Drug Class Review
on
Disease-modifying drugs for Multiple Sclerosis

Final Report

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

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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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.[1, 2] 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.[1] 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.[3]

Diagnostic criteria for MS includes a clinical presentation of two or more attacks *and* objective clinical evidence of two or more lesions in the myelinated regions of the CNS found by magnetic resonance imaging (MRI).[4] The Revised McDonald Criteria defines an attack as an episode of neurological disturbance for which causative lesions are likely to be inflammatory and demyelinating in nature.[4] A diagnosis of MS may also be made in a clinically isolated syndrome with presentation of a single attack and evidence of one or more lesions. However, criteria have become stricter to maintain specificity. For example, MRI dissemination in space and time are critical, and cerebral spinal fluid analysis may be needed to identify oligoclonal bands or increased immunoglobulin G (IgG) often present in 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[5, 6], although the Multiple Sclerosis Functional Composite (MSFC) is also used to measure disability. The scale ranges from 0, defined by a normal neurological examination, to 10, defined as death due to MS.[5] An EDSS <6 indicates the patient can walk without aid for limited distances.[5] An EDSS ≥6 and <8 indicates the patient is severely restricted in movement with aids or assistance.[5] An EDSS >8 indicates the person is restricted to a bed and use of arms and legs are severely restricted.[5] 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.[7] 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.[7]

MS causes demyelination of neuronal axons that form lesions within the white matter of the CNS (i.e., cerebral white matter, brain stem, cerebellar tracts, optic nerves, or spinal cord) when viewed on a MRI. Demyelination may cause an abnormal proliferation of sodium channels within the membrane that slows, or even blocks, axonal conduction.[8] A sodium-calcium exchanger is also upregulated within the membrane, which increases sodium efflux and calcium influx and results in neuronal degeneration.[8] The impairment of conduction down neurons ultimately causes the neurological symptoms associated with MS. Indeed, the classification of

symptoms as monofocal or multifocal are often associated with the location and number of lesions in the CNS. For example, vision loss reflects a lesion in the optic nerve.

Although more data is becoming available, the pathogenesis of MS remains elusive. Myelin-reactive T cells and B cells are present in MS.[7] Environmental factors, such as infectious agents, seem to facilitate the movement of these cells from the periphery, across the blood brain barrier, and into the CNS in persons genetically susceptible to MS. The migration of T cells and antibodies across the blood brain barrier occurs because adhesion molecules, in addition to proteases that break down the endothelial cells that make up the barrier, are activated.[7] Once within the CNS, the T cells secrete interferon γ and interleukin 17.[7] The antigen presenting cells (APC) and T helper cells form a complex by binding to a self-antigen, such as myelin basic protein via the major histocompatibility complex (MHC) and T cell receptor, respectively.[7] Antigen presentation to these cells causes an enhanced immune response. Depending on other interacting molecules, the T helper cell-APC complex may cause type 1 T helper cells (Th1) to secrete pro-inflammatory cytokines, such as interferon γ, or type 2 T helper cells (Th2), to secrete anti-inflammatory cytokines, such as interleukin 4. Macrophages, cytotoxic T cells, auto-antibodies secreted from B cells, and pro-inflammatory cytokines secreted from T helper cells are also activated during this process.[8] Acute inflammatory, demyelinating plaques occur when myelin undergoes phagocytosis by macrophages when coated with antibodies for myelin basic protein and myelin oligodendrocyte glycoprotein.[8] In addition, cytotoxic T cells and pro-inflammatory cytokines may directly damage the myelin.[8]

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 then 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®	20 mg Subcutaneously qd[9]	RRMS[9]	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.[10]
Interferon β 1a Avonex®	30 mcg Intramuscularly 1x/wk[11]	RRMS[11]	Modulates the immune system by reducing T cell migration from the periphery into the CNS by decreasing the production of adhesion molecules and increasing the production of metalloproteases on the vascular endothelium that constitutes the blood brain barrier.[12] These agents may also inhibit the proliferation of pro-inflammatory cytokines from Th1 cells
Interferon β 1a Rebif®	22 or 44 mcg Subcutaneously 3x/wk[13]	RRMS[13]	
Interferon β 1b Betaseron®	0.25 mg Subcutaneously Every other day[14]	RRMS, SPMS[14] ,CIS	

			(TNFα, IFNγ, IL-12).[12]
Mitoxantrone Novantrone®	12 mg/m^2 Intravenously Every 3 mos (Max cumulative dose is 140 mg/m^2)[15]	SPMS, PRMS, or Worsening RRMS[15]	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.[16]
Natalizumab Tysabri®	300 mg Intravenously Every 4 wks [17]	RRMS[17]	Binds to α_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.[18]

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

Three of the four immunomodulatory agents are type-1 β interferons: interferon β1b SC (Betaseron®) and interferon β1a IM and SC (Avonex® and Rebif®). The fourth agent is glatiramer acetate (Copaxone®). It is currently thought that type-1 β interferons modulate the immune system by reducing T cell migration from the periphery into the CNS by decreasing the production of adhesion molecules and increasing the production of proteases on the endothelial cells that make up the blood brain barrier.[12] These agents may also inhibit the proliferation of pro-inflammatory cytokines, such as interferon γ.[12] In contrast, glatiramer acetate (Copaxone®) interferes with antigen presentation by mimicking and competing with myelin basic protein (MBP), a self-antigen, for binding to the MHC on the APC.[10] The glatiramer-MHC complex competes with the MBP-MHC complex for binding to the T cell receptor on T helper cells, which down-regulates Th1 activity and promotes a Th2 cell response, leading to increased anti-inflammatory cytokine production.[10]

Natalizumab (Tysabri®) is a recombinant monoclonal antibody that binds to α4 integrins expressed on all leukocytes (except neutrophils), 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.[18] The inhibition of T-cell migration into the CNS prevents the induction of cytokines involved in the inflammation processes associated with MS. The drug was initially approved by the FDA in November 2004, withdrawn by the manufacturer in February 2005, and reintroduced in June 2006. The following is an excerpt from the FDA's statement about the drug's reintroduction:

> *Tysabri was initially approved by the FDA in November, 2004, but was withdrawn by the manufacturer in February 2005 after three patients in the drug's clinical trials developed progressive multifocal leukoencephalopathy (PML), a serious viral infection of the brain. FDA then put clinical trials of the drug on hold in February, 2005, allowing them to resume a year later after confirming that there were no additional cases of PML. In March, 2006, FDA consulted its Advisory Committee on drugs for peripheral and central nervous systems about the possibility of making Tysabri available to appropriate MS patients. The Advisory Committee recommended a risk-minimization program with mandatory patient registration and periodic follow-up. In response, the manufacturer,*

> *Biogen-Idec, submitted to the agency a Risk Management Plan to help ensure safe use of the product. Tysabri is available only through the Risk Management Plan, called the TOUCH Prescribing Program. In order to receive Tysabri, patients must talk to their doctor and understand the risks and benefits of Tysabri and agree to all of the instructions in the TOUCH Prescribing Program.*

See the following web site for more information on the TOUCH Prescribing Program: http://www.fda.gov/cder/drug/infopage/natalizumab/default.htm.

Mitoxantrone (Novantrone®) is an antineoplastic agent originally approved for adult acute myeloid leukemia and later approved for SPMS, PRMS, and worsening RRMS as an immunosuppressant drug. Mitoxantrone is thought to inhibit cell division and impair the proliferation of T cells, B cells, and macrophages by intercalating and crosslinking DNA, thus inhibiting DNA replication and RNA synthesis of these cells.[16] Mitoxantrone also impairs antigen presentation by causing apoptosis of APCs and other cells that associate with APCs.[16] This drug carries a black box warning about the risk of cardiotoxicity and has a life-time cumulative dose limit of 140 mg/m^2.

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

Literature Search

To identify relevant citations, we searched Ovid MEDLINE® (1966 - week 4, Sept. 2006), the Cochrane Database of Systematic Reviews® (through Sept. 2006), and the Cochrane Central Register of Controlled Trials® (through Sept. 2006) using terms for included drugs, indications, and study designs (see Appendix A for complete search strategies). We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. In addition, we searched the FDA's Center for Drug Evaluation and Research (CDER), the Canadian Agency for Drugs and Technology in Health (CADTH), and the National Institute for Health and Clinical Excellence (NICE) web sites for medical and statistical reviews and technology assessments. Finally, we searched dossiers submitted by pharmaceutical companies for the current review. All citations were imported into an electronic database (Endnote® v.9.0).

Study Selection

Two reviewers (MM, TD) 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. Results published *only* in abstract form were not included because inadequate details were available for quality assessment, however if we were provided with enough information to conduct quality assessment we did include the study. Additional results from fully published studies (e.g. relating to secondary outcome measures) found only in abstract form were included because the study quality could be assessed through the complete publication.

Study inclusion criteria

Population(s)

Adult outpatients with Multiple Sclerosis[19, 20]

- Relapsing Remitting MS (RRMS)
- Secondary Progressive MS (SPMS)
- Primary Progressive MS (PPMS)
- Progressive Relapsing MS (PRMS)

Adult outpatients with a clinically isolated syndrome (also known as 'first demyelinating event', first clinical attack suggestive of MS, or monosymptomatic presentation)[20]

Interventions (all formulations)

- Glatiramer acetate (Copaxone®)
- Interferon β1a (Avonex®, Rebif®)
- Interferon β1b (Betaseron®)
- Mitoxantrone (Novantrone®)
- Natalizumab (Tysabri®)

Effectiveness outcomes

Multiple Sclerosis
- Disability
- Clinical exacerbation/relapse
- Quality of life
- Functional outcomes (e.g. wheel-chair use, time lost from work)
- Persistence (discontinuation rates)

Clinically isolated syndrome
- Disability
- Clinical exacerbation/relapse
- Quality of life
- Functional outcomes (e.g. wheel-chair use, time lost from work)
- Persistence (discontinuation rates)
- Progression to MS diagnosis

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

Safety outcomes

- Overall rate of adverse effects
- Withdrawals due to adverse effects
- Serious adverse events
- Specific adverse events (cardiovascular, hepatotoxicity, progressive multifocal leukoencephalopathy (PML), secondary cancers, etc.)

Other outcomes

- Interferon β neutralizing antibodies
  - -Rates of occurrence
  - -Persistence with continued use
  - -Impact on clinical outcomes (above)

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 ≥1 year will be included (e.g. cohort, case-control).
- For safety, in addition to controlled clinical trials, observational studies will be included.

Data Abstraction

The following data were abstracted from included trials: 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 for each outcome. Data were abstracted by one reviewer and checked by a second. We recorded intention-to-treat results when reported. If true intention-to-treat results were not reported, but loss to follow-up was very small, we considered these results to be intention-to-treat results. In cases where only per-protocol results were reported, we calculated intention-to-treat results if the data for these calculations were available.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix B. These criteria are based on the U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (U.K.) criteria.[21, 22] We rated the internal validity of each trial based on the 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. Trials that had fatal flaws were rated "poor-quality"; trials that met all criteria were rated "good-quality"; the remainder were rated "fair-quality." As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A poor-quality trial is not valid in that the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. A fatal flaw is reflected by failing to meet *combinations* of items of the quality assessment checklist.

A particular randomized trial might receive two different ratings: one for effectiveness and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Included systematic reviews were also rated for quality based on pre-defined criteria (see Appendix B), based on a clear statement of the questions(s), inclusion criteria, adequacy of search strategy, validity assessment and adequacy of detail provided for included studies, and appropriateness of the methods of synthesis.

The external validity (applicability) of studies was recorded based how similar patients were to the target population in whom the intervention will be applied and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the role of the funding source.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. A qualitative synthesis of the evidence is undertaken for all relevant data. Trials that evaluated one disease-modifying drug for MS against another provided *direct* evidence of comparative effectiveness and adverse event rates. Where possible, these data are the primary focus of the evidence synthesis. In theory, trials that compare a disease-modifying drug for MS to placebos can also provide evidence about effectiveness.[23, 24] This is known as an *indirect* comparison and can be difficult to interpret for a number of reasons, primarily issues of heterogeneity between trial populations, interventions, and assessment of outcomes. 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. In order to determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and heterogeneity across studies in study design, patient population, interventions, and outcomes. For each meta-analysis, we conducted a test of heterogeneity using the Q-statistic.[25] We applied both a random effects model using the DerSimonian-Laird method[26] and a fixed effects model using the Mantel-Haenszel type method of Rothman and Boice[27] to produce a pooled estimate. A 95% confidence interval for the pooled

estimate is calculated using the Greenland-Robins variance formula.[28] Unless the results of these two methods differ in terms of significance, we reported the random effects model results. Meta-analysis was performed using StatsDirect (Camcode, UK) and the meta package in R.[29]

We used the method described by Bucher et al, to perform indirect analyses.[24] Indirect comparisons usually agree with direct comparisons, though large discrepancies have been reported in some cases.[30, 31] In addition, indirect comparisons also result in less precise estimates of treatment effects compared to the same number of similarly sized head-to-head trials because methods for indirect analyses incorporate additional uncertainty from combining different sets of trials.[23, 24] Because of this, we pursued an exploratory analysis combing the indirect and direct pooled estimates using a Bayesian approach. Data from indirect comparisons was synthesized with data from direct, head-to-head studies when possible. Using a Bayesian data analytical framework, effect size estimated from the indirect analysis was used as the prior probability distribution in a meta-analysis of the data from the direct head-to-head studies. Bayesian analysis was conducted using OpenBUGS and the BRugs package in R.[29, 32]

RESULTS

Overview

Literature searches identified 1,873 citations. An additional 7 citations were identified through peer review and public comment. After applying the eligibility and exclusion criteria to the titles and abstracts, we obtained full-text of 339 citations. Following full-text review of these papers, we ultimately included 168 study publications: 51 trial publications, 13 systematic reviews, 69 non-randomized, including observational, studies and 35 background papers. Dossiers were received from four pharmaceutical manufacturers: Biogen: Interferon β 1a IM (Avonex®) and Natalizumab (Tysabri®); Serono: Interferon β 1a SC (Rebif®) and Mitoxantrone (Novantrone®); Berlex: Interferon β 1b SC (Betaseron®). While most studies in the dossiers were previously identified in the literature searches, an additional paper on Interferon β 1a IM (Avonex®) was included based on the dossier supplied by Biogen.[33] The full results of the BENEFIT study of Interferon β 1b (Betaseron®)[34], published after our search date, was also included, based on the dossier provided by Berlex. Searches of the FDA and other web sites yielded no additional trial data but did provide information on safety issues associated with the included drugs. A complete list of excluded trials is reported in Appendix C; the flow of study inclusion and exclusion is detailed in Appendix D.

Throughout the report we generally refer to the included drugs by their full name, including trade name. This was done in an effort to avoid confusing the drugs, particularly the β interferons, which have differing doses and routes of administration.

Summary

RRMS

β Interferons

- In 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®) over interferon β1a IM (Avonex®) in both relapse (% relapse-free RR 1.51 95% CI 1.11-2.07; 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. Indirect analyses of placebo-controlled trial data did not result in a significant difference, although a Bayesian analyses does agree with these results.
- Two trials suggest a benefit of interferon β1a SC (Rebif®) over interferon β1a IM (Avonex®) 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. Indirect analyses of placebo-controlled trial data did not result in a significant difference, although a Bayesian analyses does agree with the results for the outcome of being relapse-free. Adverse event profiles of the 2 drugs differ, with interferon β1a IM (Avonex®) having a higher rate of flu-like syndrome and interferon β1a SC (Rebif®) 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 β1b SC (Betaseron®) and interferon β1a SC (Rebif®) in terms of effectiveness, and comparative adverse events have been inadequately studied. Indirect analyses of placebo-controlled trial data and a Bayesian analyses agree with these results.

Glatiramer acetate

- The mean difference in relapse rate between glatiramer acetate 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 questionable.
- Adverse events rates were higher for glatiramer acetate when compared to placebo, most notably post-injection systemic reactions and injection-site reactions (usually of limited duration for both; 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®) was consistently more effective than placebo for both relapse-related outcomes and disease progression in two trials. One of those trials included interferon β1a IM (Avonex®) 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®) 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

β Interferons

- Based on 5 placebo-controlled trials there is evidence that interferon β1b SC (Betaseron®) is effective in slowing progression in patients with SPMS, particularly those with more active disease. Evidence for the β1a interferons (IM or SC; Avonex® or Rebif®) is less convincing for slowing progression based on the EDSS, although the newer measure, MSFC, allowed a benefit to be seen with interferon β1a IM (Avonex®). Whether this difference is clinically important and the other β interferons would have a similar impact is not clear. Studies indicate that all of the β interferons do have an impact by reducing relapse rates. Again, those with more active disease appear to benefit more.
- 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 β1a SC (Rebif®) 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 β1b SC (Betaseron®) compared to placebo.
- No studies of glatiramer acetate, natalizumab, or mitoxantrone in patients with SPMS were found.

Mixed populations: RRMS and SPMS

β Interferons

- Quality of life is improved with interferon β1b SC (Betaseron®) 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®) 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®) 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 β1a IM (Avonex®) which found no statistically significant differences in the time to sustained progression between the placebo and β interferon groups at doses of 30 or 60 mcg once weekly. The 60 µg 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®) 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 β 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.

Neutralizing Antibodies

- Evidence for interferon β1b SC (Betaseron®) and interferon β1a SC (Rebif®) indicates that consistent positive neutralizing antibody status with high titer 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), and there is inadequate evidence to conclude that there is an impact on disease progression.
- Interferon β1a IM (Avonex®) 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 β1a SC (Rebif®) antibodies occur somewhat later (9 months) with rates of immunogenicity as low as 12% and as high as

46%, and with interferon β1b SC (Betaseron®) 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.

Adverse Events and Long-term Safety

β interferons

- Tolerability adverse events were reported frequently with all 3 β interferon products, although differences between the products are apparent:

Table 2. Comparative tolerability of β interferons

Adverse Effect	Relative Frequencies Based on Pooled Trial Rates
Injection Site Reaction	Interferon β1b SC (Betaseron®)>Interferon β1a SC (Rebif®)>Interferon β1a IM (Avonex®)
Flu-Like Syndrome	Interferon β1a IM (Avonex®)>Interferon β1b SC (Betaseron®)~Interferon β1a SC (Rebif®)
Fatigue	Interferon β1a SC (Rebif®)>Interferon β1b SC (Betaseron®)
Fever	Interferon β1b SC (Betaseron®)>Interferon β1a SC (Rebif®)>Interferon β1a IM (Avonex®)
Depression	Interferon β1b SC (Betaseron®)~Interferon β1a IM (Avonex®)>Interferon β1a SC (Rebif®)
Overall withdrawal	Interferon β1b SC (Betaseron®)>Interferon β1a SC (Rebif®)>Interferon β1a IM (Avonex®)
Discontinuation due to AE	Interferon β1b SC (Betaseron®)>Interferon β1a SC (Rebif®)>Interferon β1a IM \(Avonex®)

> = more frequent than; ~ = about the same frequency

- Evidence from non-randomized studies suggests that there is no difference among the β interferons in risk of developing thyroid dysfunction, although rates are slightly, but not significantly, higher with interferon β1b SC (Betaseron®.)
- Elevated liver enzymes are also very common among β interferon treated patients, particularly during the first year of treatment. Withdrawal rates due to elevated liver enzymes were very small across the trials, suggesting that these changes may be of little clinical significance to patients.
- Mixed data from non-randomized studies found rates of depression ranging from 5-12% for interferon β1a SC (Rebif®) and of 18% for interferon β1a IM (Avonex®).

Glatiramer acetate

- Evidence on the safety of glatiramer acetate from five non-comparative, non-randomized studies is consistent with that from randomized trials. No additional serious adverse events were reported in any of these studies, with the exception of a small, retrospective study that assessed the risk of potentially permanently disfiguring lipoatrophy with glatiramer acetate use.

β 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; results, with 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®) 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®) were consistent with those in trials, most commonly nausea/vomiting, alopecia and amennorhea 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 (t-AL) appears to be dose related, as the two known cases were reported in patients who had received 70 mg/m^2 cumulative dose. A meta-analysis that included 1,620 patients found the overall rate of t-AL to be very low overall (0.12%).

