta$ 1a SC (Rebif <sup>®</sup> ) > Interferon $\beta$ 1a IM (Avonex <sup>®</sup> )
Depression	Interferon $\beta$ 1b SC (Betaseron <sup>®</sup> ) ~ Interferon $\beta$ 1a IM (Avonex <sup>®</sup> ) > Interferon $\beta$ 1a SC (Rebif <sup>®</sup> )
Overall withdrawal	Interferon $\beta$ 1b SC (Betaseron <sup>®</sup> ) > Interferon $\beta$ 1a SC (Rebif <sup>®</sup> ) > Interferon $\beta$ 1a IM (Avonex <sup>®</sup> )

Discontinuation due to AE	Interferon $\beta$ 1b SC (Betaseron <sup>®</sup> ) > Interferon $\beta$ 1a SC (Rebif <sup>®</sup> ) > Interferon $\beta$ 1a IM (Avonex <sup>®</sup> )
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> = more frequent than; ~ = about the same frequency

### Thyroid function

Evidence from non-randomized studies suggests that there is no difference among the  $\beta$  interferons in risk of developing thyroid dysfunction, although rates are slightly, but not significantly, higher with interferon  $\beta$ 1b SC (Betaseron<sup>®</sup>).

### Liver function

Liver failure has not been reported in trials of  $\beta$  interferons. One post-marketing case report of liver failure in an MS patient taking interferon  $\beta$ 1a IM (Avonex<sup>®</sup>) appears to be linked to  $\beta$  interferon use; the relationship between interferon  $\beta$ 1a SC (Rebif<sup>®</sup>) and liver failure in a second case report is unclear due to concomitant use of a known hepatotoxic drug. No cases of liver failure have been reported with Interferon  $\beta$ 1b SC (Betaseron<sup>®</sup>). Although overall incidence of ALT elevations was lower in the placebo-controlled trials than in observational studies, ALT elevations were common with all three products.

### Depression

A meta-analysis of 6 randomized controlled trials and 17 postmarketing, unpublished studies provided little additional comparative evidence on depression rates among  $\beta$  interferon products, instead focusing on comparing  $\beta$  interferons and placebo. Six-month data showed little difference in depression rates between the interferon  $\beta$ 1a products: 5-12% for interferon  $\beta$ 1a SC (Rebif<sup>®</sup>) and 18% for interferon  $\beta$ 1a IM (Avonex<sup>®</sup>). Withdrawals rate due to depression were not significantly different between the interferon  $\beta$ 1a products.

Our own analysis of the all published trials reporting rates of depression indicates a non-significant increase in risk for both interferon  $\beta$ 1a products and a non-significant decrease in risk with interferon  $\beta$ 1b SC (Betaseron<sup>®</sup>). Our adjusted indirect analysis indicates no significant difference among the interferons for risk of depression although the relative risks favored interferon  $\beta$ 1b SC (Betaseron<sup>®</sup>) over the  $\beta$ 1a products, and interferon  $\beta$ 1a SC (Rebif<sup>®</sup>) had a higher pooled estimate compared to interferon  $\beta$ 1a IM (Avonex<sup>®</sup>).

### **Glatiramer acetate**

Safety data from five non-randomized studies of glatiramer acetate (Copaxone<sup>®</sup>) is consistent with that from randomized trials, with adverse events being more common with glatiramer use compared to placebo. Reports of lipoatrophy from a non-randomized trial identified 34/76 glatiramer acetate-treated patients as having drug induced lipoatrophy. This finding is inconclusive based on the small number of patients and lack of confirmation from other studies.

### **$\beta$ interferons vs. glatiramer acetate**

There is little additional evidence regarding the comparative safety of interferons and glatiramer acetate based on data from observational and other non-randomized studies. While the types of adverse events reported in these studies and the rates of withdrawals due to adverse events are similar to those reported in controlled trials of these drugs, rates of other adverse events varied widely. These discrepant rates may be the result of study design, as higher rates of flu-like syndrome, injection-site reactions and fever were found in the trials, regardless of intervention.

### **Natalizumab**

Natalizumab (Tysabri<sup>®</sup>) use has been potentially linked to three cases of progressive multifocal leukoencephalopathy in trials. An observational study of 3,389 patients failed to identify any further cases.

### **Mitoxantrone**

Adverse events in non-randomized studies of mitoxantrone (Novantrone<sup>®</sup>) were consistent with those in trials, most commonly nausea/vomiting, alopecia and amenorrhea in women. An observational study that used data from one trial and two open-label studies found relatively low rates of cardiac adverse events (CHF: 0.15%; asymptomatic LVEF <50%: 2.18%). Subgroup analysis suggested that higher cumulative doses of mitoxantrone were potentially associated with greater risk of asymptomatic LVEF <50%, although this failed to reach statistical significance (p=0.06). The risk of therapy-related acute leukemia appears to be dose related, as the two known cases were reported in patients who had received 70 mg/m<sup>2</sup> cumulative dose. A meta-analysis that included 1,620 patients found the overall rate of PML to be very low overall (0.12%).