Clinically Isolated Syndrome

- Evidence suggests that all 3 interferon β1 products reduce the probability of converting from clinically isolated syndrome to clinically definite MS over 2 to 5 year periods. At 3 years, interferon β1a IM (Avonex®) was superior to placebo (RR 0.56 95% CI 0.38-0.81; NNT 7). At 2 years, interferon β1a SC (Rebif®) was similarly superior to placebo (RR 0.65 95% CI 0.45-0.94; NNT 9). At 2 years, both Betaseron® and Rebif® were also superior to placebo: rate ratios 0.50 (95% CI 0.36-0.70; NNT 6) and 0.65 (95% CI 0.45-0.94; NNT 9) respectively.
- No evidence was found for glatiramer acetate, natalizumab, or mitoxantrone in patients with clinically isolated syndrome.

Evidence of comparative effectiveness or safety in subgroups of patients

- Evidence of the benefits or harms of the drugs to treat subpopulations of patients with MS is limited to 2 studies and an individual patient-data meta-analysis, all assessing β interferons. These studies do not provide evidence on comparative benefits or adverse effects of the β interferons in subgroups (African-Americans and pregnancy), nor do they provide conclusive evidence about β interferons as a group in these patients.

Detailed Assessment

Key Questions 1 and 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?

Previously conducted systematic reviews of disease-modifying drugs for MS

We found 5 systematic reviews that assessed multiple drugs for the treatment of MS.[35-39] The most recent of these focuses on treatment of symptoms rather than disease modification and will not be discussed here.[37] Another focuses on the association of depression and β interferon and glatiramer acetate treatment and is discussed under Key Question 3 below.[38] The 3 remaining reviews include β interferons, glatiramer acetate, and mitoxantrone. The best quality review is the one conducted for the National Institute for Clinical Excellence (NICE) by Clegg and Bryant and a related article that updates that review.[35, 36] This review assessed the general effectiveness of the interventions compared to placebo. No attempts were made to compare the drugs to one another; however the review will be used in the appropriate sections below. Additional systematic reviews of individual drugs are considered as appropriate below.

RRMS

β interferons

While we found 1 systematic review that directly compared the interferons,[40] 2 additional studies directly comparing β interferons have been published recently, limiting the usefulness of that review for our purposes.

Direct evidence

Four trials directly compared one β interferon to another, ranging from 16 to 24 months in duration in patients with RRMS.[41-44] While these were all fair quality trials, there was variation in their features and risk of bias. However, none met all criteria for good quality, and none presented sets of flaws that appeared to indicate high risk for bias. The INCOMIN trial of Interferon β1a IM (Avonex®) and. Interferon β1b SC (Betaseron®) was open-label, while the other 3 were single blinded studies. The Etemadifar study was small, with only 30 patients per group. At baseline the mean or median EDSS in the groups ranged from 1.9 to 2.98, and the mean number of relapses in the 2 years prior to the study ranged from 1.38 to 3.2. Based on these parameters, the Danish Multiple Sclerosis Study Group patients were more severely ill compared to the other studies. In addition, while dosing for interferon β1b SC (Betaseron®) 250 µg every other day and interferon β1a IM (Avonex®) 30 µg once weekly were consistent across the studies, the dosing for interferon β1a SC (Rebif®) ranged from 22 µg *once weekly* to 44 µg three times a week. Results from these trials are presented in Tables 3 and 4 below. Overall, these studies support the use of the β interferons for improving relapse-related outcomes, with less effect on the disability-related outcomes.

Table 3. Relapse related outcomes in trials comparing β interferons

Study N, Duration	Intervention, Dose, N	Annualized relapse rate	Relapse-Free (%)	Rate of Steroid Use
Durelli 2002	Interferon β1a IM (Avonex®) 30 mcg vs.	0.7 vs. 0.5	36% vs. 51%	0.5 vs. 0.38

INCOMIN trial N = 188, 2 years	Interferon β1b SC (Betaseron®) 250 mcg	p=0.03	p=0.03	p=0.09
Koch-Henriksen 2006 Danish Multiple Sclerosis Study Group N = 301, 2 years	Interferon β1a SC (Rebif®) 22 mcg *weekly* vs. Interferon β1b SC (Betaseron®) 250 mcg	0.70 vs. 0.71 p=0.91	Not Reported	0.21 vs. 0.20 p=0.77
Etemadifar 2006 N = 90, 2 years	Interferon β1a IM (Avonex®) 30 mcg vs. Interferon β1a SC (Rebif®) 44 mcg vs. Interferon β1b SC (Betaseron®) 250 mcg	NR	20% vs. 57% vs. 43% P<0.05 Betaseron® vs. Rebif® P = 0.3017	NR
Panitch 2002 EVIDENCE trial N = 677, 16 months	Interferon β1a IM (Avonex®) 30 mcg vs. Interferon β1a SC (Rebif®) 44 mcg	0.65 vs. 0.54 p=0.033	48% vs. 56% p= 0.023	0.28 vs. 0.19 p=0.033
Pooled Relative Risk	Interferon β1b SC (Betaseron®) 250 mcg vs. Interferon β1a IM (Avonex®) 30 mcg	--	**RR 1.51 (1.11 to 2.07)**	--

*RR = Relative risk (95% confidence interval), random effects model

Table 4. Disease progression related outcomes in trials comparing β interferons

Study N, Duration	Intervention, Dose, N	Disease Progression*	Mean Change in EDSS	Mean EDSS at Endpoint
Durelli 2002 INCOMIN trial N = 188, 2 years	Interferon β1a IM (Avonex®) 30 ug vs. Interferon β1b SC (Betaseron®) 250 ug	30% vs. 13% p=0.0036	0.54 vs. 0.13 p<0.0001	2.5 vs. 2.1 p=0.0002
Koch-Henriksen 2006 Danish Multiple Sclerosis Study Group N = 301, 2 years	Interferon β1a SC (Rebif®) 22 mcg weekly vs. Interferon β1b SC (Betaseron®) 250 mcg	36% vs. 33% p=0.3736	NR	NR
Etemadifar 2006 N = 90, 2 years	Interferon β1a IM (Avonex®) 30 mcg vs. Interferon β1a SC (Rebif®) 44 mcg vs. Interferon β1b SC (Betaseron®) 250 mcg	NR	-0.1 vs. -0.3 vs. -0.7 Interferon β1b SC (Betaseron®) vs. Interferon β1a SC (Rebif®) p=0.001	1.8 vs. 1.8 vs. 1.2 Interferon β1b SC (Betaseron®) vs. Interferon β1a SC (Rebif®) p=0.0023
Panitch 2002 EVIDENCE trial N = 677, 16 months	Interferon β1a IM (Avonex®) 30 mcg vs. Interferon β1a SC (Rebif®) 44 mcg	54% vs. 57%	Not reported	Not reported

*Weighted mean difference, random effects model; ** Relative Risk, random effects model

Interferon β1b SC (Betaseron®) vs. Interferon β1a SC (Rebif®)

Neither the small study by Etemadifar nor the Danish study by Koch-Henriksen found a significant benefit of interferon β1b SC (Betaseron®) over interferon β1a SC (Rebif®) at 2 years. While the smaller trial by Etemadifar found interferon β1b SC (Betaseron®) numerically superior to interferon β1a SC (Rebif®) for outcomes related to disease progression (EDSS at endpoint and mean change in EDSS; see Table 4 above), the difference was not statistically significant. Koch-Henrikson enrolled a somewhat more severely ill population, but also did not find significant differences in annualized relapse rates, rate of steroid use, or the proportion with disease progression at 2 years. Other outcomes reported in the Koch-Henriksen trial also were unable to identify a difference between the 2 β interferons, including exacerbations requiring hospitalization and time to confirmed progression.

Adverse events were not well reported in these trials, with the Etemadifar trial not reporting adverse event data, the Koch-Henriksen study only reporting combined incidence for a few selected adverse effects, and none reporting compliance. Withdrawal or early discontinuation due to an adverse event or any other reason from the Koch-Henriksen trial was not found to be different between the drugs.

Interferon β1a IM (Avonex®) vs. Interferon β1a SC (Rebif®)

Two trials compared the 2 forms of interferon β1a SC (Rebif®) and IM (Avonex®).[41, 43] Both trials found higher rates of patients who were relapse-free at the end of study in the interferon β1a SC (Rebif®) groups compared to interferon β1a IM (Avonex®). Statistical heterogeneity was large enough to discourage statistical pooling in this case (p=0.0278). Additionally, the EVIDENCE trial[41] also found interferon β1a SC (Rebif®) superior to interferon β1a IM (Avonex®) in annualized relapse rates (a primary outcome measure in this trial), the use of steroids to treat relapse, and in the time to first relapse; median 13.4 days vs. 6.7 days HR 0.70 CI: 0.56-0.88. The Etemadifar trial did not report these outcomes, but did report a greater change in relapses per person-per year in the interferon β1a SC (Rebif®) group compared to the interferon β1a IM (Avonex®) group (1.8 vs. 0.8; p<0.001).

Disability-related outcomes were reported differently in the 2 trials, but statistically significant differences between the drugs were not found. Disease progression was very similar in the EVIDENCE study regardless of the classification scheme; although this study was only 16 months in duration, shorter than the standard 2 years for monitoring progression of MS. The EDSS at endpoint was identical between the groups in the 2 studies. While Etemadifar noted that the change from baseline EDSS was statistically significant in the interferon β1a SC (Rebif®) group (mean change 0.3) and not in the interferon β1a IM (Avonex®) group (mean change 0.1), the difference between these change scores is small and most likely not clinically important.

The Panitch study found statistically significant differences in the rates of specific adverse events between the 2 interferon β1a's. Significantly more patients taking interferon β1a IM (Avonex®) experienced flu-like symptoms (53% vs. 45%; p=0.031). However, significantly more patients taking interferon β1a SC (Rebif®) experienced injection site reactions (85% vs. 33%; p<0.001), abnormal liver function tests (18% vs. 10%, P=0.003), and white blood cell dysfunction (14% vs. 5%; p<0.001). Differences in withdrawal or early discontinuation overall or due to adverse events were not found. Data on compliance or patient satisfaction with treatment were not recorded.

Interferon β1b SC (Betaseron®) vs. Interferon β1a IM (Avonex®)

Two trials evaluated the comparison of interferon β1b SC (Betaseron®) and interferon β1a IM (Avonex®) and found higher rates of patients who were relapse free at 2 years with interferon β1b SC (Betaseron®); pooled RR 1.51, 95% CI 1.11-2.07.[43, 44] However, data for disease progression is somewhat conflicting. The mean change in the EDSS was greater with interferon β1a IM (Avonex®) in the Durelli trial (INCOMIN), but larger with interferon β1b SC (Betaseron®) in the small trial by Etemadifar. Both trials reported a lower final EDSS with interferon β1b SC (Betaseron®) compared to interferon β1a IM (Avonex®); pooled difference 0.46 (95% CI 0.20-0.71; p=0.0005). In addition, the Durelli trial found the rate of disease progression to be significantly lower in the interferon β1b SC (Betaseron®) group compared to the interferon β1a IM (Avonex®) group. Of the 4 head to head trials, these 2 represent the lowest quality evidence such that these findings should be interpreted with caution.

As noted above, adverse events were not reported in the trial by Etemadifar, and differences between the drugs were not found in the Durelli trial. Data on compliance or patient satisfaction with treatment were not recorded.

Post-Marketing Studies

While abstracts of multiple non-randomized controlled studies have been identified previously,[40] we found only 3 such studies have been fully published.[45-48]

The best of these studies is a retrospective cohort study based on data from patients in Austria, Switzerland and Germany, with 4754 patients exposed to one of the 3 interferons. [48] Eighty-four percent of these patients were exposed to the interferon as their first DMD. The group receiving Interferon β1b (Betaseron®) was older, had MS longer and had higher baseline EDSS scores compared to the other groups, and the group receiving interferon β1a SC 44 mcg (Rebif®) was smaller and patients were more likely to be receiving it as 'follow-up' therapy, rather than initial therapy. In the 'initial therapy' group the analyses of disability data revealed no differences in the mean change in EDSS among the groups, but for the proportion progression-free at 2 years, interferon β1a IM (Avonex®) was found superior to interferon β1b (Betaseron®) (83.4% vs. 76.2%, p=0.001), and compared to the interferon β1a SC 44 mcg (Rebif®) group (83.4% vs. 69.4%, p<0,001), but not significantly different to interferon β1a SC (Rebif®) 22mg (83.4% vs. 82.9%). The analyses controlled for baseline EDSS, age and duration of MS, but an analysis of patients who received treatment within 1 year of diagnosis revealed no differences among the drugs. No differences were found between the drugs based on relapse rates over 1 and 2 years, including the group treated within 1 year of diagnosis.

An analysis of the reasons for discontinuation of treatment indicated that discontinuations due to injection site reactions were lower in the interferon β1a IM (Avonex®) group compared to either the interferon β1a SC (Rebif®) 22 mcg or interferon β1b (Betaseron®) groups. Flu-like syndrome, however, was lower in the interferon β1a SC (Rebif®) 22 mcg group compared to the interferon β1b (Betaseron®) group. Discontinuations due to lack of efficacy was greatest in the interferon β1a SC (Rebif®) 22 mcg group, compared to the Interferon β1a IM (Avonex®) group or the interferon β1b (Betaseron®) group (Table 5.)

Table 5. Differences in discontinuation rates among β interferons in cohort study[48]

	Statistically Significant Differences Found*
Flu-like syndrome	Interferon β1a SC (Rebif®) 22 mcg< Interferon β1b (Betaseron®) 0.2% vs 1.2%, p=0.0038
Injection-site reactions	Interferon β1a IM (Avonex®)<Interferon β1a SC (Rebif®) 22 mcg 0.1% vs 2%, p=0.0001 Interferon β1a IM (Avonex®)<Interferon β1b (Betaseron®) 0.1% vs 2.5%, p<0.0001
Lack of efficacy	Interferon β1a SC (Rebif®) 22 mcg> Interferon β1a IM (Avonex®) 9.3% vs 7.4%, p=0.0027 Interferon β1a SC (Rebif®) 22 mcg>Interferon β1b (Betaseron®) 9.3% vs 6.8%,p<0.001

*Adjusted analysis, significance indicated by P<0.0083.

The other 2 studies are of patients being treated at large MS specialty centers (1 in Spain, 1 in Italy) enrolled and followed every 3 months. Most patients had RRMS, and all 3 β interferons were available for use within the clinic. For the Italian study, only the most recently reported data are discussed here. In both studies, it appears that at the outset of data collection

only Betaseron® was marketed in those countries, while Avonex® and Rebif® were approved during the time period of the study. Baseline patient characteristics vary significantly among the groups, with patients receiving Betaseron® having longer durations of disease, and higher EDSS at start of treatment. While both studies found significant improvements in relapse rates with all 3 β interferons, no differences were found across the groups. Likewise, all 3 groups showed disease progression, but again no differences could be found among the groups. The most important limitation of these studies is that the significant differences seen at baseline were not controlled for in the analyses, and therefore these results should be interpreted with caution.

Summary

Direct trial evidence is unable to identify differences between interferon β1b SC (Betaseron®) and interferon β1a SC (Rebif®) in terms of effectiveness, and comparative adverse events have been inadequately studied. This body of evidence supports a benefit of interferon β1a SC (Rebif®) over Interferon β1a IM (Avonex®) in terms of relapse outcomes, with no differences found in disease progression outcomes. Adverse event profiles of the two drugs differ, with interferon β1a IM (Avonex®) having a higher rate of flu-like syndrome but interferon β1a SC (Rebif®) have higher rates of injection site reactions, elevated liver function tests, and white blood cell abnormalities. The direct trial evidence also supports a benefit of interferon β1b SC (Betaseron®) over Interferon β1a IM (Avonex®) in both relapse and disease progression outcomes, with no differences in adverse event profiles.

The observational evidence conflicts with trial evidence, based on a single cohort study.[48] This study found no differences in relapse related outcomes, or change in EDSS from baseline. While the results do not conflict with the trials finding of no differences between interferon β1b SC (Betaseron®) and interferon β1a SC (Rebif®) overall, they directly conflict with other findings. The study found Interferon β1a IM (Avonex®) superior to both interferon β1a SC (Rebif®) at the 44 mcg dose, and interferon β1b SC (Betaseron®) in the proportion progression-free at 2 years, while trial data indicates no differences in this outcome for the comparison of Interferon β1a IM (Avonex®) and interferon β1a SC (Rebif®), and conflicting evidence for the comparison of Interferon β1a IM (Avonex®) superior to both interferon β1b SC (Betaseron®). Because of the small number of trials and observational studies and their somewhat conflicting findings, further analysis of the indirect evidence was undertaken.

Indirect evidence

Multiple systematic reviews have reviewed placebo-controlled trials of β interferons.[35, 36, 39, 49] Two good quality and comprehensive reviews include all the studies relevant to this review.[35, 49] The review by Rice, et al. conducted for the Cochrane Collaboration pooled all interferons together, including interferon α, while the review by Clegg and Bryant considered data on the 2 interferon β1a products together. These reviews are based on the 5 trials of β interferons; a pilot study and a multicenter trial of interferon β1b SC (Betaseron®),[50, 51] 1 multicenter trial of 2 doses of interferon β1a IM (Avonex®)[52, 53] and 2 trials of interferon β1a SC (Rebif®) (one including 2 doses 3 times weekly versus placebo, the other comparing the same 2 doses once weekly to placebo but only 48 weeks in duration).[54, 55] The authors of these reviews identify multiple problems with some of these studies, including the poor blinding in the study of interferon β1b SC (Betaseron®) and the early discontinuation and lack of intention-to-treat analysis in the trial of interferon β1a IM (Avonex®). Table 6 summarizes the findings reported in these reviews.

Table 6. Interferon β1b and 1a compared to placebo: efficacy measures

Outcome Measure	Interferon β1b SC (Betaseron®)	Interferon β1a IM (Avonex®)	Interferon β1a SC (Rebif®)
Disability Progression			
Progressed at 2 yrs RR (95% CI) vs. Placebo , NNT Absolute Risk, %	0.73 (0.46-1.15) 20.2% vs. 27.6%	0.56 (0.33-0.97), NNT 12 11.4% vs. 20.3%	0.73 (0.54-0.99), NNT 11** 26.6% vs. 36.4%
Difference in Mean change in EDSS vs. Placebo (95% CI)	-0.28 (-0.64-0.08)	--	-0.24 (-0.48-0.00)**
Relapses			
Patients with ≥ 1 relapse at 2 yrs* RR (95% CI) vs. Placebo , NNT Absolute Risk, %	0.83 (0.71-0.98), NNT 8 63.7% vs. 76.4%	0.75 (0.56-1.00), NNT 9 33.5% vs. 44.8%	0.81 (0.72-0.91), NNT 7** 67.9% vs. 84.0%
Annualized/Mean Relapse Rate, P value	0.96 1.6 MIU vs. 1.12, p=0.0057 0.78 8 MIU vs.1.12, p=0.0006	0.61 vs. 0.90, p=0.002	1.82 22 mcg 3/wk vs. 2.56 p<0.05** 1.73 44 mcg 3/wk vs. 2.56, p<0.05** 1.08 22 mcg vs. 1.08, NS† 0.87 44 mcg vs. 1.08, p = 0.0069†

*inverse of % relapse-free **PRISMS trial data, 2 years; † OWIMS trial data, 48 weeks, RR, relative risk `

Overall, the data indicate that both interferon β1a products result in reductions in the proportions of patients having progressed at 2 years, while interferon β1b SC (Betaseron®) was not statistically significantly different to placebo (pooled analysis from the review Rice, et al.).[49] The mean change in EDSS was not different to placebo. The proportions of patients relapse-free and the annualized or mean relapse rates were significantly lower in the interferon groups (pooled analysis from the review Rice, et al.).[49] The shorter study of interferon β1a SC (Rebif®) using weekly instead of thrice weekly dosing was unable to show a difference between the β interferon and placebo at 48 weeks, although the primary outcome measure, MRI findings, did indicate a benefit.[54]

Adjusted indirect comparison meta-analysis indicates no significant differences between the drugs for progression, the change in the EDSS (data available only for comparison of interferon β1a SC (Rebif®) and interferon β1b (Betaseron®) or the proportion without relapse at 2 years (see Table 7). Inadequate data were available to conduct this analysis with annualized relapse rates.