### **Key Question 3. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?**

Evidence suggests that all 3 interferon  $\beta$ 1 products reduce the probability of converting from clinically isolated syndrome to clinically definite MS over 2 to 5 year periods. At 3 years, interferon  $\beta$ 1a IM (Avonex<sup>®</sup>) was superior to placebo (RR 0.56 95% CI 0.38 – 0.81; NNT 7). At 2 years, interferon  $\beta$ 1a SC (Rebif<sup>®</sup>) was similarly superior to placebo (RR 0.65 95% CI 0.45 to 0.94; NNT 9). At 2 years, both Betaseron<sup>®</sup> and Rebif<sup>®</sup> were also superior to placebo: rate ratios 0.50 (95% CI 0.36-0.70; NNT 6) and 0.65 (95% CI 0.45 to 0.94; NNT 9) respectively. No evidence was found for glatiramer acetate, natalizumab, or mitoxantrone in patients with clinically isolated syndrome.

### **Key Question 4. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), other medications, or co-morbidities for which one disease-modifying treatment is more effective or associated with fewer adverse events?**

Only 2 studies assessed the effects of disease modifying treatments for MS in subgroups of patients, one in pregnant women and a subgroup analysis of African-Americans from a larger trial population. Both studies assessed  $\beta$  interferons. Neither study provides evidence on comparative benefits or adverse effects of the  $\beta$  interferons in these subgroups, nor do they provide conclusive evidence about  $\beta$  interferons as a group in these patients. An individual patient-data meta-analysis of interferons 1a (Avonex<sup>®</sup> and Rebif<sup>®</sup>) found an increased rate of loss of pregnancy among those with exposure in utero, but the small sample size indicates the results are uncertain. Further research is needed to clarify the risk.

**Table 3. Summary of evidence by key question**

Key question	Conclusion
<p><b>Key Question 1: What is the comparative effectiveness of disease-modifying treatments for multiple sclerosis, including use of differing routes and schedules of administration?</b></p> <p><b>Quality of the Evidence: Fair</b></p>	<p><b>RRMS:</b> <u>Direct evidence-</u></p> <ul style="list-style-type: none"> <li>• Direct evidence from four fair-quality head-to-head trials showed little difference in relapse and disease progression outcomes between interferon <math>\beta</math>1a SC (Rebif<sup>®</sup>) and interferon <math>\beta</math>1b (Betaseron<sup>®</sup>), while interferon <math>\beta</math>1a IM (Avonex<sup>®</sup>) was less effective than interferon <math>\beta</math>1a SC (Rebif<sup>®</sup>) for relapse outcomes and interferon <math>\beta</math>1b (Betaseron<sup>®</sup>) for relapse and disease progression outcomes.</li> </ul> <p><u>Indirect evidence-</u></p> <ul style="list-style-type: none"> <li>• Evidence from placebo-controlled trials demonstrated the superiority of the interferon <math>\beta</math>1a products in slowing disease progression relative to placebo, while interferon <math>\beta</math>1b (Betaseron<sup>®</sup>) was not significantly better than placebo for this outcome. This contradicts the findings from the head-to-head trials. Conversely, interferon <math>\beta</math>1a IM (Avonex<sup>®</sup>) rates of relapse-free patients in placebo-controlled trials were similar to the other <math>\beta</math> interferons, which also contradict the findings from the head-to-head trials.</li> <li>• Glatiramer, natalizumab and mitoxantrone were more effective than placebo for relapse-related outcomes in placebo-controlled trials. Natalizumab and mitoxantrone were more effective than placebo in slowing disease progression; the evidence on the effect of glatiramer on disease progression is inconclusive based on data from one trial. Evidence for all three drugs is based on a small number of trials (3 for glatiramer, 2 for natalizumab and 1 for mitoxantrone).</li> </ul> <p><b>SPMS:</b> There is no direct evidence. Evidence from placebo-controlled trials showed that the all of <math>\beta</math> interferons were similarly effective at reducing relapse rates. A positive effect on disease progression was observed with interferon <math>\beta</math>1b (Betaseron<sup>®</sup>) although similar effects were not consistently observed with the interferon <math>\beta</math>1a products.</p> <p><b>PPMS:</b> The only evidence available (from one small, good quality trial comparing interferon <math>\beta</math>1a IM (Avonex<sup>®</sup>) to placebo) is insufficient to make any judgments regarding effectiveness in PPMS patients.</p> <p><b>PRMS:</b> No studies of DMD use in PRMS patients were identified through literature searches.</p>
<p><b>Key Question 2: What is the comparative tolerability and safety of disease-modifying treatments for multiple sclerosis?</b></p> <p><b>Quality of the Evidence: Fair</b></p>	<p><u>Withdrawals due to adverse events:</u> No difference in withdrawal rates among <math>\beta</math> interferons in head-to-head trials, although adverse events in generally were poorly reported in these trials. Withdrawal rates ranged from 3% (Interferon <math>\beta</math>1a IM [Avonex<sup>®</sup>]), glatiramer acetate) to 9% (Interferon <math>\beta</math>1b SC [Betaseron<sup>®</sup>]) in placebo-controlled trials.</p> <p><u>Serious adverse events:</u></p> <p><u>NABs:</u> The clinical impact of the presence of neutralizing antibodies is unclear although limited data suggests they may negatively impact relapse rate after 3-4 years of treatment.</p> <p><u>Liver function:</u> ALT elevations are common with all <math>\beta</math> interferon products, with little difference in rates of occurrence. Most elevations are asymptomatic and transitory.</p> <p><u>Thyroid function:</u> Limited data from two observational studies found similar rates of clinical and subclinical thyroid autoimmunity with Interferon <math>\beta</math>1a IM (Avonex<sup>®</sup>) and Interferon <math>\beta</math>1b SC (Betaseron<sup>®</sup>)</p> <p><u>Depression:</u> There were no significant differences in rates of depression among the <math>\beta</math> interferons based on limited trial data. One small observational study comparing <math>\beta</math> interferons and glatiramer also found no differences in depression rates, although our own analysis of the all published trials reporting rates of depression indicates a non-significant increase in risk for both interferon <math>\beta</math>1a products and a non-significant decrease in risk with interferon <math>\beta</math>1b SC (Betaseron<sup>®</sup>.)</p> <p><u>Cancer:</u> Data from one cohort study found a potentially increased risk of cancer development in women with either <math>\beta</math> interferon or glatiramer acetate use; these results are inconclusive. Therapy-related acute leukemia was reported in 2/1,620 patients taking mitoxantrone.</p> <p><u>Cardiotoxicity:</u> Two cases of CHF were potentially linked to mitoxantrone use in one meta-</p>