Table 7. Adjusted indirect analyses of placebo-controlled trials in RRMS

	Betaseron vs Rebif	Betaseron vs Avonex	Rebif vs Avonex
Progression rates*	RR 1.00 (0.58, 1.73)	1.30 (0.64, 2.64)	1.30 (0.70, 2.42)
EDSS change**	–0.04 (–0.41, 0.33)	NA	NA
Relapse free*	1.02 (0.85, 1.23)	1.11 (0.80, 1.53)	1.08 (0.79, 1.48)

*Relative Risk (95% confidence interval); **weighted mean difference (95% confidence interval)

Synthesis of Direct and Indirect Evidence

In the placebo-controlled trials, the rates of progression at 2 years ranged from 11.4% to 26.6% while in the head-to-head trials the rates ranged from 13% to 57%. While the placebo-controlled trial of interferon β1b SC (Betaseron®) would indicate a lower potential for benefit in disease progression compared to the interferon β1a's, the head-to-head trials and our adjusted indirect analysis of placebo-controlled trial data contradict this conclusion. These differences

could be attributed to differences in definition of progression, or baseline population characteristics, but the proportion of patients relapse-free at 2 years also shows some differences between head-to-head and placebo-controlled trials. For interferon β1b SC (Betaseron®) the rate in the placebo-controlled trial was 56%, while the head-to-head trial rates were somewhat lower (43% and 51%). Rates for interferon β1a SC (Rebif®) were better in head-to-head trials (57% and 56%) than in the placebo-controlled trial (31.1%). The largest difference between placebo-controlled and head-to-head trial results lies in the rates of relapse-free patients with interferon β1a IM (Avonex®). The placebo-controlled trial rate was good, 66.5%, while the head-to-head trial rates were lower (20% and 36%), resulting in interferon β1a IM (Avonex®) being inferior to the other β interferons.

Because there is only a small amount of evidence available from which to make these comparisons, we undertook an exploratory Bayesian analysis using the adjusted indirect analysis of the placebo-controlled trials as the 'prior' assumptions and using the direct evidence from head-to-head trials as the primary evidence. This analysis resulted in no statistically significant differences for the comparison of interferon β1a SC (Rebif®) and interferon β1b SC (Betaseron®). For the comparison of interferon β1a IM (Avonex®) with either interferon β1b SC (Betaseron®) or interferon β1a SC (Rebif®) the results of our exploratory analysis is consistent with the findings of our direct and indirect analyses (see Table 8). Inadequate data were available to conduct this analysis with annualized relapse rates.

Table 8. Exploratory Bayesian analysis of direct and indirect evidence in RRMS

	Betaseron vs Rebif	Betaseron vs Avonex	Rebif vs Avonex
Progression rates*	1.18 (0.80, 1.71)	**0.48 (0.27, 0.86)**	1.05 (0.93, 1.22)
EDSS change**	–0.19 (–0.51, 0.14)	NA	NA
Relapse free*	0.85 (0.56, 1.25)	**1.48 (1.11, 2.02)**	**1.22 (1.06, 1.41)**

*Relative Risk (95% confidence interval); **weighted mean difference (95% confidence interval)

Adverse events occurred significantly more frequently in the β interferon groups compared to the placebo groups. Looking across the results from 4 trials (Table 9) only three times weekly interferon β1a SC (Rebif®) was not associated with significantly increased rates of flu-like syndrome, fever, and myalgias. The incidence of leukopenia, however, was significantly higher with three times weekly interferon β1a SC (Rebif®), while interferon β1b SC (Betaseron®) and interferon β1a IM (Avonex®) were not. Comparing the 2 dosing regimens of interferon β1a SC (Rebif®), dosing once weekly resulted in statistically significantly greater rates of flu-like syndrome, fever and headache while dosing three times weekly did not.

Table 9. Interferon β1b and 1a compared to placebo: adverse events

Adverse Effect	Interferon β1b SC (Betaseron®)	Interferon β1a IM (Avonex®)	Interferon β1a SC (Rebif®)
	RR (95% CI) vs. Placebo	RR (95% CI) vs. Placebo	RR (95% CI) vs. Placebo
Flu-Like Syndrome	2.89 (1.91, 4.37)	1.52 (1.20, 1.93)	1.13 (0.80, 1.60) PRISMS 1.70 (1.23, 2.37) OWIMS
Injection Site Reaction	12.19 (5.88, 25.26)	2.00 (0.22-17.89)	2.83 (2.11, 3.79) PRISMS 5.78 (3.35, 9.99) OWIMS
Fever	1.70 (1.28, 2.27)	1.86 (1.11, 3.12)	1.86 (0.95, 3.65) PRISMS 3.50 (1.58, 7.74) OWIMS
Myalgias	1.69 (1.16, 2.46)	2.28 (1.45, 3.59)	1.69 (0.92, 3.11) PRISMS 1.86 (0.94, 3.67) OWIMS
Fatigue	--	1.66 (0.98, 2.81)	1.19 (0.76, 1.87) PRISMS 1.02 (0.30, 3.41) OWIMS

Headache	--	1.17 (0.98, 1.40)	1.08 (0.86, 1.36) PRISMS 1.44 (1.03, 2.02) OWIMS
Lymphopenia	1.60 (1.15, 2.23)	--	3.48 (1.54, 7.89) PRISMS
Leukopenia	8.93 (0.49, 164.08)	0	5.08 (1.50, 17.26) PRISMS
Increased AST	2.73 (0.89, 8.33)	0	3.05 (0.62, 14.91) PRISMS
Increased ALT	2.76 (1.34, 5.66)	0	6.10 (1.38, 26.87) PRISMS

RR=relative risk

Neutralizing Antibodies

Neutralizing antibodies are known to develop in some patients taking β interferons, potentially interfering with effectiveness. Two recent reviews of neutralizing antibodies summarize the current state of understanding about the impact of these antibodies on relapse and disease progression, and how the products differ.[56, 57] Based on these reviews, there are several factors that can impact the prevalence of such antibodies, including assay method (varying sensitivity/specificity), dose (conflicting evidence), host cell source (*Escherichia coli* more antigenic than mammalian source), definition of positive status, and route of administration (SC more antigenic than IM). Because there is no standardized universal assay, making comparisons across studies of the β interferons is fraught with uncertainty. In addition, the duration of many studies is not adequate to assess the impact of antibody status on progression clearly. It appears that the rate of antibody development occurs earlier and in greater frequency with interferon β1b SC (Betaseron®), appearing as early as 3 months into treatment in approximately 30-40% of patients. Evidence reported in the Namaka review[57] indicates that antibodies occur somewhat later (9 months) with interferon β1a SC (Rebif®); with rates as low as 12% and as high as 46%. Interferon β1a IM (Avonex®) appears to have the lowest immunogenicity with rates of 2-8.5% reported, starting around 9 months of treatment. 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.

Correlating positive antibody status with reductions in clinical benefits, Namaka, et al, find that in the first 2 years of treatment a difference in outcome based on antibody status cannot be identified, but that relapse rates are lower in years 3 and 4 among patients who are antibody positive (Table 10). The review by Goodin, et al,[56] also finds that relapse rates are affected by positive neutralizing antibody status of high titer only in studies of 2 years or longer in duration. The evidence for the impact on disease progression is less compelling, with only 2 of 8 studies showing a significant increase in progression among those with neutralizing antibodies.

These reviews are recent and fair quality, thus although we found several additional studies that met our inclusion criteria, they are not discussed here as they provided no additional evidence regarding neutralizing antibodies.[58-67] To date, evidence correlating *comparative* clinical outcomes to the antibody status of the individual β interferons is incomplete and inadequate to make conclusions. This is particularly true in light of the evidence that while interferon β1a IM (Avonex®) appears to have lower immunogenicity, clinical trial evidence indicates that the other two β interferons may be superior in regards to clinical outcomes. Longer term trials will be needed to clarify the role of this difference in antigenicity and its correlation of clinical outcomes over longer periods of time.

Table 10. Duration of treatment and clinical impact of antibody status[57]

Duration	Interferon β1b SC (Betaseron®)	Interferon β1a SC (Rebif®)	Interferon β1a IM (Avonex®)
2nd year	"correlation not observed"	1.8 vs. 1.77 22mcg (NS) 1.75 vs. 1.74 44mcg (NS)	"No clinical impact of relapse rate or disease progression"
13 to 36 months	1.08 vs. 0.56	--	--
4th year follow-up	--	0.81 vs. 0.5	--

NS, no t statistically significant

Glatiramer acetate

Direct evidence

No trials directly comparing glatiramer acetate (Copaxone®) to another disease-modifying drug were identified.

Indirect evidence: Placebo-controlled trials

One fair-quality meta-analysis[68] and one good-quality systematic review[69] analyzed trials of glatiramer acetate versus placebo. Martinelli Boneschi[68] only included trials (n=3) in RRMS patients while Munari[69] included the same three trials and an additional trial of glatiramer acetate versus placebo in 'chronic progressive' MS (CPMS) patients. Further discussion of the use of glatiramer acetate in CPMS patients appears in the 'Mixed Populations: PPMS and SPMS' section below.

The two reviews used different meta-analytic methods and drew different conclusions regarding the effectiveness of glatiramer acetate. Martinelli Boneschi concluded that glatiramer acetate was effective at 'reducing relapse rate and disability accumulation'[68] while Munari concluded that there was no evidence of a 'beneficial effect on the main outcome measures in MS, i.e. disease progression, and (glatiramer acetate) does not significantly affect the risk of clinical relapses.'[69] Due to the conflicting nature of these conclusions, we conducted a separate analysis of the three relevant trials,[70-72] and pooled results where possible.

Relapse-related outcomes were reported in the three trials of glatiramer acetate versus placebo, most commonly mean relapse rate and proportion of relapse-free patients (Table 11.) 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 the three trials were pooled. Since the absolute difference in relapse rate between glatiramer acetate and placebo was considerably higher in the Bornstein[70] study, a sensitivity analysis was conducted for this outcome. That analysis found the difference in mean relapse rate to be much smaller, but still statistically significant (-0.31 [-0.5227; -0.106], p=0.0031.) When results from the 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.) Again, the Bornstein[70] study had a much higher absolute rate difference compared to the two larger studies: 30.0% vs. 6.3% and 6.6% respectively. There was inadequate data to pool annualized relapse rates, although rates were lower for glatiramer acetate in both trials that reported this outcome.

Table 11. Relapse-related outcomes: glatiramer acetate vs. placebo

Trial	Mean relapse rate		% of relapse-free patients		Annualized relapse rate	
	GA	placebo	GA	placebo	GA	placebo
Bornstein 1987[70] n=50; 2 yrs	0.60	2.7	56.0%	26.0%	NR	NR

Mean baseline EDSS: GA 2.9; placebo 3.2						
Comi 2001[71] n=239; 9 mos Mean baseline EDSS: GA 2.3; placebo 2.4	0.51	0.76	55.5%	49.2%	0.81	1.21
Johnson 1995[72] n=251; 2 yrs Mean baseline EDSS: GA 2.8; placebo 2.4	1.19	1.68	33.6%	27.0%	0.59	0.84
Pooled rates	***Difference in mean relapse rate: -0.64 (-1.19-0.09) p=0.024***		***RR % of relapse-free patients: 1.23 (0.97-1.57) p=0.086***			

Two of the trials provided evidence on other effectiveness outcomes. The single trial providing data on the proportion of patients requiring use of rescue medications showed no difference between the glatiramer acetate and placebo groups (33.6% vs. 39.2%; p=0.557) There was a significantly higher percentage of hospitalizations due to uncontrolled exacerbations in the placebo group in the same trial(13.4% glatiramer acetate versus 25.0% placebo; p= 0.046)[71] 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.[72]

A re-analysis of data from one of the trials (Johnson 1995)[72] used 'area under the disability/time curve' to compare the effect of glatiramer acetate versus placebo on EDSS.[73] The results of this re-analysis, confirming that glatiramer acetate had a positive effect on EDSS when compared to placebo, were consistent with the results of the original trial publication.

Results from the three trials showed a significant difference between the intervention groups for the following adverse events: injection-site reactions consisting of itching, swelling, redness and/or pain, 'patterned' (systemic) reactions, and palpitations (Table 12)[69] although the clinical significance of these differences may be minimal. Withdrawals due to adverse events were also higher, but not significantly so, in glatiramer acetate-treated RRMS patients when compared to placebo-treated RRMS patients: 10/269 (3.7%) vs. 3/269 (1.1%); p=0.08. Other reported adverse events (i.e. headache, nausea, anxiety, etc.) were mild and transient and not more common with glatiramer acetate than placebo.

Table 12. Adverse event rates: glatiramer acetate vs. placebo

Data source	Adverse event	Rate	*P*
2 trials[70, 72] Total n=251	Injection-site reactions	Itching: 43% vs. 7% Swelling: 37% vs.19% Redness/erythema: 59% vs. 19% Pain: 39% vs. 20%	<0.0001 for all comparisons
3 trials[70-72] Total n=540	Immediate post-injection reactions/ systemic reactions*	33% vs. 8%	<0.0001
2 trials[70, 72] Total n=301	Palpitations	9% vs. 2%	0.0178

**consisting of transient flushing, chest tightness, sweating, palpitations and anxiety*

An additional five publications provided data on the long-term safety of glatiramer acetate use.[74-77] An open-label trial compared the effects of glatiramer acetate in RRMS patients who were prior users of interferon β1b SC (Betaseron®) versus treatment-naive patients.[74] Patients were followed for a mean of 14.8 and 20.3 months respectively. Reported adverse

events (most commonly injection-site reactions) and rates were similar between the two groups and to those reported in the placebo-controlled trials. For both groups in this study, withdrawal rates due to adverse events were significantly higher when compared to the placebo-controlled trials (10.9% vs. 3.7%; p=0.001). The reason for this difference may be due to study design. The open-label trial enrolled patients based on compassionate-use and used very few exclusion criteria, while the placebo-controlled trials were more restrictive in enrolling patients.

One of the glatiramer acetate placebo-controlled trials, Johnson, et al.,[72] was extended to an open-label phase in which all patients had the option of receiving glatiramer acetate treatment. Results of this ongoing study have been reported at six, eight, and ten years following randomization.[75-77] Of 232 who received at least one dose of glatiramer acetate, 108 (47%) were still enrolled at the 10-year follow-up. Adverse events accounted for the greatest number of withdrawals (87/124; 70%). Despite this, a Kaplan-Meier estimate of median time from initiation of therapy with glatiramer acetate to withdrawal was 9.2 years. No serious adverse events were reported over the course of follow-up. Consistent with results from other studies, injection-site reactions and post-injection systemic reactions continue to be the most commonly reported adverse events, although incidence of both appears to dissipate with long-term use.[77] These data should be interpreted as representing a highly selected population of patients tolerant to and receiving benefit from glatiramer acetate.

β interferons vs. glatiramer acetate

Direct evidence

In a study using data obtained through a prospectively designed clinical database, Haas, et al.[78] compared all 3 β interferons and glatiramer acetate. This study included patients with first exposure to drug treatment and those with prior treatment, with approximately one quarter of patients having had prior treatment except for the interferon β1a SC (Rebif®) group of whom 63% had prior treatment ($p< 0.0001$). Another significant difference at baseline was the mean progression index (EDSS/disease duration), which was greater in the interferon β1b SC (Betaseron®) group (1.03 vs. 0.43-0.55; $p<0.001$). An additional caveat to interpreting this evidence is the fact that the authors indicate that for at least some portion of the time period covered, glatiramer acetate (Copaxone®) was not available except in exceptional circumstances. 283 patient records contributed to the analysis, and by entry criteria had to have baseline EDSS of ≤ 3.5. The results are presented in Table 13. At 2 years, glatiramer acetate had a significantly greater decrease in annualized relapse rate and significantly fewer patients discontinuing treatment after 6 months of treatment. No significant differences were seen across the groups in the percent relapse or progression-free, although the proportions of both were highest in the glatiramer acetate group. While not statistically significant, the glatiramer acetate group was younger, had a lower baseline EDSS, the lowest progression index, and the lowest percent of patients with prior treatment than the other groups.While these data appear to support the superiority of glatiramer acetate in relapse outcomes and tolerability over low-dose interferon β1a SC (Rebif®), the contribution of the potentially important differences among the population treated with glatiramer acetate compared to the others needs to be taken into account.

Table 13. Comparison of disease-modifying drugs at 2 years in observational data[78]

Outcome Measure	Ifn β1b	Ifn β1a SC	Ifn β1a IM	Glatiramer acetate	P-value
Annualized Relapse Rate	0.69	0.66	0.8	0.36	p<0.001*
% Relapse-free	45.5	45.8	35.4	58.2	p=0.22
DC Treatment after 6 mos	22.9	31.2	32.9	8.9	p<0.001
% Progression-free	71.7	73.3	74.5	87.5	p=0.13

. *p-value based on mean change from baseline

Natalizumab

Direct evidence

No studies compared natalizumab (Tysabri®) to another disease-modifying drug for MS.

Indirect evidence

Two well-conducted trials compared natalizumab to placebo in patients with RRMS (Table 14).[79, 80] Patient population, natalizumab dose, and study duration were similar in the two trials, however in one of these trials,[80] interferon β1a IM (Avonex®) was used concomitantly in both groups. Both cumulative probability of disease progression and annualized relapse rate at two years were significantly lower with natalizumab when compared to placebo, while the proportion of relapse-free patients was significantly higher (Table 15). These data indicate that natalizumab is more effective than placebo in patients with RRMS.

Table 14. Trials of natalizumab in RRMS

Trial	Patient characteristics	Interventions	Study duration
Polman 2006[79] AFFIRM	n=942 Mean EDSS: 2.3 Mean relapse rate: 1.52/yr	300 mg every 4 wks vs. Placebo	up to 116 wks
Rudick 2006[80] SENTINEL	n=1171 Mean EDSS: 2.4 Mean relapse rate: 1.47/yr	300 mg every 4 wks + 30 ug Ifn-β1a IM (Avonex®) 1/wk vs. Placebo every 4 wks+ 30 ug Ifn-β1a IM (Avonex®) 1/wk	up to 116 wks

Table 15. Effectiveness outcomes in natalizumab trials in patients with RRMS

Outcome at 2 years	Trial	Natalizumab vs. Placebo, *P* value
Cumulative probability of disease progression	Polman 2006[79]	17% vs. 29%, *P*<0.001
	Rudick 2006[80]	23% vs. 29%, *P*=0.02
Annualized relapse rate	Polman 2006[79]	0.23 vs. 0.73, *P*<0.001
	Rudick 2006[80]	0.34 vs. 0.75, *P*=0.001
Proportion of relapse-free patients	Polman 2006[79]	67% vs. 41%, *P*<0.001
	Rudick 2006[80]	61% vs. 37%, *P*<0.001

Adverse events were reported by most patients in these two trials, regardless of intervention. Combined data from both trials found that 97% of natalizumab patients and 98% of control patients reported some adverse event (p=0.086), although more natalizumab patients withdrew due to adverse events compared to control patients (2.9% vs. 0.89%; p=0.549). Overall, rates of non-serious adverse events were similar in both trials (Table 16).

Table 16. Adverse events in natalizumab trials in patients with RRMS (natalizumab vs. control)

Trial	Any AE	Headache	Depression	Flu-like illness	Injection-site reactions
Polman 2006[79]	95% vs. 96% p=0.459	38% vs. 33% p=0.137	19% vs. 16% p=0.197	NR	3% vs. 2% p=0.386
Rudick 2006[80]	99% vs. 99% p=0.772	46% vs. 44% p=0.439	21% vs. 18% p=0.195	20% vs. 19% p=0.679	NR

Serious adverse events were reported in both trials; however there were no significant differences in adverse event rates between the interventions. The exception was two cases of progressive multifocal leukoencephalopathy (PML), a potentially fatal neurologic disorder, that were reported in patients enrolled in the SENTINEL trial and were possibly linked to natalizumab use.[80] This led to early cessation of the SENTINEL trial; no cases of PML were reported in the AFFIRM trial.[79] Further discussion of the association between natalizumab use and PML appears below.

Mitoxantrone

Direct evidence

No studies offered direct evidence comparing mitoxantrone (Novantrone®) to another disease-modifying drug for MS.

Indirect evidence

One small trial compared mitoxantrone to placebo in 51 patients with RRMS.[81] The primary outcome of this two-year study was confirmed disease progression, as measured by a 1-point increase in the EDSS. At the conclusion of the study, 2/27 (7%) of mitoxantrone patients and 9/24 (37%) of placebo patients had confirmed disease progression (Absolute Difference in Risk 30%, 95% CI 8-52%; NNT 3). Mitoxantrone patients also fared better than placebo patients both in the number of exacerbations experienced during the course of the study (0.89 vs. 2.62; p=0.0002) and in the number of exacerbation-free patients at the study's conclusion (63% vs. 21%; p=0.006; NNT 2.4). An interim, subgroup analysis of 25 patients at 1-year of follow-up found a similar pattern in the rates of confirmed disease progression.[82]

In this same trial, no patients reported any serious adverse events, and there were no withdrawals from either group due to adverse events. Transient amenorrhea was reported in 5/17 (29%) of women in the mitoxantrone group; these cases resolved with treatment cessation. Other adverse events reported in mitoxantrone patients were nausea and vomiting (18%), urinary tract infection (6%), headache (6%), and respiratory infection (4%). For unexplained reasons, no adverse event data for the placebo arm was provided by the study's authors.

SPMS

β Interferons

Indirect evidence

Five trials reported in multiple publications of β interferons compared to placebo provide evidence on the effectiveness and safety in SPMS.[58, 83-91] These include 1 study of interferon β1a IM (Avonex®),[58] 2 studies of interferon β1a SC (Rebif®),[89, 91] 2 studies of interferon β1b SC (Betaseron®),[84, 87-90] and one combined analysis of these 2 trials.[86] Trial characteristics are summarized in Table 17. The primary outcome measures assessed progression and disability,

reflecting the nature of SPMS. Relapse was evaluated as a secondary outcome only. While 3 studies used time to progression as an outcome measure, there were differences in how the outcome was defined or confirmed, and one trial used a measure of functionality (the MSFC) in an effort to avoid the potential lack of sensitivity and variability associated with the EDSS. [92] Across the studies, the patient populations appeared similar, although the specific interferon and dosing varied.

Table 17. Characteristics of studies of β interferons for SPMS

Study Name, Year N	Patient Characteristics	Interventions Duration of follow up	Primary Outcomes
Interferon β1a IM (Avonex®)			
IMPACT 2002 N=436	Mean age 48 yrs Baseline EDSS 5.2 MS Duration 16.5 yrs	Ifn β1a (Avonex®) 60µg or Placebo IM weekly x 2 years	Change in MSFC from baseline to 24 months
Interferon β1a SC (Rebif®)			
SPECTRIMS 2001 N=618	Mean age 43 yrs Baseline EDSS 5.4 MS Duration 13 yrs	Ifn β1a SC (Rebif®) 22 or 44µg or Placebo SC 3 x weekly x 3 years	Time to documented progression: ΔEDSS ≥ 1 or ≥ 0.5 if baseline ≥ 5.5 x 2 measurements
Andersen 2004 N=364	Mean age 46 Baseline EDSS 4.8 MS Duration 14 yrs	Ifn β1a (Rebif®) 22µg or Placebo SC weekly x 3 years	Time to documented progression: ΔEDSS ≥ 1 or ≥ 0.5 if baseline ≥ 5.5 x 2 measurements
Interferon β1b (Betaseron®)			
North American Study Group 2004 N=939	Mean age 48 Baseline EDSS 5.1 MS Duration 15 yrs	Ifn β1b (Betaseron®) 250 µg or 160 µg/m^2 or Placebo SC every other day x 3 years	Time to documented progression: ΔEDSS ≥ 1 or ≥ 0.5 if baseline 6-6.5 x 2 measurements
European Study Group 2001 N=718	Mean age 441 Baseline EDSS 5.2 MS Duration 13 yrs	Ifn β1b (Betaseron®) 250 µg or Placebo SC every other day x 3 years	Time to documented progression: ΔEDSS ≥ 1 or ≥ 0.5 if baseline 6-6.5 x 2 measurements

Only 2 studies found a significant benefit of β interferons in slowing progression.[58, 90] In IMPACT [58] (interferon β1a IM [Avonex®] 60µg vs. placebo) a significant difference in the change on the MSFC score was found (a difference in Z-score of 0.133), however the clinical importance of such a difference is not clear. Similar to the other studies, no significant difference was found using the EDSS time to progression measure (HR 0.98 [0.68-1.4]).

Two studies of interferon β1a SC (Rebif®) were unable to differentiate β interferon and placebo on time to progression with either 22 or 44 µg doses.[89, 91] However, the larger study did find a benefit on annualized relapse rates and hospitalizations with both doses. While the rates of relapse are different between the 2 trials, the relative benefit of interferon β1a SC (Rebif®) are similar, with a pooled relative risk for yearly relapse of 0.76 (95% CI 0.59-0.97). The SPECTRIMS study found that women responded better to interferon β1a IM (Avonex®) than men. These results are discussed in Key Question 3 below.

The 2 studies of interferon β1b SC (Betaseron®) used the same outcome measure and report conflicting results. Both studies were stopped early, based on planned interim analyses, but for opposite reasons. In the European study[90] the time to progression for the β interferon 250 µg group was similar to that seen in the North American study (893 vs. 981 days, respectively), but the placebo groups differed (549 vs.750 days, respectively). Kappos, et al.[86] investigated potential differences between the studies using primary data from both trials. While this analysis

showed that there was a 6.5% greater variability in the EDSS scores from the North American study, the difference that was not large enough to account for the difference in study findings. Pooled results indicate an overall benefit (see Table 18), and in further analysis those with active disease (higher relapse rates and greater progression at entry) appeared to benefit the most. In the SPECTRIMS study of interferon β1a SC (Rebif®), a similar finding was observed.

Making indirect comparisons across these trials in a qualitative way, there is evidence that interferon β1b SC (Betaseron®) is effective in slowing progression in patients with SPMS, particularly those with more active disease. Evidence for the β1a interferons (IM or SC; Avonex® or Rebif®) is less convincing for slowing progression based on the EDSS, although the newer measure, MSFC, allowed a benefit to be seen with interferon β1a IM (Avonex®). Whether this difference is clinically important and the other β interferons would have a similar impact is not clear. Studies indicate that all of the β interferons do have an impact by reducing relapse rates. Again, those with more active disease appear to benefit more.

Table 18. Results of studies of β interferons for SPMS

Study Name, Year **N**	**Primary Outcomes** Ifn vs. Placebo (95% CI)	**Secondary Outcomes** Ifn vs. Placebo (95% CI)
Interferon β1a IM (Avonex®)		
IMPACT 2002 N = 436 Ifn β1-a 60μg IM vs. Placebo	Change in MSFC -0.362 vs. -0.495 (40% difference; p = 0.033)	Annualized Relapse Rate 0.2 vs. 0.3 (p = 0.008) Relapse Free 74% vs. 63% (p = 0.023) HRQOL Ifn significantly better on 8 of 11 subscales
Interferon β1a SC (Rebif®)		
SPECTRIMS 2001 N = 618 Ifn β1-a SC 22 vs. 44μg vs. Placebo	Time to Progression 44μg vs. PL HR 0.83 (0.65-1.07) 22 μg vs. PL HR 0.88 (p = 0.31)	Annualized Relapse Rate 44μg 0.5 vs. 22 μg 0.5 vs. 0.71 44μg vs. PL RR 0.69 (0.56-0.85) 22 μg vs. PL RR 0.69 (0.56-0.84) Hospitalizations 44μg vs. PL RR 0.63 (0.46-0.88) 22 μg vs. PL 0.64 (0.46-0.88)
Andersen 2004 N=364 Ifn β1-a SC 22μg vs. Placebo	Time to Progression HR 1.13 (0.82-1.57) Proportion with Progression: 41% vs. 38% (NS)	Annualized Relapse Rate 0.25 vs. 0.27 RR 0.9 (0.64-1.27) Relapse Free 61% vs. 62% OR 1.03 (0.67-1.58) Time to first relapse and hospitalizations: NS
Interferon β1b SC (Betaseron®)		
North American Study Group 2004 N=939 Ifn β1-b 250 μg vs. 160 μg/m^2 vs. Placebo SC	Time to Progression Days to event: 981 vs. 668 vs. 750 250 μg vs. PL p = 0.61 160 μg vs. PL /m^2 = 0.26 Proportions Progressing 32% vs. 39% vs. 34% (NS)	Annualized Relapse Rate 0.16 vs. 0.2 vs. 0.28 250 μg vs. PL p = 0.009 160 μg vs. PL p = 0.109 Combined Ifn vs. PL p = 0.014
European Study Group 2001 N=718 Ifn β1-b SC 250 μg vs. Placebo	Time to Progression Days to event: 893 vs. 549, p = 0.0008 Proportion with Progression: 50% vs. 39%	Annualized Relapse Rate 0.44 vs. 0.64 , p = 0.002 Hospitalizations 46% vs. 53%, p = 0.04 HRQOL Ifn significantly better on physical scale at 6+12 months and last visit. Total and Psychosocial scores not different to placebo.

Kappos 2004 Pooled Analysis of European and North American Studies	Time to Progression HR 0.79 (0.66-0.93) Patients with relapses and Δ EDSS >1 at baseline: HR 0.53 (0.37-0.78)	Data not pooled

While mixed results were found for disease progression, relapse rates were more consistently affected by the β interferons. Four trials indicated that β interferon therapy reduces relapse and associated hospitalizations in patients with SPMS compared to placebo. Body surface area dosing (160 μg/m^2) of interferon β1b SC (Betaseron®) was generally less effective than the 250 μg dose. Health related quality of life was measured in 2 studies using different tools, both finding a benefit of the respective β interferon used.[58, 88]

Adverse events were considered typical in all of the trials, with flu-like syndrome and injection site reactions being common, however across the studies and types of β interferons, the ranges were wide even within studies of the same β interferon. For example, the range of flu-like syndrome was 37% with 22 μg of interferon β1a SC (Rebif®) to 70% with interferon β1a IM (Avonex®). Clearly definition and ascertainment varied among the studies. Withdrawal due to adverse events was generally less than 10%, with most studies showing double the rate of discontinuation in the β interferon arm compared to the placebo arm. Differences across the β interferons were not apparent. Rates of depression were reported in three trials (see Table 19), with no statistically significant difference found between either interferon β1a formulation and their respective placebo groups. Depression was not a reported outcome in the trials of interferon β1b (Betaseron®). In the SPECTRIMS trial of interferon β1a SC (Rebif®), the proportion of patients reporting depression was higher in the β interferon groups, but evaluation of validated depression scales did not reveal a difference between β interferon and placebo groups.[93]

Pooled analysis suggests significantly higher rates of injection site reactions, abnormal liver function tests, and withdrawal due to adverse events with interferon β1a SC (Rebif®) and flu-like syndrome and withdrawal due to adverse events with interferon β1b SC (Betaseron®) compared to placebo.

Table 19. Adverse events in trials of β interferons in patients with SPMS (β interferon vs. placebo)

Study	Flu-like Syndrome	Injection Site Reactions	Depression	Elevated LFTs	Myalgia	Withdrawal Due to AE
Ifn β1a IM (Avonex®) vs. Placebo						
IMPACT 2002 N = 436 Ifn β1-a 60μg IM vs. Placebo	70% vs. 33% P<0.001	16% vs. 20% P=0.261	26% vs. 22% P=0.435	NR	30% vs. 31% P=0.917	8% vs. 4% P=0.05
Ifn β1a SC (Rebif®) vs. Placebo						
SPECTRIMS 2001 N = 618 Ifn β1-a SC 22 vs. 44μg vs. Placebo	50% vs. 51% vs. 52% (ns)	87% vs. 81% vs. 41% P<0.05 for each Ifn vs. placebo	35% vs. 32% vs. 29% NS	36% vs. 33% vs. 10% P<0.05 for each Ifn vs. placebo	NR	3% vs. 3.8% vs. 1.5% (NS)
Andersen	37% VS. 22%	27% vs. 8%	20% vs. 14%	3% vs. 0%	15% vs.	8.6% vs.

2004 N = 364 Ifn β1-a SC 22µg vs. Placebo	P = 0.002	p < 0.001	p= 0.128	p = 0.061	8% p = 0.048	3.4% P = 0.036
Pooled Analysis of 22 µg dose RR (95% CI)	1.27 (0.73-2.19)	**2.51 (1.56- 4.04)**	1.25 (0.98- 1.59)	**3.38 (2.16-5.27)**	**--**	**2.61 (1.23- 5.53)**
Ifn β1b (Betaseron®) vs. Placebo						
North American Study Group 2004 N =939 Ifn β1-b 250 µg vs. 160 µg/m^2 vs. Placebo SC	43% vs. 45% vs. 33% P = 0.0107 for 250 µg, P=0.003 for 160 µg/m^2	55% vs. 52% vs. 13% P<0.001 for both ifn doses	NR	NR	29% vs. 24% vs. 19% P =0.003 for 250 µg P = 0.117 for 160 µg/m^2	9% vs. 10% vs. 4% P = 0.002 fpr 250 µg P = 0.005 for 160 µg/m^2
European Study Group 2001 N = 718 Ifn β1-b SC 250 µg vs. Placebo	59.2% vs. 37.2% P < 0.0001	NR	NR	NR	22.8% vs. 8.9% P < 0.0001	1.4% vs. 1.1% NS
Pooled analysis for 250 mcg dose vs. placebo RR (95% CI)	**1.37 (1.02- 1.85)**				1.77 (0.88-3.56)	**2.24 (1.26-4.00)**

LFTs, liver function tests AE, adverse events *statistical heterogeneity, P = 0.0159, ** statistical heterogeneity, P = 0.004

Glatiramer acetate, Natalizumab or Mitoxantrone

No studies of glatiramer acetate, natalizumab or mitoxantrone in patients with SPMS were found.

PPMS

β Interferons

The only evidence of the effectiveness of drug treatment in PPMS comes from a single, small (n = 50) trial of interferon β1a IM (Avonex®) at doses of 30 µg, 60 µg ,or placebo once a week for 2 years.[94] While no statistically significant differences were found between the groups at baseline, the baseline EDSS in the placebo group was 1 point lower (4.5 vs. 5.5) compared to either β interferon group. The time to sustained progression (increase of ≥1 point on EDSS at baseline ≤ 5.0, ≥ 0.5 point if EDSS at baseline, ≥ 5.5 seen at 2 consecutive 3-month visits) was not different between the placebo and β interferon groups at either dose. There was no sample size calculation complete by the study's authors; the small sample size and potentially clinically important differences at baseline leave the possibility of benefit in a larger trial open to speculation. Statistically significant differences on secondary outcome measures (the 10-minute walk test and the nine-hole peg test) were also not found. However, the authors suggest that a benefit in right hand side nine-hole peg test was seen with the β interferon 30 µg group (p =

0.08) and relate this to the sensitivity of the test to upper extremity changes, while the EDSS is more affected by lower extremity changes. The 60 µg 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.

While a pilot trial of interferon β1b SC (Betaseron®) has been done, it has only been partially reported to date.[95] Details in this publication were inadequate for inclusion here.

Glatiramer Acetate, Natalizumab and Mitoxantrone

No studies of natalizumab or mitoxantrone in patients with PPMS were found. One study of glatiramer acetate included a mixed population, see below.

Mixed Populations: RRMS and SPMS

β Interferons

A cohort study of RRMS and SPMS patients compared quality-of-life in patients treated with interferon β1b (Betaseron®) to untreated controls.[96] Patients were recruited during regular office visits and asked to complete a QOL questionnaire based on the previous month. Additional data regarding hospitalizations and days of work/leisure time lost for the three months preceding study entry were also collected. When patients were stratified according to disease severity, those patients with the lowest EDSS (<3.0) fared the best in terms of QOL, hospitalizations, and work/leisure time lost (Table 20). While these data suggest that baseline disease severity has a important impact on QOL measures, additional data from well-designed RCTs and/or observational studies assessing these measures are needed in order to draw more definitive conclusions.

Table 20. Quality of life measures by disease severity[96]

	EDSS <3.0		**EDSS 3.0-6.0**		**EDSS >6.0**	
Outcome	**Interferon β1b SC (Betaseron®) n=30**	**Untreated controls** n=53	**Interferon β1b SC (Betaseron®) n=32**	**Untreated controls** n=58	**Interferon β1b SC (Betaseron®) n=18**	**Untreated controls** n=40
Summary QOL physical score (±SD)	67.2 (±22.4)	47.8 (±19.5)	47.3 (±19.2)	43.5 (±7.8)	34.8 (±17.5)	31.5 (±19.0)
Summary QOL mental score (±SD)	63.7 (±25.0)	57.9 (±27.9)	57.9 (±20.2)	54.1 (±22.5)	52.5 (±20.8)	47.8 (±21.7)
Hospitalizations*	2 (7%)	NR	1 (3%)	NR	3 (17%)	NR
Days of work lost*	2.0	15.6	25.0	29.9	NR	NR
Other time lost* (i.e. leisure time)	33.8	41.9	53.1	46.0	65.7	67.4

**during the three months preceding study entry*

Natalizumab

Indirect Evidence

Three trials compared natalizumab (Tysabri®) to placebo in RRMS and SPMS patients. While there were some similarities in patient characteristics across the trials, the size and quality of the trials varied and relevant baseline data was not uniformly reported across all trials. For example, Sheremata[97] did not provide baseline EDSS while Tubridy[98] omitted mean number of relapses prior to study entry. Instead, Tubridy provided data on number of patients with previous

relapses within a specified range. Most patients (47/72; 65%) in this trial had experienced 1-2 relapses in the 18 months prior to study entry. Natalizumab doses were weight-based in all three trials, although the only dosage that was common amongst the trials was 3 mg/kg. Two of the trials reported effectiveness outcomes, although these were not the primary outcomes in either trial.[98, 99] The third trial, a single-dose pharmacokinetic study that included 8 patients at the 3 mg/kg dose, was designed to assess safety and did not include reporting of any effectiveness outcomes.[73, 97] The longest trial, Miller, et al.,[99] had a duration of 12 months, while the other trials were considerably shorter (14 weeks and 24 weeks respectively, for Sheremata[97] and Tubridy[98]).

Effectiveness data appears in Table 21. There was no significant difference in change in EDSS between the natalizumab and placebo groups at the final timepoint in both trials that reported this as an outcome,[98, 99] although trials of longer duration are needed to confirm this finding. The total number of relapses reported in each study arm varied considerably between the two trials. Miller, et al. reported a 4% relapse rate for natalizumab 3 mg/kg, while Tubridy reported a 39% relapse rate at the same dosage. Relapse rates for placebo were 21% and 44% respectively, resulting in a significant difference between natalizumab and placebo in only one of the trials.[99] Possible reasons for this discrepancy include trial duration (12 months of follow-up vs. 24 weeks of follow-up), total natalizumab dose (up to 18 mg/kg vs. 9 mg/kg), and criteria used to assess relapse. Miller, et al. used a more restrictive criteria to determine relapse (physician-assessed, sustained for at least 48 hours) than did Tubridy (Poser criteria, either objectively or subjectively defined, sustained for 24 hours.)[19] Due to these discrepant findings, it is difficult to draw a definitive conclusion regarding the effect of natalizumab on relapse rate.