	<p>analysis of three (two unpublished) studies (incidence 0.15%)  <u>Progressive multifocal leukoencephalopathy (PML)</u>: Estimates of PML incidence with natalizumab use is 1.0/1,000 patients based on three known cases.</p> <p><i>Tolerability:</i>  <u>Flu-like syndrome</u>: Interferon <math>\beta</math>1a IM (Avonex<sup>®</sup>) was associated with the highest rates of flu-like syndrome compared to the other <math>\beta</math> interferons (~58% vs ~41%)  <u>Injection-site reactions</u>: Interferon <math>\beta</math>1b SC (Betaseron<sup>®</sup>) was associated with the highest rates of injection-site reactions (60.5% vs 10.0-  <u>Systemic reactions</u>: Post-injection systemic reactions were observed in 24% of glatiramer acetate patients, although these were usually limited to a single episode. There were no reports of this outcome in trials of <math>\beta</math> interferons, natalizumab or mitoxantrone.</p> <p><i>Long-term safety in observational studies</i>: Long-term safety data from comparative and non-comparative, non-randomized studies was consistent with that reported in trials and did not substantially add to the evidence base or alter the strength of evidence for any of the included drugs.</p>
<p><b>Key Question 3: What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?</b></p> <p><b>Quality of the Evidence: Fair to Poor</b></p>	<p>No direct evidence comparing one DMD to another in patients with a clinically isolated syndrome was available. Indirect comparison of interferon <math>\beta</math>1a IM (Avonex<sup>®</sup>), interferon <math>\beta</math>1a SC (Rebif<sup>®</sup>) and interferon <math>\beta</math>1b (Betaseron<sup>®</sup>) from 3 placebo-controlled trials found them all more effective than placebo at reducing the probability of converting to clinically definite MS. The drugs had higher rates of adverse events relative to placebo.</p> <p>There is no evidence on glatiramer (Copaxone<sup>®</sup>), mitoxantrone (Novantrone<sup>®</sup>) or natalizumab (Tysabri<sup>®</sup>) use in clinically isolated syndromes.</p>
<p><b>Key Question 4: Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), other medications, or co-morbidities for which one disease-modifying treatment is more effective or associated with fewer adverse events?</b></p> <p><b>Quality of the Evidence: Poor</b></p>	<p>Only 3 studies provided evidence of effectiveness or safety in subgroups. Conclusions regarding DMD use in these subgroups cannot be drawn from these small studies.</p> <p><u>Race</u>: Evidence from one observational study African-American RRMS patients is insufficient to draw conclusions regarding the comparative effectiveness or safety of DMDs in this subgroup.</p> <p><u>Pregnancy</u>: 2 studies; a small observational study, assessing rates of live birth in pregnant women with MS using <math>\beta</math> interferons compared to a healthy cohort and an individual patient data meta-analysis based on 8 trials of interferon <math>\beta</math>1a both found lower rates of live-birth among women exposed to interferons during pregnancy. However, these studies are small and do not provide comparative data on the safety of one <math>\beta</math> interferon versus another. The first study reports that the <math>\beta</math> interferon-exposed pregnancies were more likely to result in non-live birth compared to the healthy cohort (OR 6.94, 95% CI 1.18 to 40.70) and the individual patient data meta-analysis found a rate of 29% pregnancy loss among women with exposure to interferons <math>\beta</math>1a during an 'in utero' phase, compared to 0 in either the placebo or prior exposure groups.</p> <p>However, these studies provided no conclusive evidence regarding <math>\beta</math> interferon use in pregnancy.</p>