Table 21. Effectiveness of natalizumab vs. placebo in RRMS and SPMS

Trial	Patient Characteristics	Natalizumab Regimen	Disease Progression outcomes	Relapse Outcomes
Miller et al. 2003[99] n=213	Mean EDSS: 4.3 Mean relapses 2 yrs prior to study: 3.0	3 mg/kg or 6 mg/kg every 28 days for 6 mos	Mean change in EDSS: 3 mg/kg: -0.14 6 mg/kg: -0.03 placebo: 0.03	Total relapses 3 mg/kg: 3 (4%); p=0.004 vs. placebo 6 mg/kg: 8 (11%); p=0.11 vs. placebo Placebo: 18 (21%) Use of rescue medication for relapse 3 mg/kg: 5/13 pts; p<0.001 vs. placebo 6 mg/kg: 7/14 pts; p=0.002 vs. placebo placebo: 22/27 pts
Tubridy 1999[98] n=72	Mean EDSS: 4.8 ≥ 2 relapses in 18 mos prior to study entry	3 mg/kg every 28 days*	Mean change in EDSS: 3 mg/kg: -0.02 placebo: 0.02	Total relapses: 3 mg/kg: 15/38 (39%) Placebo: 4/9 (44%)
Sheremata 1999[97] n=28	Mean EDSS ≤5.5 Mean relapses 2 yrs prior to study: range 0.7-2.3	Dose ranging study: 0.03-3.0 mg/kg; 8 pts received 3.0 mg/kg	NR	NR

**Natalizumab given at wks 0 and 4; outcomes based on follow-up of up to 24 wks*

No serious treatment-related adverse events were reported in any of the trials with the exception of one anaphylactic reaction in a natalizumab 3 mg/kg patient. In one trial, a

significantly higher number of natalizumab patients reported fatigue compared to placebo patients (p=0.065) but there were no other significant differences in adverse events between the natalizumab and placebo groups; other adverse event rates were similar across the three trials. The only safety outcome that was reported in all three trials was the total number of patients reporting any adverse event (Table 22). Again, the percentage of patients varied widely across the trials (5.4%-81% for natalizumab, 9.9%-85.7% for placebo), but in all of them there was no significant difference between the natalizumab and placebo arms.

Table 22. Tolerability of natalizumab vs. placebo in RRMS and SPMS

Study Adverse Event	Miller et al. 2003[99] n=213	Tubridy 1999[98] n=72	Sheremata 1999[97] n=28
Total pts reporting any AE:	3 mg/kg: 5/68 (7.4%) 6 mg/kg: 4/74 (5.4%) placebo: 7/71 (9.9%)	3 mg/kg: 19/37 (51.4%) placebo: 24/35 (68.6%)	All doses: 17/21 (81%) Placebo: 6/7 (85.7%)
Withdrawals due to AEs:	3 mg/kg: 4/68 (5.9%) 6 mg/kg: 3/74 (4.1%) placebo: 3/71 (4.2%)	NR	NR
Headache:	3 mg/kg:27/68 (39.7%) 6 mg/kg:20/74 (27%) placebo: 27/71 (38%)	NR	NR
Infections	3 mg/kg: 15/68 (22.1%) 6 mg/kg: 14/74 (18.9%) placebo: 11/71 (15.5%)	NR	NR
UTIs	3 mg/kg: 15/68 (22.1%) 6 mg/kg: 13/74 (17.6%) placebo: 11/71 (15.5%)	NR	NR
Weakness/muscle weakness	3 mg/kg: 12/68 (17.6%) 6 mg/kg: 7/74 (9.5%) placebo: 11/71 (15.5%)	NR	NR
Fatigue/Tiredness		3 mg/kg: 12/37 (32.4%) Placebo: 4/35 (11.4%)	

Mitoxantrone

Indirect Evidence

A well-conducted systematic review compared mitoxantrone (Novantrone®) to placebo using data from four trials(Table 23).[100] A second review included the same four trials, preliminary and unpublished data from an ongoing study.[101] Among the four trials included in both reviews, there was some heterogeneity among the types of patients, mitoxantrone doses employed, and study duration. Three of the studies enrolled mixed patient populations[102-104] while the remaining study enrolled only RRMS patients[81] and had a lower a mean baseline EDSS score (further discussion of the results of this trial appear in the RRMS section of this report). Mitoxantrone doses also varied widely across the included studies, while study duration ranged from 6-32 months.

Mitoxantrone was found to be more effective than placebo in reducing relapse rate and disease progression.[100] No statistically significant difference in EDSS at one year was detected in a small subset of patients (data available from one study) but 2-year results from a larger group of patients did statistically favor mitoxantrone (Table 24).

Table 23. Placebo-controlled trials of mitoxantrone

Trial	Patient characteristics	Mitoxantrone dose	Comparator	Study duration

Edan, 1997[102] n= 44	RR or SPMS Mean baseline EDSS: 4.6 (±1.7) Mean relapses 1 yr prior to study entry: 2.8 (±1.8)	20mg/mo + methylprednisolone	methylprednisolone	6 mos
Millefiorini, 1997[81] n=51	RRMS Mean baseline EDSS: 3.6(±1.1) Mean relapses 2 yrs* prior to study entry: 2.8(±1.2)	8 mg/m² of body surface/mo	placebo	12 mos
Van de Wyngaert, 2001[103] n=49	RR or SPMS Mean baseline EDSS: 5.2 Mean relapses 1 yr prior to study entry: 2.3(±1.1)	12 mg/m² of body surface/mo for 3 mos, then every 3 mos	placebo	32 mos
Hartung, 2002[104] n= 188	SP or worsening RRMS Mean baseline EDSS: 4.6(±1.01) Mean relapses 1 yr prior to study entry: 1.3(±1.2)	5 mg/m² of body surface every 3 mos** 12 mg/m² of body surface every 3 mos	placebo	24 mos

**Mean relapse rate at 1 yr NR in this study*
***Results from this study arm were excluded from the systematic review analysis. The study authors determined that the dose was too difficult to compare to the dosing schedules employed in the other studies.*

Table 24. Effectiveness outcomes in trials of mitoxantrone vs. placebo[100]

Outcome	Time point	n=	Results
Relapse rate	6mo/1 yr*	n=93	68.7% vs. 28.8% OR 5.4 (95% CI 2.2-13.1; p=0.0002)
	2 yrs	n=179	56.6% vs. 31.4% OR 3.11 (95% CI 1.68-5.72; p=0.0003)
Disease progression**	1 yr	n=51	7.4% vs. 25% OR 0.24 (95% CI 0.04-1.33, p=0.1)
	2 yrs	n=179	6.6% vs. 23.6% OR 0.23 (95% CI 0.09-0.59; p=0.0002)
EDSS – treatment effect	1 yr	n=25	-0.35 (95% CI -0.86-0.16; p=0.18)
	2 yrs	n= 175	-0.36 (95% CI -0.7- -0.02; p=0.04)

**Based on fixed effects model*
***Based on confirmed disease progression and change in EDSS at study's end*

Pooled data found withdrawals due to adverse events to be significantly higher among mitoxantrone patients relative to placebo: 9.4% compared to 2.3% (p=0.145). No serious adverse events were reported in any of the four included trials, including serious cardiac events. A non-serious decrease in left ventricular ejection fraction (LVEF) below 50% was reported in 5/138 (3.6%) of mitoxantrone patients; this was not statistically significant compared to placebo patients (p=0.1). Other commonly reported adverse events in mitoxantrone patients were nausea and vomiting, alopecia, amenorrhea and urinary tract infection (Table 25).

Table 25. Adverse events in placebo-controlled trials of mitoxantrone[100]

Adverse event	Mitoxantrone (%)	Placebo (%)	p
Amenorrhea*	20/77 (26%)	0/75 (0%)	p=0.0004
Cardiac: LVEF <50%	5/138 (3.6%)	0/130 (0%)	p=0.1
Nausea/vomiting	86/138 (62.3%)	20/130 (15.4%)	p<0.00001
Alopecia	65/135 (47.1%)	25/130 (19.2)	p<0.00001
Urinary tract infection (UTI)	35/138 (25.4%)	14/130 (10.8%)	p=0.003

**Amenorrhea persisted in 6/77(7.8%) of mitoxantrone patients following treatment cessation*

Mixed Populations: PPMS and SPMS

Glatiramer acetate

An early, good-quality study of glatiramer acetate (Copaxone®) was conducted in a population of 106 patients described as Chronic Progressive (a chronic progressive course for at least 18 months, no more than 2 exacerbations in the past 2 years, EDSS ≥2 and ≤6.5, and exhibiting progression in a pre-trial period).[105] Many clinicians consider this group of patients to represent a mix of patients with what would now be called PPMS or SPMS. The drug used in this study was available from 2 laboratories in Israel, not the commercially available glatiramer acetate (known as COP-1 at the time). The dosing of the drug was 15 mg SC twice daily, a dose that is higher than currently used (20mg SC daily). The mean baseline EDSS was slightly higher in the glatiramer acetate group (5.7 vs. 5.5) and both mean baseline scores are higher than seen in other glatiramer acetate studies. Comparing time to sustained progression curves (the primary outcome) while the glatiramer acetate curve showed slower progression, no significant difference was found between the groups over a 2 year period. This study did not conduct a sample size calculation, and with 106 patients may have been underpowered to show a difference of this magnitude. Further, subgroup analyses indicated that patients enrolled at the 2 centers responded differently while on study, and that overall patient disease activity differed on trial compared to the pre-trial assessment period.

Analysis of secondary outcomes indicated that statistically significant differences in proportions with progression (defined as an increase on EDSS of ≥ 1 if baseline ≥ 5, and 1.5 if baseline < 5) were not seen at 12 and 24 month time points, although glatiramer acetate was numerically superior (11%.vs. 18.5%, p = 0.088; 20.4% vs. 29.5%, p = 0.086 respectively). The authors also explored a definition of progression of an increase of only 0.5 points on the EDSS from baseline. Using this definition, the probability of progression was significantly lower with glatiramer acetate compared to placebo only at the 24 month time point (44.6% vs. 58.3%, P = 0.03).

The glatiramer acetate group experienced significantly more injection site reactions than the placebo group: soreness 83% vs. 47%, itchiness 61% vs. 17%, swelling 80% vs. 47%, and redness 85% vs. 30%; P = 0.001 overall. Significantly more patients taking glatiramer acetate reported vasomotor symptoms (flushing, palpitations, muscle tightness, difficulty breathing, and anxiety) transiently during treatment (24% vs. 5.5%, RR calculated here as 4.31, 95% CI1.41-13.7). No differences were seen between the groups in reporting of other adverse events. Withdrawals due to adverse events are not discussed in detail.

Additional Evidence of Safety

β Interferons

Tolerability

Pooled rates of tolerability of adverse effects and discontinuation for each of the β interferons, based on all head-to-head and placebo controlled trial rates and controlling for study effects, are presented in Table 26 below. This analysis indicates higher rates of injection site reactions, fever, and overall or adverse event-related discontinuation with interferon β1b SC (Betaseron®). Interferon β1a IM (Avonex®) led to higher rates of flu-like syndrome than the others, but the lowest rates of fatigue, fever, injection-site reaction and overall or adverse event-

related discontinuations. Interferon β1a SC (Rebif®) had slightly higher rates of fatigue, but lower rates of depression than the others.

Table 26. Interferon β1b and 1a: pooled adverse event rates

Adverse Effect	Interferon β1b SC (Betaseron®)	Interferon β1a IM (Avonex®)	Interferon β1a SC (Rebif®)
	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)
Injection Site Reaction	60.5% (45.6%, 75.5%)	10.0% (3.3%-26.8%)	48.4% (25.5%, 71.3%)
Flu-Like Syndrome	41.4% (17.1%, 65.6%)	58.5% (29.9%, 87.2%)	42.3% (25.3%, 59.3%)
Fatigue	--	18.3% (0.0%, 45.0%)	23.9% (10.0%, 37.9%)
Myalgias	29.1% (23.0%, 35.1%)		
Fever	38.1% (12.4%, 63.7%)	14.2% (0.3%, 28.1%)	22.7% (10.6%, 34.8%)
Depression	21.5% (3.1%, 39.9%)	21.9% (8.5%, 35.3%)	17.7% (8.2%, 27.3%)
Overall withdrawal	20.4% (15.5%, 25.4%)	12.2% (7.0%, 17.4%)	14.6% (10.4%, 18.7%)
Discontinuation due to AE	8.6% (5.7%, 11.5%)	3.0% (0.8%, 5.3%)	5.4% (3.2%, 7.7%)

Non-trial evidence is limited and low quality, with 4 open-label studies of interferon β1b (Betaseron®),[106-109] 3 open-label studies of interferon β1a IM (Avonex®),[33, 67, 110] 2 studies (1 with 3 publications) reporting adverse event data for more than one β interferon,[111-114] and 1 study comparing open-label use of interferon β1b SC (Betaseron®) to an untreated control group.[115] These studies are not longer in duration than the trials, nor do they provide data on rare but serious adverse events. Because of the limitations of these designs and lack of controlling for potential confounding, these studies do not provide better information on tolerability than the trial data.

In a study of patient perceptions of adverse events associated with β interferon therapy, 40 patients taking interferon β1b SC (Betaseron®) or interferon β1a IM (Avonex®) were questioned on the impact of adverse effects on their lives.[116] Results of this study indicate that most adverse effects were mild and did not have a strong impact on the patients' lives, although fatigue was rated moderate or severe. The study found wide variation in patient response to both systemic and local adverse events, but did not make comparisons between the products.

Thyroid Function

The effect of β interferons on thyroid function in RRMS patients was assessed in two observational studies (Table 27). The larger study[117] found that thyroid autoimmunity was common at baseline in RRMS patients (8.5%), however this finding was not confirmed by the second, smaller study.[64] Thyroid dysfunction, defined as clinical or subclinical hyper- or hypothyroidism, was observed in 22% of interferon β1a IM (Avonex®) patients and in 27% of interferon β1b SC (Betaseron®) patients; this difference was not significant (p=0.68). Thyroid autoimmunity was the only outcome that was reported by both studies. Pooled relative risk of developing thyroid autoimmunity was 0.86 (95% CI 0.43-1.72) for interferon β1a IM (Avonex®) and 0.63 (95% CI 0.17-2.69) interferon β1b SC (Betaseron®). Based on this limited data, there appears to be little difference between the two drugs regarding the risk of developing thyroid autoimmunity.

Table 27. Effect of β interferons on thyroid functioning

Trial	Design	Population	Intervention	Results
Caraccio 2005[117]	prospective cohort; up to 84 mos follow-up	n=106 RRMS	Inf β1a: 6 mIU/wk IM Inf β1b: 8mIU every other day SC	Thyroid dysfunction: 22% Inf β1a vs. 27% Inf β1b Thyroid autoimmunity: 20.8% Inf β1a vs. 25% Inf β1b
Martinelli 1998[64]	prospective controlled cohort; up to 18 mos	n=17 RRMS	Inf β1a: 6 mIU/wk SC Inf β1b: 8mIU every other day SC	Thyroid autoimmunity: 25% Inf β1a vs. 40% Inf β1b

Three additional non-comparative observational studies of thyroid dysfunction in interferon β1b SC (Betaseron®) patients reported 17 cases of thyroid dysfunction in a total of 227 patients.[65, 118, 119] Of those 17 cases, there were eight cases of clinical hyperthyroidism and one case of hypothyroidism in a patient with baseline subclinical hypothyroidism; all other cases were deemed subclinical.

Liver Failure

Liver failure has not been reported in trials of β interferons, however one post-marketing case report of liver failure in an MS patient taking interferon β1a IM (Avonex®) appears to be linked to β interferon use.[120] The relationship between interferon β1a SC (Rebif®) and liver failure in a second case report is unclear due to concomitant use of a known hepatotoxic drug.[121] No cases of liver failure have been reported with Interferon β1b SC (Betaseron®).

ALT elevations

ALT elevations, the most commonly reported hepatic outcome, are classified according to the National Cancer Institute's Common Toxicity Criteria for grade 1 (≥ 2.5 x ULN), grade 2 (2.5-5.0 x ULN) or grade 3 (5-20 x ULN) elevations. Although overall incidence of ALT elevations was lower in the placebo-controlled trials than in observational studies, ALT elevations are common with all three products (Table 28.)

Table 28. Proportion of β interferon-treated patients experiencing ALT elevations (≥ grade 1; ≥ 1 yr follow-up)

Intervention	Dosage	Trial data*[122]	Post-marketing data[123, 124]
Interferon β1a IM (Avonex®)	30 ug 1x/week	NR	23%-38%
Interferon β1a SC (Rebif®)	22 ug 3x/week	20%	34%-53%
	44 ug 3x/week	27%	38%-67%
Interferon β1b SC (Betaseron®)	250 ug every other day	11%	38%-39%

**Data from 'pivotal' placebo-controlled trials*

Interferon β1a

A meta-analysis of six randomized, placebo-controlled trials ranging up to two years in duration assessed the risk of hepatic reactions, specifically ALT elevations, in interferon β1a-treated RRMS patients.[124] That review found that most patients taking one of the interferon β1a products were likely to develop elevated ALT levels at some time during treatment, and that onset of ALT elevation occurred fairly soon following treatment initiation (mean 2.1-2.9 months for all interventions). Male gender and concomitant propionic acid derivative use (i.e. naproxen or ibuprofen) significantly influenced the chances of developing elevated ALT levels ($p<0.001$

for both factors). Using age 39 as a cut-off point, younger patients developed elevated ALT levels less frequently than older patients. This difference reached statistical significance only when all interferon β1a-treated patients were combined (39% vs. 46%; p=0.0001). ALT elevations also occurred more frequently in patients receiving interferon β1a SC (Rebif®) 44ug three times a week (p<0.001) compared to the other interventions. Resolution of ALT elevations were only reported for interferon β1a SC (Rebif®) at the 22 and 44ug three times a week dose. Of those patients, 4.1% of 22 ug and 5.5% of 44 ug patients had persisting ALT elevations. Withdrawals due to ALT or other liver enzyme elevations were uncommon across the trials (0.4% of all interferon β1a-treated patients). The rate of serious, symptomatic changes in liver function, based on trial and postmarketing data of interferon β1a, is estimated to be 1/2,300 patients.

These findings are similar to those in two single-arm studies of interferon β1a IM (Avonex®)[62, 67] where ≥grade 1 ALT elevation rates ranged from 26% to 36%.

Interferon β1b

A prospective, 1-year study of 156 interferon β1b SC (Betaseron®)-treated RRMS patients found 37.5% of had *de novo* liver function alteration (an endpoint that included both ALT and AST elevations).[125] That study also found that irrespective of severity of liver function alteration, all patients had liver functions within normal ranges by 3-6 months.

Interferon β1a vs Interferon β1b

A retrospective chart review of 844 patients compared ALT elevations based on treated with interferon β1a IM (Avonex®), interferon β1a SC (Rebif®), or interferon β1b SC (Betaseron®).[123] There were significant baseline differences in the patients involved; differences in gender, age at initiation of treatment and at diagnosis with MS, median EDSS, and ethnicity were all statistically significant. Perhaps most important clinically, mean duration of treatment was also different among the included drugs, ranging from 14.7 months to 29.5 months. *De novo* ALT elevations ≥grade 1 ranged from 23% for interferon β1a IM (Avonex®) to 38.9% for interferon β1b SC (Betaseron®). *De novo* changes ≥grade 2 and ≥grade 3 occurred less frequently (pooled rate 5.0% and 1.4% respectively, for all interferons; p<0.005); only one interferon β1a IM (Avonex®) patient had a ≥grade 2 elevation, and no interferon β1a IM (Avonex®) patient had a ≥grade 3 elevation (Table 29). While these changes were significant from baseline, there was no statistically significant difference in between-group comparisons.

Table 29. Severity of ALT elevations in β interferon-treated patients[123]

Intervention	Dosage	Mean duration	Mean *de novo* ALT elevation		
			≥Grade 1	≥Grade 2	≥Grade 3
Interferon β1a IM (Avonex®)	30 ug 1x/week	14.7 months	23. 0%	1.9%	0.0%
Interferon β1a SC (Rebif®)	22 ug 3x/week	15.7 months	33.6%	4.7%	1.6%
	44 ug 3x/week		38.0%	7.8%	1.6%
Interferon β1b SC (Betaseron®)	250 ug every other day	29.5 months	38.9%	4.3%	1.1%

Depression

A meta-analysis of 6 randomized controlled trials and 17 postmarketing, unpublished studies compared the rate of depression with interferon β1a use to placebo.[126] While these studies were primarily of interferon β1a SC (Rebif®), one trial of interferon β1a IM (Avonex®) was also included. This meta-analysis focused on making comparisons between the β interferon products

as a group to placebo; there was little evidence providing direct comparisons of β interferon products. Six-month data, based on the 6 included RCTs, showed that a significantly higher percentage of interferon β1a patients reported depression as an adverse effect of treatment when compared to placebo patients (p=0.017) with little difference in depression rates between the interferon β1a products: 5-12% for interferon β1a SC (Rebif®) and 18% for interferon β1a IM (Avonex®). Long-term evidence, again based on the 6 included RCTs, showed that there was no longer a significant difference between interferon β1a SC (Rebif®) and placebo (p=0.83) at 2 years. Suicide or suicide attempt rates, adjusted for length of exposure, were similar for both interferon β1a and placebo groups (OR 0.77 95% CI 0.30-1.3) although results were not stratified by type of interferon β1a and dose. Similarly, withdrawal rates due to depression as an adverse event were not significantly different between the interferon β1a products (1.3% in trials, 1.5% in postmarketing studies) and placebo (0.6% in trials; p=0.116.)

Our own analysis of the all published trials reporting rates of depression indicates a non-significant increase in risk for both interferon β1a products and a non-significant decrease in risk with interferon β1b SC (Betaseron®), see Table 30. Our adjusted indirect analysis (Table 31) indicates no significant difference among the interferons for risk of depression although the relative risks favored interferon β1b SC (Betaseron®) over the β1a products, and interferon β1a SC (Rebif®) had a higher pooled estimate compared to interferon β1a IM (Avonex®). Because these analyses are based on so few trials, these results should be interpreted with caution. These results do, however agree with the results of the meta-analysis above.

Table 30. Risk of depression with Interferons in placebo-controlled trials

Drug	N studies	Relative Risk (85% CI)
Interferon β1a IM (Avonex®) vs. Placebo	1	1.15 (0.82 to1.60)
Interferon β1a SC (Rebif®) (22 µg) vs. Placebo	2	1.26 (0.99 to1.61)
Interferon β1b SC (Betaseron®) vs Placebo	1	0.90 (0.53 to 1.54)

Table 31. Adjusted indirect analysis of risk of depression with interferon use

Comparison	Relative Risk (85% CI)
Interferon β1b SC (Betaseron®)vs interferon β1a SC (Rebif®)	0.72 (0.40 to1.29)
Interferon β1b SC (Betaseron®)vs interferon β1a IM (Avonex®)	0.79 (0.42 to1.48)
Interferon β1a SC (Rebif®) vs interferon β1a IM (Avonex®)	1.10 (0.73 to 1.66)

Two other small, single-arm studies assessed depression symptom scores with β interferon use. A study (n=106) of interferon β1a IM (Avonex®) showed no difference in baseline and 1-year follow-up depression ratings in RRMS patients (p=0.63), although a depression scale that included somatic complaints commonly linked to MS was used (Beck Depression Inventory II).[127] An open-label study (n=90) of interferon β1b SC (Betaseron®) found that patients' depression scores improved following two years of treatment.[128]

Glatiramer acetate

Evidence on the safety of glatiramer acetate (Copaxone®) from five non-comparative, non-randomized studies is consistent with that from previously discussed trials.[129-132] No additional serious adverse events were reported in any of these studies, with the exception of a small, retrospective study that assessed the risk of potentially permanently disfiguring lipoatrophy with glatiramer acetate use.[133] That study found that 34/76 (45%) of patients

identified through chart review had evidence of lipoatrophy. Five of these cases were identified as severe, all cases occurred in women, and four withdrawals were attributed to lipoatrophy.

β interferons vs. glatiramer acetate

Tolerability

There is little additional evidence regarding the comparative safety of interferons and glatiramer acetate based on data from observational and other non-randomized studies (Table 32).[112, 134-136] 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.

Table 32. Tolerability outcomes of β interferons vs. glatiramer acetate: trials vs non-randomized studies

Intervention	Flu-like syndrome		Injection-site reaction		Fever		Withdrawals due to AEs	
	Trials	Non-RCTs	Trials	Non-RCTs	Trials	Non-RCTs	Trials	Non-RCTs
Interferon β1a IM (Avonex®)	59%	35%	10%	8%	14%	12%	3%	2%
Interferon β1a SC (Rebif®)	42%	6%	48%	6%	23%	3%	5%	8%
Interferon β1b SC (Betaseron®)	41%	15%	61%	24%	38%	17%	9%	5%
Glatiramer acetate*	NR	0.2%	51%	24%	NR	0%	3%	8%

*Systemic reactions were also reported in 24% and 7% of glatiramer patients in trials and non-RCTs respectively; there are no reports of this outcome associated with β interferon use.

Depression

A small (n=163) cohort study by Patten, et al.[137] used a Canadian reimbursement database to assess the incidence of depression in RRMS patients receiving any β interferon (n=66) compared to glatiramer acetate (n=97). There was some heterogeneity between the groups. Specifically, the β interferon-treated patients had slightly higher EDSS and depression scores and slightly lower quality of life scores at baseline. In addition, depression was common among MS patients, both at baseline (28.8% for β interferons and 22.7% for glatiramer acetate) and at follow-up, regardless of intervention. While glatiramer acetate-treated patients tended to have lower depression scores, there was no significant difference in depression score at 3 month follow-up between β interferons and glatiramer acetate (40.0% vs 21.3% respectively, p=0.12). This difference remained insignificant when any time points of follow-up were considered: 34.0% for β interferons and 25.3% for glatiramer acetate, p=0.312.

Cancer

A cohort of patients in Israel with MS (type not specified) treated with β interferons or glatiramer acetate was compared to healthy controls to assess the incidence of cancer and the effect of β interferon or glatiramer acetate use on cancer rates.[138] This study found that baseline non-breast cancer incidence is lower in women with MS when compared to the general population and that use of either β interferons or glatiramer acetate may increase the risk of

developing cancer in women. However, this difference did not reach statistical significance and there was no significant risk difference for breast cancer in women or men. Larger studies could potentially validate a causal link between β interferon or glatiramer acetate use and increased cancer risk, however based on the results of this study no such link can be proven or disproven.

Natalizumab

Progressive Multifocal Leukoencephalopathy (PML)

PML is a serious, progressive neurologic disorder caused by infection of the central nervous system by JC virus, a member of the papovavirus family. JC virus is carried in a latent form by 70-75% of the general population but generally does not cause symptoms. PML is rare, but when it occurs it frequently results in irreversible neurologic deterioration and death, and there is no known effective treatment for the disease.[139] Two patients with MS and one with Crohn's disease treated with natalizumab (Tysabri®) were reported to have developed PML.[140-142]

An evaluation of all patients who had received natalizumab in clinical trials or via compassionate use criteria or after FDA approval (n=3417) was undertaken.[143] 3389 patients were followed up, using neurological exam, brain MRI, and cerebrospinal fluid samples. 44 patients (1.3%) had findings of possible PML. Data were then examined by an expert panel; 43 potential cases were ruled out, and one patient refused further follow-up. The authors then estimate the incidence of PML at 1.0 per 1000 treated patients (95% CI 0.2 to 2.8 per 1000) based on the 3 original cases. Because these 3 patients had also been receiving immunomodulators or immunosuppressants, it is recommended that natalizumab be used only as monotherapy.

Mitoxantrone

Small (n= 7 to 31) before-after studies of patients with various categories of MS have been reported.[144-146] These studies used differing dosing and schedules (5 mg/m^2 every 3 months x 12, vs. 8 mg/m^2 every 3 weeks x 7, vs. 10mg/m^2 every month x 3, then every 3 months to a total dose of 150 mg/m^2). The most common adverse events reported were nausea (39 to 71%), alopecia (13 to 29%), fatigue (7%), and in one study 57% of women reported transient secondary amenorrhea.

Cardiotoxicity

Thirteen percent of 31 patients receiving 5 mg/m^2 every 3 months required discontinuation of treatment due to reduction of left ventricular ejection fraction to </= 50%, although cumulative dose at the time of discontinuation was not reported.[144] In a very small study, 7 patients who had received cumulative doses of 66 to 198 mg/m^2 had "normal quantitative cardiac function" after 12 months of treatment.[146]

The long-term risk of serious cardiac adverse events with mitoxantrone (Novantrone®) use in patients with RR, SP, PPMS, or another/unknown diagnosis was assessed in a meta-analysis of three studies.[147] The meta-analysis was based on patient data (n=1378) from one phase-III trial and two open-label, noncomparative studies available in abstract form only. The full results of the trial[104] were included in the Martinelli Boneschi systematic review discussed above. Two cases of fatal congestive heart failure (CHF) were reported (0.15%, 95% CI 0.02-0.52%), although one of the CHF deaths could not be definitively linked to mitoxantrone use.

Asymptomatic LVEF<50% was reported in 17/779 patients for whom data was available (2.18%, 95% CI 1.28-3.47%). Further analysis by the study's authors found that patients receiving a cumulative dose <100mg/m^2 had a lower incidence of asymptomatic LVEF <50% than those patients receiving ≥100mg/m^2, although this did not reach statistical significance (incidence of 1.8% vs. 5.0%; p=0.06).

Cancer

The risk of therapy-related acute leukemia (t-AL) in a mixed MS population (n=1378) was assessed in a meta-analysis that included patient data from three studies (one placebo-controlled trial and two open-label studies; mean length of follow-up 36 months).[148] There were two reports of t-AL, both in young women who had received 70 mg/m^2 cumulative dose of mitoxantrone (incidence 0.15%). An additional nine publications (one trial, one open-label study and seven abstracts) comprising 242 MS patients were searched for reports of t-AL, however no additional cases were identified.

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

Clinically isolated syndrome (CIS)

Summary

The evidence on the use of disease-modifying drugs in patients with a CIS to ultimately prevent progression to MS is limited to 3 trials (7 publications) involving the β interferons[34, 149-155] (Tables 28 and 29.) Evidence suggests that all three β interferon products reduce the probability of converting from CIS to clinically definite MS over 2 to 5 year periods. At 3 years, Avonex® was superior to placebo with a rate ratio of 0.56 (95% CI 0.38-0.81). At 2 years, both Betaseron® and Rebif® were also superior to placebo: rate ratios 0.50 (95% CI 0.36-0.70) and 0.65 (95% CI 0.45 to 0.94) respectively.

No evidence was found for glatiramer acetate, natalizumab or mitoxantrone.

Detailed Assessment

Direct evidence

No head-to-head trials have been conducted.

Indirect evidence

Three placebo-controlled trials (with multiple publications) have been conducted, one with each of the interferon products versus placebo (Table 33.)[34, 149, 151-155] All 3 trials show a statistically significant reduction in the proportion of patients and the time to converting to clinically definite MS compared to placebo (see Table 28) with relative risks or hazard ratios in the 0.5 to 0.65 range and NNT of 6 for interferon β 1b (Betaseron®), 7 for interferon β 1a (Avonex®), and 10 for interferon β 1a (Rebif®). The two trials of interferon β 1a products were low dose, with weekly injections; while the recent study of interferon β 1b (Betaseron®), the BENEFIT study, used every other day dosing. The patient populations enrolled in the studies are somewhat different, with the study of interferon β 1a SQ (Rebif®)[154] enrolling patients multifocal presentation, a higher percentage with gadolinium enhancing brain lesions, and lesions with larger median volume compared to the compared to the other 2 studies (see Table 33).[34, 155] All

patients enrolled in The Controlled High Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) received standardized corticosteroid treatment for the initial episode and were enrolled within 2 weeks of initial symptom presentation, while patients in the other 2 studies were enrolled within 2 or 3 months of initial presentation and treatment of the episode was not standardized. [34, 155] The recent BENEFIT study of interferon β 1b (Betaseron®) enrolled patients with at least 2 silent MRI lesions, and may represent a group of patients at higher risk for progressing to MS.[156] Because there are apparent clinical differences in the populations enrolled, and because there is only 1 trial of each drug, an indirect meta-analysis of these data was not undertaken. CHAMPS was stopped early after a planned interim analysis indicated a significant difference in benefit between the groups.[155] While the primary endpoint of conversion to clinically definite MS was defined slightly differently in the 3 studies, they were based primarily on a relapse of the initial or new symptoms. The study of interferon β 1b (Betaseron®) also used the McDonald criteria which incorporates MRI findings.

In a post-hoc analysis of the CHAMPS data, only patients considered at high risk of conversion to MS (≥9 T2-weighted hyperintense lesions and >/=1 gadolinium enhanced lesion) were included. This was a small group of patients (n=91; 24% of the total enrolled). This analysis found the rate ratio to be 0.344 (95% CI 0.17-0.70; p=0.002). This compares to a rate ratio of 0.56 (95% CI 0.38-0.81; p=0.002) in the total population. In the BENEFITs study of interferon β 1b (Betaseron®), multiple subgroup analyses were undertaken, examining the effects in monofocal versus multifocal presentation, and patients with or without gadolinium enhanced lesions or ≥ 9 T2-weighted hyperintense lesions. The results indicated a significant benefit in all groups, with hazard ratios ranging from 0.40 in patients with <9 T2 lesions, to 0.63 inpatients with multifocal presentation (compared to a hazard ratio of 0.50, 95% CI 0.36-0.70 in the overall study group). Because these are subgroup analyses, with relatively small numbers of patients in each group, these results should be interpreted with caution.

Table 33. Efficacy of β interferons in patients with a clinically isolated syndrome

Study Quality	Interferon Dose/Schedule	N Mean Age	Baseline Presentation	Conversion to MS
Interferon β 1a:				
CHAMPS Jacobs 2000 (Avonex®) Fair	30 mcg IM weekly x 3 years	Ifn β1a 193 Placebo 190 33 yrs	Site of Involvement: Spinal Cord 22% Optic neuritis 50% Brain Stem/Cerebellum 28% % with gadolinium enhancing lesions 28% Median volume of lesions on T2 weighted MRI 2051 mm^2 % treated with steroids: 100%	Cumulative probability Ifn β1a 35% Placebo 50% Rate ratio 0.56 (95% CI 0.38–0.81) NNT 7
Comi 2001 (Rebif®) Fair	22 mcg SC weekly x 2 years	Ifn β1a 154 Placebo 155 29 yrs	Site of Involvement: Spinal Cord 28% Optic neuritis 32% Brain Stem/Cerebellum 52%* % with gadolinium enhancing lesions on T1: 58% Median volume of lesions on T2 weighted MRI: 4964 – 5542 mm^2 % treated with steroids: 70%	Ifn β1a 52/154 (34%) Placebo 69/154 (45%) Rate ratio 0.65 (95% CI 0.45-0.94) NNT 10
Interferon β 1b:				
BENEFIT Kappos 2006 (Betaseron®) Good	250µg SC every other day x 2 years	Inf β 1b 292 Placebo 176	Site of Involvement: Monofocal- 53% Spinal Cord 17% Optic Nerve 17%	Poser criteria (CDMS): Inf β 1b 75/292 (26%) Placebo 77/176 (44%) Hazard ratio 0.50

			Brain Stem/Cerebellum 12% Other 7% Multifocal- 47% % with gadolinium enhancing lesions on T1: 42% Median volume of T2 lesions: 1951.5—1858.5 mm^2 (range 592-5029) % treated with steroids: 71%	(95% CI 0.36-0.70) NNT 6 McDonald criteria (McDonald MS): Inf β 1b 191/292 (65%) Placebo 142/176 (81%) Hazard ratio 0.54 (95% CI 0.43-0.67) HrQOL: No significant change from baseline in either group

**Total exceeds 100% - more than one site counted.*

Discontinuation of assigned treatment for reasons other than conversion to MS were not significantly greater in the β interferon groups, although in the trial of interferon β 1b (Betaseron®) more patients either discontinued interferon early *or* were lost to follow up compared to placebo (21% vs. 16%). Withdrawals due to adverse events were significantly higher with interferon β 1b (Betaseron®) and significantly *lower* with interferon β 1a IM (Avonex®) compared to placebo. The trial of interferon β 1a SQ (Rebif®) reported only 3 withdrawals due to adverse events, but did not specify to which group(s) the patients had been assigned (see Table 34).

The studies did not describe methods of ascertaining adverse events and the reporting of adverse events is sparse. The incidence of adverse events were significantly higher in the β interferon groups compared to the placebo groups for most commonly occurring adverse events, such as influenza-like syndrome. Rates of serious adverse events were not different in any trial, and rates of depression were not significantly higher in the 2 trials reporting this outcome (interferon β 1b (Betaseron®) and interferon β 1a (Avonex®.)

Table 34. Adverse events of β interferons in Clinically Isolated Syndrome

Study Quality	Interferon Dose/Schedule	Withdrawal due to Adverse Events	Adverse Event Rates Ifn-β1a vs. Placebo, p value
Interferon β 1a:			
CHAMPS 2000 (Avonex®) Fair	30 mcg IM weekly x 3 years	Ifn-β1a 4/193 (0.5%) Placebo 7/190 (4%) *P* = 0.0355*	Flu-like syndrome (1st 6 mos) 54% vs. 26% p<0.001 Depression 20% vs.13%, p=0.0645 Serious adverse events 6% vs.10%, NS Neutralizing antibodies; <1% at 12, 18 mos, 2% at 24, 30 mos
Comi 2001 (Rebif®) Fair	22 mcg SC weekly x 2 years	A total of 3 withdrew due to adverse events – stratification by group not reported. (0.78% overall; 1.95% if assumed all from Rebif® group)	Injection site reactions 60% vs. 12%, p<0.0001* Fever 28% vs. 12%, p=0.0006* Myalgia 17% vs. 9%, p=0.0419* Chills 11% vs. 5%, p=0.0604* Serious adverse events 4% vs. 3%, NS*
Interferon β 1b:			
Kappos 2006	250µg SC every other day x 2	Inf β 1b 32/292 (11%) Placebo 1/176 (0.6%)	Injection-site reactions 48.3% vs 8.5%, p<0.0001*

(Betaseron®) Fair/Good	years	p<0.0001*	Flu-like syndrome 44.2% vs 18.2%, p<0.0001* Fever 13.0% vs 4.5%, p=0.003* Depression 10.3% vs 11.4%, p=NS Serious adverse events 6.8% vs 6.8%, NS ALT elevation (≥5x baseline) 17.8% vs 4.5%, p<0.0001* AST elevation (≥5x baseline) 6.2% vs 0.6%, p=0.0027*

*Calculated here using chi-square test, StatsDirect

Patients enrolled in the CHAMPS who had not converted to MS at the end of the 3-year trial were offered enrollment in CHAMPIONS, a 5-year open-label extension study.[150] Patients who had been assigned to interferon β1a during the trial were considered the immediate treatment group and those assigned to placebo and given interferon β1a during the extension study were considered the delayed treatment group. The analysis compared the conversion rate between these 2 groups and found that the 5-year cumulative incidence rate in the immediate treatment group was 36% vs. 49% in the delayed treatment group, adjusted hazard ratio 0.57 (95% CI 0.38 to 0.86, p = 0.008). Multivariate analysis indicated that the factors associated with conversion to MS were randomization to the delayed treatment group and younger age at enrollment in the CHAMPS. Rates of adverse events were very poorly reported in this study. Only serious adverse events (n = 13 in 6% of patients overall) are reported and none were considered related to interferon β1a. Other typical and concerning adverse events associated with interferon β1a were not discussed or reported. Further publications with 3 and 5 year data are also expected from the BENEFIT study of interferon β 1b (Betaseron®).

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?

Summary

Two observational studies and an individual patient data meta-analysis were identified that assessed the use of DMDs in subgroups of MS patients, including African-Americans with MS and pregnant women with MS. Due to small sample sizes, along with other concerns regarding study design, it is impossible to draw conclusions about the use of DMDs in these subpopulations based on the available data.

Detailed assessment

β Interferons

Race

A post-hoc subgroup analysis of EVIDENCE, a head-to-head trial of interferon β1a products (Avonex® and Rebif®) compared the response to treatment in African-American and white patients.[157] The proportion of African-American patients in the EVIDENCE trial was small (6%). The subgroup analysis found that although the two groups were similar at baseline, the African-American patients experienced more exacerbations and were less likely to be

exacerbation-free compared to the white patients over the course of the study. The small number of patients in the African-American group means that these results should be interpreted with caution. This analysis was not intended to identify differences in response between the products. The disproportionate numbers of patients in this group randomized to Avonex® (n = 23) compared to Rebif® (n = 13) greatly hindered that ability to make any comparisons between the treatments.

Pregnancy

In a meta-analysis of individual patient data from 8 studies of interferon β 1a SQ (Rebif®) or IM (Avonex®), including open-label extension phase studies and involving patients with RRMS, SPMS, or CIS, 41 pregnancies occurred with in utero exposure to interferon, 22 in women with previous exposure (had discontinued interferon more than 2 weeks prior to conception), and only 6 in women receiving placebo.[158] In the group with in utero exposure to interferon β1a, pregnancy loss occurred in 29%, compared to 0 in either the placebo or prior exposure groups. The authors indicate that the rate of pregnancy loss with in utero exposure is greater than the average reported in the overall population, although they report that taking the small sample size into consideration, the rate may be within the expected range. Prematurity and full-term infants with congenital anomalies occurred in 4.9% in the in utero exposure group, 9.1% in the prior treatment group, and 16.7% in the placebo group and no teratogenic effects were seen.

A small study described as a longitudinal controlled cohort study evaluated the risk of exposure to β interferons during pregnancy.[159] This study reports that the β interferon-exposed pregnancies were more likely to result in non-live birth compared to the healthy cohort (OR 6.94, 95% CI 1.18-40.70). The group with MS *not* exposed to β interferons also had an increased risk of non-live birth (OR 2.91) but statistical significance was not reached (95% CI 0.48-31.67). A direct comparison of the β interferon exposed and unexposed MS group was not presented. Mean birth weight was lower in the β interferon-exposed group (3189 grams) versus in the unexposed group with MS (3498 grams). This study presents a number of concerns in terms of study validity because of potential confounding, recall bias, use of a statistical model with multiple parameters, and too few data. Therefore, these results should be interpreted cautiously and be used as the basis for future research rather than for treatment decisions.

SUMMARY

Indirect comparisons from placebo-controlled trials and non-randomized studies provide the majority of available information for all interventions. The only direct comparisons available were from four trials comparing one β interferon to another. There were no direct comparisons of the other included drugs. Non-comparative, non-randomized studies added little to the evidence of long-term safety. The findings of this review of are summarized in Table 35:

Table 35. Summary of evidence by key question

Key question	Quality of the Evidence	Conclusion
Key Question 1: What is the comparative effectiveness of disease-modifying treatments for	Fair	*RRMS:* Direct evidence- • Direct evidence from four fair-quality head-to-head trials showed little difference in relapse and disease progression outcomes between interferon β1a SC (Rebif®) and interferon β1b (Betaseron®), while interferon β1a IM (Avonex®) was

multiple sclerosis, including use of differing routes and schedules of administration?		less effective than interferon β1a SC (Rebif®) for relapse outcomes and interferon β1b (Betaseron®) for relapse and disease progression outcomes. Indirect evidence- • Evidence from placebo-controlled trials demonstrated the superiority of the interferon β1a products in slowing disease progression relative to placebo, while interferon β1b (Betaseron®) was not significantly better than placebo for this outcome. This contradicts the findings from the head-to-head trials. Conversely, interferon β1a IM (Avonex®) rates of relapse-free patients in placebo-controlled trials were similar to the other β interferons, which also contradict the findings from the head-to-head trials. • 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). *SPMS:* There is no direct evidence. Evidence from placebo-controlled trials showed that the all of β interferons were similarly effective at reducing relapse rates. A positive effect on disease progression was observed with interferon β1b (Betaseron®) although similar effects were not consistently observed with the interferon β1a products. *PPMS:* The only evidence available (from one small, good quality trial comparing interferon β1a IM (Avonex®) to placebo) is insufficient to make any judgments regarding effectiveness in PPMS patients. *PRMS:* No studies of DMD use in PRMS patients were identified through literature searches.
Key Question 2: What is the comparative tolerability and safety of disease-modifying treatments for multiple sclerosis?	Fair	*Withdrawals due to adverse events:* No difference in withdrawal rates among β interferons in head-to-head trials, although adverse events in generally were poorly reported in these trials. Withdrawal rates ranged from 3% (Interferon β1a IM [Avonex®]), glatiramer acetate) to 9% (Interferon β1b SC [Betaseron®]) in placebo-controlled trials. *Serious adverse events:* NAbs: 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. Liver function: ALT elevations are common with all β interferon products, with little difference in rates of occurance. Most elevations are asymptomatic and transitory. Thyroid function: Limited data from two observational studies found similar rates of clinical and subclinical thyroid autoimmunity with Interferon β1a IM (Avonex®) and Interferon β1b SC (Betaseron®) Depression: There were no significant differences in rates of depression among the β interferons based on limited trial data. One small observational study comparing β 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 β1a products and a non-significant decrease in risk with interferon β1b SC (Betaseron®.) Cancer: Data from one cohort study found a potentially increased risk of cancer development in women with either β interferon or glatiramer acetate use; these results are inconclusive. Therapy-related acute leukemia was reported in 2/1,620 patients taking mitoxantrone. Cardiotoxicity: Two cases of CHF were potentially linked to mitoxantrone use in one meta-analysis of three (two unpublished) studies (incidence 0.15%) Progressive multifocal leukoencephalopathy (PML): Estimates of PML incidence with natalizumab use is 1.0/1,000 patients based on three known cases. *Tolerability:* Flu-like syndrome: Interferon β1a IM (Avonex®) was associated with the highest rates of flu-like syndrome compared to the other β interferons (~58% vs ~41%) Injection-site reactions: Interferon β1b SC (Betaseron®) was associated with the highest rates of injection-site reactions (60.5% vs 10.0- Systemic reactions: 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 β interferons, natalizumab or mitoxantrone. *Long-term safety in observational studies:* 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.
Key Question 3: What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?	Fair to poor	No direct evidence comparing one DMD to another in patients with a clinically isolated syndrome was available. Indirect comparison of interferon β1a IM (Avonex®), interferon β1a SC (Rebif®) and interferon β1b (Betaseron®) 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. There is no evidence on glatiramer (Copaxone®), mitoxantrone (Novantrone®) or natalizumab (Tysabri®) use in clinically isolated syndromes.
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	Poor	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. Race: 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. Pregnancy: 2 studies; a small observational study, assessing rates of live birth in pregnant women with MS using β interferons compared to a healthy cohort and an individual patient data meta-analysis based on 8 trials of interferon β1a 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 β interferon

fewer adverse events?		versus another. The first study reports that the β 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 β1a during an 'in utero' phase, compared to 0 in either the placebo or prior exposure groups. However, these studies provided no conclusive evidence regarding β interferon use in pregnancy.

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131. Fiore APP, Fragoso YD. Tolerability, adverse events and compliance to glatiramer acetate in 28 patients with multiple sclerosis using the drug continuously for at least six months. *Arquivos de Neuro-Psiquiatria.* Sep 2005;63(3B):738-740.

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134. Pollmann W, Erasmus LP, Feneberg W, Then Bergh F, Straube A. Interferon beta but not glatiramer acetate therapy aggravates headaches in MS. *Neurology.* Aug 27 2002;59(4):636-639.

135. Flechter S, Vardi J, Pollak L, Rabey JM. Comparison of glatiramer acetate (Copaxone) and interferon beta-1b (Betaferon) in multiple sclerosis patients: an open-label 2-year follow-up. *Journal of the Neurological Sciences.* May 15 2002;197(1-2):51-55.

136. Sorensen PS, Koch-Henriksen N, Ravnborg M, et al. Immunomodulatory treatment of multiple sclerosis in Denmark: a prospective nationwide survey. *Multiple Sclerosis.* Jun 2006;12(3):253-264.

137. Patten SB, Fridhandler S, Beck CA, Metz LM. Depressive symptoms in a treated multiple sclerosis cohort. *Multiple Sclerosis.* Dec 2003;9(6):616-620.

138. Achiron A, Barak Y, Gail M, et al. Cancer incidence in multiple sclerosis and effects of immunomodulatory treatments. *Breast Cancer Research & Treatment.* Feb 2005;89(3):265-270.

139. Koralnik IJ. New insights into progressive multifocal leukoencephalopathy. *Current Opinion in Neurology.* June 2004;17(3):365-370.

140. Van Assche G, Van Ranst M, Sciot R, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *New England Journal of Medicine.* Jul 28 2005;353(4):362-368.

141. Langer-Gould A, Atlas SW, Green AJ, Bollen AW, Pelletier D. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. *New England Journal of Medicine.* Jul 28 2005;353(4):375-381.

142. Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis.[see comment]. *New England Journal of Medicine.* Jul 28 2005;353(4):369-374.

143. Yousry TA, Major EO, Ryschkewitsch C, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *New England Journal of Medicine.* Mar 2 2006;354(9):924-933.

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148. Ghalie RG, Mauch E, Edan G, et al. A study of therapy-related acute leukaemia after mitoxantrone therapy for multiple sclerosis. *Multiple Sclerosis.* Oct 2002;8(5):441-445.

149. O'Connor P. The effects of intramuscular interferon beta-1a in patients at high risk for development of multiple sclerosis: a post hoc analysis of data from CHAMPS. *Clinical Therapeutics.* 2003;25(11):2865-2874.

150. Kinkel RP, Kollman C, O'Connor P, et al. IM interferon beta-1a delays definite multiple sclerosis 5 years after a first demyelinating event. *Neurology.* 2006;66(5):678-684.

151. Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. *The New England Journal of Medicine.* 2000;343(13):898-904.

152. Galetta SL. The controlled high risk Avonex multiple sclerosis trial (CHAMPS Study). *Journal of Neuro-ophthalmology : the official journal of the North American Neuro-Ophthalmology Society.* 2001;21(4):292-295.

153. Filippi M, Rovaris M, Inglese M, et al. Interferon beta-1a for brain tissue loss in patients at presentation with syndromes suggestive of multiple sclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2004;364(9444):1489-1496.

154. Comi G, Filippi M, Barkhof F, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. *Lancet.* 2001;357(9268):1576-1582.

155. Champs Study Group. Interferon beta-1a for optic neuritis patients at high risk for multiple sclerosis. *American Journal of Ophthalmology.* Oct 2001;132(4):463-471.

156. Koch MW, Mostert JP, de Vries JJ, De Keyser J. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes.(comment). *Neurology.* Apr 3 2007;68(14):1163; author reply 1163-1164.

157. Cree BAC, Al-Sabbagh A, Bennett R, Goodin D. Response to interferon beta-1a treatment in African American multiple sclerosis patients. *Archives of Neurology.* Nov 2005;62(11):1681-1683.

158. Sandberg-Wollheim M, Frank D, Goodwin TM, et al. Pregnancy outcomes during treatment with interferon beta-1a in patients with multiple sclerosis. *Neurology.* Sep 27 2005;65(6):802-806.

159. Boskovic R, Wide R, Wolpin J, Bauer DJ, Koren G. The reproductive effects of beta interferon therapy in pregnancy: a longitudinal cohort. *Neurology.* Sep 27 2005;65(6):807-811.

Appendix A. Search Strategies

Ovid MEDLINE(R) <1966 to September Week 4 2006>
Search Strategy:

1 exp Multiple Sclerosis/ (28292)
2 "first demyelinating event".mp. (24)
3 1 or 2 (28292)
4 mitoxantrone.mp. (5399)
5 1 and 4 (204)
6 glatiramer.mp. (342)
7 interferon beta.mp. (5478)
8 natalizumab.mp. (173)
9 5 or 6 or 7 or 8 (5937)
10 3 and 9 (2057)
11 limit 10 to (humans and english language) (1720)
12 from 11 keep 1-1720 (1720)

All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, and CCTR
Search Strategy:

1 multiple sclerosis.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (1796)
2 glatiramer.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (63)
3 interferon beta.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (489)
4 mitoxantrone.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (619)
5 natalizumab.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (16)
6 2 or 3 or 4 or 5 (1165)
7 1 and 6 (376)
8 from 7 keep 1-376 (376)

Appendix B. Quality assessment methods of the Drug Effectiveness Review Project

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

<u>Assessment of Internal Validity</u>

1. Was the assignment to the treatment groups really random?
Adequate approaches to sequence generation:
    Computer-generated random numbers
    Random numbers tables
Inferior approaches to sequence generation:
    Use of alternation, case record numbers, birth dates or week days
    Not reported

2. Was the treatment allocation concealed?
    Adequate approaches to concealment of randomization:
        Centralized or pharmacy-controlled randomization
        Serially-numbered identical containers
        On-site computer based system with a randomization sequence that is not readable until allocation
        Other approaches sequence to clinicians and patients
    Inferior approaches to concealment of randomization:

Use of alternation, case record numbers, birth dates or week days
Open random numbers lists
Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to follow-up or overall high loss to follow-up? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of follow-up? (Give numbers at each stage of attrition)

For Non-randomized Studies Reporting Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

2. Is there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainers; validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of follow-up correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Systematic Reviews:

Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

> A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making,

i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

1. Is there evidence of a substantial effort to search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

2. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

3. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results and adverse events.

4. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Appendix C. Excluded Studies

Excluded Studies	Reason for Exclusion
Abdul-Ahad AK, Galazka AR, Revel M, Biffoni M, Borden EC. Incidence of antibodies to interferon-beta in patients treated with recombinant human interferon-beta 1a from mammalian cells. *Cytokines, cellular & molecular therapy.* 1997;3(1):27-32.	Outcome did not meet inclusion criteria
Annunziata P, Giorgio A, De Santi L, et al. Absence of cerebrospinal fluid oligoclonal bands is associated with delayed disability progression in relapsing-remitting MS patients treated with interferon-beta. *Journal of the Neurological Sciences.* May 15 2006;244(1-2):97-102.	Outcome did not meet inclusion criteria
Antonelli G, Simeoni E, Bagnato F, et al. Further study on the specificity and incidence of neutralizing antibodies to interferon (IFN) in relapsing remitting multiple sclerosis patients treated with IFN beta-1a or IFN beta-1b. *Journal of the Neurological Sciences.* Oct 15 1999;168(2):131-136.	Outcome did not meet inclusion criteria
Arnett PA, Randolph JJ. Longitudinal course of depression symptoms in multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry.* May 2006;77(5):606-610.	Study design did not meet inclusion criteria
Avasarala JR, Cross AH, Clifford DB, Singer BA, Siegel BA, Abbey EE. Rapid onset mitoxantrone-induced cardiotoxicity in secondary progressive multiple sclerosis. *Multiple Sclerosis.* Feb 2003;9(1):59-62.	Outcome did not meet inclusion criteria
Barbero P, Bergui M, Versino E, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis (INCOMIN Trial) II: analysis of MRI responses to treatment and correlation with Nab. *Multiple sclerosis (Houndmills, Basingstoke, England).* 2006;12(1):72-76.	Outcome did not meet inclusion criteria
Barbero P, Verdun E, Bergui M, et al. High-dose, frequently administered interferon beta therapy for relapsing-remitting multiple sclerosis must be maintained over the long term: the interferon beta dose-reduction study. *Journal of the neurological sciences.* 2004;222(1-2):13-19.	Study design did not meet inclusion criteria
Barkhof F, van Waesberghe JH, Filippi M, et al. T(1) hypointense lesions in secondary progressive multiple sclerosis: effect of interferon beta-1b treatment. *Brain : a journal of neurology.* 2001;124(Pt 7):1396-1402.	Outcome did not meet inclusion criteria
Baum K, Mannitol Formulation Study G. Safety and tolerability of a 'refrigeration-free' formulation of interferon beta-1b--results of a double-blind, multicentre, comparative study in patients with relapsing-remitting or secondary progressive multiple sclerosis. *Journal of International Medical Research.* Jan-Feb 2006;34(1):1-12.	Intervention did not meet inclusion criteria
Beck RW, Chandler DL, Cole SR, et al. Interferon beta-1a for early multiple sclerosis: CHAMPS trial subgroup analyses. *Annals of Neurology.* Apr 2002;51(4):481-490.	Study design did not meet inclusion criteria
Bellomi F, Scagnolari C, Tomassini V, et al. Fate of neutralizing and binding antibodies to IFN beta in MS patients treated with IFN beta for 6 years. *Journal of the neurological sciences.* 2003;215(1-2):3-8.	Outcome did not meet inclusion criteria
Bertolotto A, Malucchi S, Milano E, Castello A, Capobianco M, Mutani R. Interferon beta neutralizing antibofidies in multiple sclerosis: Neutralizing activity and cross-reactivity with three different preparations. 1176. *Immunopharmacology. Vol.* 2000;48:95-100.	Outcome did not meet inclusion criteria

Excluded Studies	Reason for Exclusion
Bertolotto A, Malucchi S, Sala A, et al. Differential effects of three interferon betas on neutralising antibodies in patients with multiple sclerosis: a follow up study in an independent laboratory.[see comment]. *Journal of Neurology, Neurosurgery & Psychiatry.* Aug 2002;73(2):148-153.	Outcome did not meet inclusion criteria
Bramanti P, Sessa E, Rifici C, et al. Enhanced spasticity in primary progressive MS patients treated with interferon beta-1b.[see comment]. *Neurology.* Dec 1998;51(6):1720-1723.	Outcome did not meet inclusion criteria
Bryant J, Clegg A, Milne R. Systematic review of immunomodulatory drugs for the treatment of people with multiple sclerosis: Is there good quality evidence on effectiveness and cost? *Journal of Neurology, Neurosurgery & Psychiatry.* May 2001;70(5):574-579.	Intervention did not meet inclusion criteria
Caon C, Din M, Ching W, Tselis A, Lisak R, Khan O. Clinical course after change of immunomodulating therapy in relapsing-remitting multiple sclerosis. *European Journal of Neurology.* May 2006;13(5):471-474.	Study design did not meet inclusion criteria
Carra A, Onaha P, Sinay V, et al. A retrospective, observational study comparing the four available immunomodulatory treatments for relapsing-remitting multiple sclerosis. *European Journal of Neurology.* Nov 2003;10(6):671-676.	Study design did not meet inclusion criteria
Clanet M, Kappos L, Hartung HP, Hohlfeld R. Interferon beta-1a in relapsing multiple sclerosis: four-year extension of the European IFNbeta-1a Dose-Comparison Study. *Multiple sclerosis (Houndmills, Basingstoke, England).* 2004;10(2):139-144.	Study design did not meet inclusion criteria
Clanet M, Radue EW, Kappos L, et al. A randomized, double-blind, dose-comparison study of weekly interferon beta-1a in relapsing MS. *Neurology.* 2002;59(10):1507-1517.	Outcome did not meet inclusion criteria
Coppola G, Lanzillo R, Florio C, et al. Long-term clinical experience with weekly interferon beta-1a in relapsing multiple sclerosis. *European Journal of Neurology.* Sep 2006;13(9):1014-1021.	Study design did not meet inclusion criteria
Correale J, Rush C, Amengual A, Goicochea MT. Mitoxantrone as rescue therapy in worsening relapsing-remitting MS patients receiving IFN-beta. *Journal of Neuroimmunology.* May 2005;162(1-2):173-183.	Study design did not meet inclusion criteria
Cramer JA, Cuffel BJ, Divan V, Al-Sabbagh A, Glassman M. Patient satisfaction with an injection device for multiple sclerosis treatment. *Acta Neurologica Scandinavica.* Mar 2006;113(3):156-162.	Study design did not meet inclusion criteria
De Castro S, Cartoni D, Millefiorini E, et al. Noninvasive assessment of mitoxantrone cardiotoxicity in relapsing remitting multiple sclerosis. *Journal of Clinical Pharmacology.* Jun 1995;35(6):627-632.	Outcome did not meet inclusion criteria
Durelli L, Oggero A, Verdun E, et al. Does high-dose interferon beta-1b improve clinical response in more severely disabled multiple sclerosis patients? *Journal of the Neurological Sciences.* Sep 1 2000;178(1):37-41.	Study design did not meet inclusion criteria
Elgart GW, Sheremata W, Ahn YS. Cutaneous reactions to recombinant human interferon beta-1b: the clinical and histologic spectrum.[see comment]. *Journal of the American Academy of Dermatology.* Oct 1997;37(4):553-558.	Study design did not meet inclusion criteria
Feinstein A, O'Connor P, Feinstein K. Multiple sclerosis, interferon beta-1b and depression A prospective investigation. *Journal of Neurology.* Jul 2002;249(7):815-820.	Study design did not meet inclusion criteria
Fernandez O, Antiquedad A, Arbizu T, et al. Treatment of relapsing-remitting multiple sclerosis with natural interferon beta: a multicenter, randomized clinical trial. *Multiple sclerosis.* 1995;1(1).	Intervention did not meet inclusion criteria

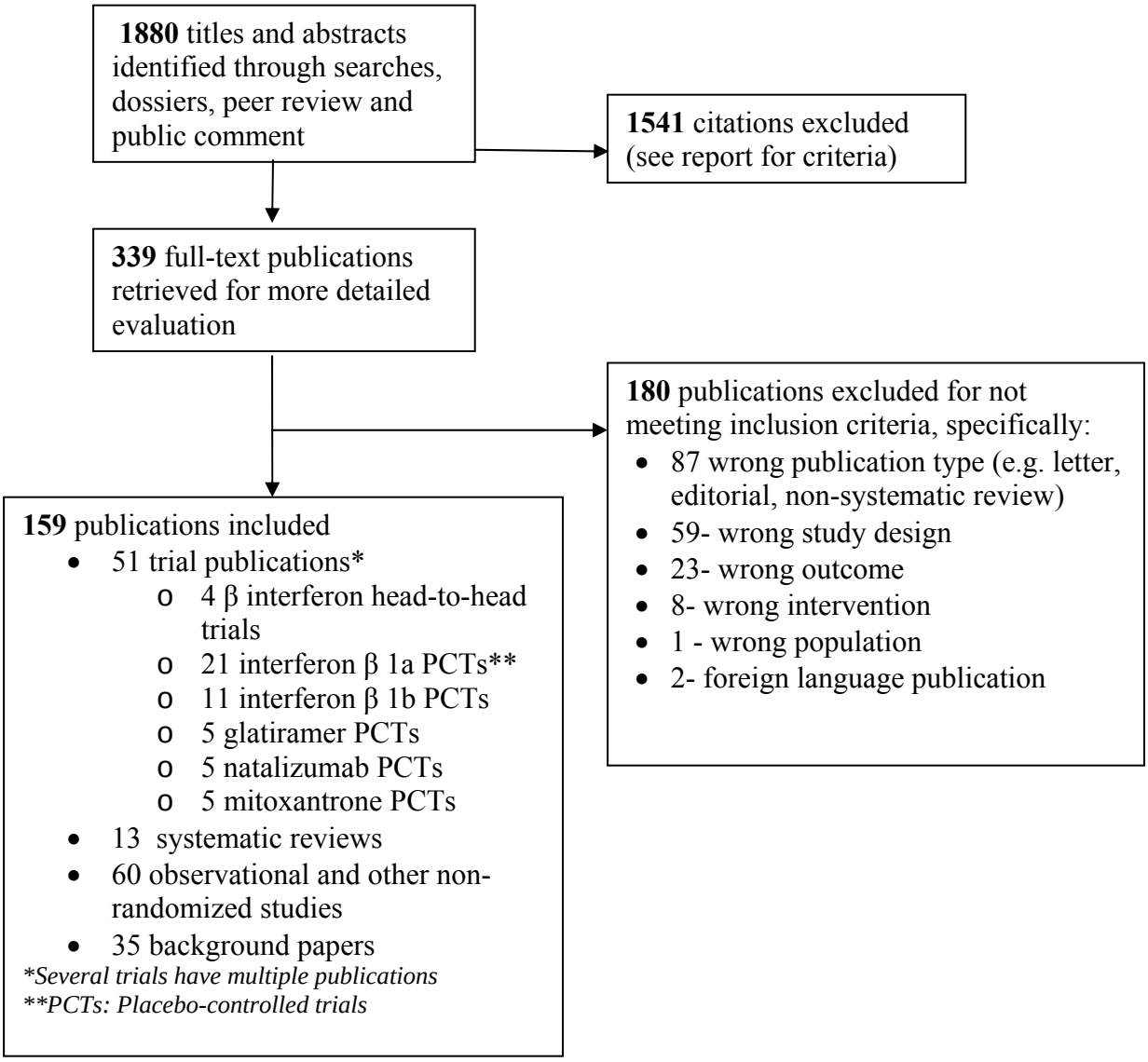
Excluded Studies	Reason for Exclusion
Filippi M, Wolinsky JS, Comi G. Effects of oral glatiramer acetate on clinical and MRI-monitored disease activity in patients with relapsing multiple sclerosis: a multicentre, double-blind, randomised, placebo-controlled study. *Lancet neurology.* 2006;5(3):213-220.	Intervention did not meet inclusion criteria
Fischer JS, Priore RL, Jacobs LD, et al. Neuropsychological effects of interferon beta-1a in relapsing multiple sclerosis. Multiple Sclerosis Collaborative Research Group. *Annals of Neurology.* Dec 2000;48(6):885-892.	Outcome did not meet inclusion criteria
Fraser C, Hadjimichael O, Vollmer T. Predictors of adherence to Copaxone therapy in individuals with relapsing-remitting multiple sclerosis. *Journal of Neuroscience Nursing.* Oct 2001;33(5):231-239.	Study design did not meet inclusion criteria
Fraser C, Hadjimichael O, Vollmer T. Predictors of adherence to glatiramer acetate therapy in individuals with self-reported progressive forms of multiple sclerosis. *Journal of Neuroscience Nursing.* Jun 2003;35(3):163-170.	Study design did not meet inclusion criteria
Fraser C, Morgante L, Hadjimichael O, Vollmer T. A prospective study of adherence to glatiramer acetate in individuals with multiple sclerosis. *Journal of Neuroscience Nursing.* Jun 2004;36(3):120-129.	Outcome did not meet inclusion criteria
Goebel MU, Czolbe F, Becker H, Janssen OE, Schedlowski M, Limmroth V. Effects of interferon-beta 1a on the hypothalamic-pituitary-adrenal axis, leukocyte distribution and mood states in multiple sclerosis patients: results of a 1-year follow-up study. *European Neurology.* 2005;53(4):182-187.	Study design did not meet inclusion criteria
Gold R, Hartung HP, Toyka KV. Immunomodulating therapy of multiple sclerosis. Application of beta interferon and copolymer-1 in relapsing-remitting multiple sclerosis. 1189. *Die Therapiewoche. Vol.* 1996;46:532-536.	Language did not meet inclusion criteria
Gold R, Rieckmann P, Chang P, Abdalla J. The long-term safety and tolerability of high-dose interferon beta-1a in relapsing-remitting multiple sclerosis: 4-year data from the PRISMS study. *European journal of neurology : the official journal of the European Federation of Neurological Societies.* 2005;12(8):649-656.	Study design did not meet inclusion criteria
Goodkin DE, Priore RL, Wende KE, et al. Comparing the ability of various compositive outcomes to discriminate treatment effects in MS clinical trials. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Multiple sclerosis (Houndmills, Basingstoke, England).* 1998;4(6):480-486.	Study design did not meet inclusion criteria
Gottesman MH, Friedman-Urevich S. Interferon beta-1b (betaseron/betaferon) is well tolerated at a dose of 500 microg: interferon dose escalation assessment of safety (IDEAS). *Multiple Sclerosis.* Jun 2006;12(3):271-280.	Study design did not meet inclusion criteria
Jacobs L, O'Malley JA, Freeman A, et al. Intrathecal interferon in the treatment of multiple sclerosis. Patient follow-up. *Arch Neurol.* 1985;42(9):841-847.	Study design did not meet inclusion criteria
Jacobs L, Rudick R, Simon J. Extended observations on MS patients treated with IM interferon-beta1a (Avonex (TM)): implications for modern MS trials and therapeutics. *Journal of neuroimmunology.* 2000;107(2):167-173.	Study design did not meet inclusion criteria
Jacobs L, Salazar AM, Herndon R, et al. Intrathecally administered natural human fibroblast interferon reduces exacerbations of multiple sclerosis. Results of a multicenter, double-blind study. *Archives of neurology.* 1987;44(6):589-595.	Intervention did not meet inclusion criteria
Johnson KP, Brooks BR, Cohen JA, et al. Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability. Copolymer 1 Multiple Sclerosis Study Group.[see comment]. *Neurology.* Mar	Study design did not meet inclusion criteria

Excluded Studies	Reason for Exclusion
1998;50(3):701-708.	
Johnson KP, Ford CC, Lisak RP, Wolinsky JS. Neurologic consequence of delaying glatiramer acetate therapy for multiple sclerosis: 8-year data. *Acta Neurologica Scandinavica.* Jan 2005;111(1):42-47.	Study design did not meet inclusion criteria
Kalanie H, Gharagozli K, Hemmatie A, Ghorbanie M, Kalanie AR. Interferon Beta-1a and intravenous immunoglobulin treatment for multiple sclerosis in Iran. *European Neurology.* 2004;52(4):202-206.	Intervention did not meet inclusion criteria
Kargwell H, Yaqub BA, Al-Deeb SM. Response to beta interferon 1b among Saudi patients with multiple sclerosis. *Saudi Medical Journal.* Jan 2003;24(1):44-48.	Population did not meet inclusion criteria
Khan OA, Dhib-Jalbut SS. Neutralizing antibodies to interferon beta-1a and interferon beta-1b in MS patients are cross-reactive. *Neurology.* Dec 1998;51(6):1698-1702.	Outcome did not meet inclusion criteria
Khan OA, Hebel JR. Incidence of exacerbations in the first 90 days of treatment with recombinant human interferon beta-1b in patients with relapsing-remitting multiple sclerosis. *Annals of Neurology.* Jul 1998;44(1):138-139.	Study design did not meet inclusion criteria
Khan OA, Tselis AC, Kamholz JA, Garbern JY, Lewis RA, Lisak RP. A prospective, open-label treatment trial to compare the effect of IFN beta-1a (Avonex), IFNbeta-1b (Betaseron), and glatiramer acetate (Copaxone) on the relapse rate in relapsing-remitting multiple sclerosis.[see comment]. *European Journal of Neurology.* Mar 2001;8(2):141-148.	Study design did not meet inclusion criteria
Khan OA, Tselis AC, Kamholz JA, Garbern JY, Lewis RA, Lisak RP. A prospective, open-label treatment trial to compare the effect of IFNbeta-1a (Avonex), IFNbeta-1b (Betaseron), and glatiramer acetate (Copaxone) on the relapse rate in relapsing--remitting multiple sclerosis: results after 18 months of therapy. *Mulitple Sclerosis.* 2001;7(6):349-353.	Study design did not meet inclusion criteria
Kivisakk P, Alm GV, Tian WZ, Matusevicius D, Fredrikson S, Link H. Neutralising and binding anti-interferon-beta-I b (IFN-beta-I b) antibodies during IFN-beta-I b treatment of multiple sclerosis. *Multiple Sclerosis.* Jun 1997;3(3):184-190.	Study design did not meet inclusion criteria
Koch-Henriksen N, Sorensen PS. The Danish National Project of interferon-beta treatment in relapsing-remitting multiple sclerosis. The Danish Multiple Sclerosis Group. *Mulitple Sclerosis.* 2000;6(3):172-175.	Study design did not meet inclusion criteria
Kreisler A, de Seze J, Stojkovic T, et al. Multiple sclerosis, interferon beta and clinical thyroid dysfunction. *Acta Neurologica Scandinavica.* Feb 2003;107(2):154-157.	Study design did not meet inclusion criteria
La Mantia L, D'Amico D, Rigamonti A, Mascoli N, Bussone G, Milanese C. Interferon treatment may trigger primary headaches in multiple sclerosis patients. *Multiple Sclerosis.* Aug 2006;12(4):476-480.	Study design did not meet inclusion criteria
Lanzillo R, Prinster A, Scarano V, et al. Neuropsychological assessment, quantitative MRI and ApoE gene polymorphisms in a series of MS patients treated with IFN beta-1b. *Journal of the Neurological Sciences.* Jun 15 2006;245(1-2):141-145.	Outcome did not meet inclusion criteria
Li DK, Zhao GJ, Paty DW. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: MRI results. *Neurology.* 2001;56(11):1505-1513.	Outcome did not meet inclusion criteria

Excluded Studies	Reason for Exclusion
Metz LM, Patten SB, Archibald CJ, et al. The effect of immunomodulatory treatment on multiple sclerosis fatigue. *Journal of Neurology, Neurosurgery & Psychiatry.* Jul 2004;75(7):1045-1047.	Study design did not meet inclusion criteria
Mikol D, Lopez-Bresnahan M, Taraskiewicz S, Chang P, Rangnow J. A randomized, multicentre, open-label, parallel-group trial of the tolerability of interferon beta-1a (Rebif) administered by autoinjection or manual injection in relapsing-remitting multiple sclerosis. *Mulitple Sclerosis.* 2005;11(5):585-591.	Study design did not meet inclusion criteria
Mohr DC, Boudewyn AC, Likosky W, Levine E, Goodkin DE. Injectable medication for the treatment of multiple sclerosis: the influence of self-efficacy expectations and injection anxiety on adherence and ability to self-inject. *Annals of Behavioral Medicine.* 2001;23(2):125-132.	Study design did not meet inclusion criteria
Mohr DC, Goodkin DE, Likosky W, Gatto N, Baumann KA, Rudick RA. Treatment of depression improves adherence to interferon beta-1b therapy for multiple sclerosis. *Archives of Neurology.* May 1997;54(5):531-533.	Study design did not meet inclusion criteria
Mohr DC, Likosky W, Dwyer P, Van Der Wende J, Boudewyn AC, Goodkin DE. Course of depression during the initiation of interferon beta-1a treatment for multiple sclerosis. *Archives of Neurology.* Oct 1999;56(10):1263-1265.	Study design did not meet inclusion criteria
Monzani F, Caraccio N, Casolaro A, et al. Long-term interferon beta-1b therapy for MS: is routine thyroid assessment always useful? *Neurology.* Aug 22 2000;55(4):549-552.	Study design did not meet inclusion criteria
O'Connor P, Miller D, Riester K, et al. Relapse rates and enhancing lesions in a phase II trial of natalizumab in multiple sclerosis. *Mulitple Sclerosis.* 2005;11(5):568-572.	Study design did not meet inclusion criteria
Oger J, Francis G, Chang P. Prospective assessment of changing from placebo to IFN beta-1a in relapsing MS: the PRISMS study. *Journal of the neurological sciences.* 2005;237(1-2):45-52.	Study design did not meet inclusion criteria
Palumbo R, Salmaggi A, La Mantia L, Solari A, Milanese C. Treatment with Interferon beta 1b and Azathioprine in the relapsing- remitting MS. Clinical and quality of life evaluation. *Rivista di Neurobiologia.* 1999;45(5-6):519-521.	Language did not meet inclusion criteria
Panitch H, Goodin DS, Francis G, et al. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. *Neurology.* 2002;59(10):1496-1506.	Study design did not meet inclusion criteria
Parkin D, McNamee P, Jacoby A, Miller P, Thomas S, Bates D. A cost-utility analysis of interferon beta for multiple sclerosis. *Health Technology Assessment (Winchester, England).* 1998;2(4):iii-54.	Outcome did not meet inclusion criteria
Patti F, L'Episcopo MR, Cataldi ML, Reggio A. Natural interferon-beta treatment of relapsing-remitting and secondary-progressive multiple sclerosis patients. A two-year study. *Acta Neurologica Scandinavica.* Nov 1999;100(5):283-289.	Study design did not meet inclusion criteria
Patti F, Pappalardo A, Florio C, et al. Effects of interferon beta-1a and -1b over time: 6-year results of an observational head-to-head study. *Acta Neurologica Scandinavica.* Apr 2006;113(4):241-247.	Study design did not meet inclusion criteria
Pliskin NH, Hamer DP, Goldstein DS, et al. Improved delayed visual reproduction test performance in multiple sclerosis patients receiving interferon beta-1b. *Neurology.* 1996;47(6):1463-1468.	Outcome did not meet inclusion criteria
Pollmann W, Erasmus LP, Feneberg W, Straube A. The effect of glatiramer acetate treatment on pre-existing headaches in patients with MS. *Neurology.* 2006;66(2):275-277.	Study design did not meet inclusion criteria

Excluded Studies	Reason for Exclusion
Polman C, Barkhof F, Kappos L, et al. Oral interferon beta-1a in relapsing-remitting multiple sclerosis: a double-blind randomized study. *Mulitple Sclerosis.* 2003;9(4):342-348.	Intervention did not meet inclusion criteria
Polman CH, Kappos L, Dahlke F, et al. Interferon beta-1b treatment does not induce autoantibodies. *Neurology.* 2005;64(6):996-1000.	Study design did not meet inclusion criteria
Pozzilli C, Prosperini L, Sbardella E, De Giglio L, Onesti E, Tomassini V. Post-marketing survey on clinical response to interferon beta in relapsing multiple sclerosis: the Roman experience. *Neurological Sciences.* Dec 2005;26 Suppl 4:S174-178.	Study design did not meet inclusion criteria
Rio J, Porcel J, Tellez N, et al. Factors related with treatment adherence to interferon beta and glatiramer acetate therapy in multiple sclerosis. *Multiple Sclerosis.* Jun 2005;11(3):306-309.	Outcome did not meet inclusion criteria
Rotondi M, Oliviero A, Profice P, et al. Occurrence of thyroid autoimmunity and dysfunction throughout a nine-month follow-up in patients undergoing interferon-beta therapy for multiple sclerosis. *Journal of Endocrinological Investigation.* Dec 1998;21(11):748-752.	Outcome did not meet inclusion criteria
Rudick RA, Goodkin DE, Jacobs LD, et al. Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Neurology.* 1997;49(2):358-363.	Study design did not meet inclusion criteria
Ruggieri RM, Settipani N, Viviano L, et al. Long-term interferon-beta treatment for multiple sclerosis. *Neurological Sciences.* Dec 2003;24(5):361-364.	Study design did not meet inclusion criteria
Russo P, Paolillo A, Caprino L, Bastianello S, Bramanti P. Effectiveness of interferon beta treatment in relapsing-remitting multiple sclerosis: an Italian cohort study. *Journal of Evaluation in Clinical Practice.* Nov 2004;10(4):511-518.	Study design did not meet inclusion criteria
Saida T, Tashiro K, Itoyama Y, Sato T, Ohashi Y, Zhao Z. Interferon beta-1b is effective in Japanese RRMS patients: a randomized, multicenter study. *Neurology.* 2005;64(4):621-630.	Study design did not meet inclusion criteria
Sandberg-Wollheim M, Bever C, Carter J, et al. Comparative tolerance of IFN beta-1a regimens in patients with relapsing multiple sclerosis. The EVIDENCE study. *Journal of neurology.* 2005;252(1):8-13.	Study design did not meet inclusion criteria
Schwartz CE, Coulthard-Morris L, Cole B, Vollmer T. The quality-of-life effects of interferon beta-1b in multiple sclerosis. An extended Q-TWiST analysis. *Archives of Neurology.* Dec 1997;54(12):1475-1480.	Study design did not meet inclusion criteria
Schwid SR, Thorpe J, Sharief M, et al. Enhanced benefit of increasing interferon beta-1a dose and frequency in relapsing multiple sclerosis: the EVIDENCE Study. *Archives of neurology.* 2005;62(5):785-792.	Study design did not meet inclusion criteria
Strotmann JM, Spindler M, Weilbach FX, Gold R, Ertl G, Voelker W. Myocardial function in patients with multiple sclerosis treated with low-dose mitoxantrone. *American Journal of Cardiology.* May 15 2002;89(10):1222-1225.	Study design did not meet inclusion criteria
Tremlett HL, Oger J. Elevated aminotransferases during treatment with interferon-beta for multiple sclerosis: actions and outcomes. *Multiple Sclerosis.* Jun 2004;10(3):298-301.	Study design did not meet inclusion criteria
Vallittu AM, Peltoniemi J, Elovaara I, et al. The efficacy of glatiramer acetate in beta-interferon-intolerant MS patients. *Acta Neurologica Scandinavica.* Oct 2005;112(4):234-237.	Study design did not meet inclusion criteria

Excluded Studies	Reason for Exclusion
Verdun E, Isoardo G, Oggero A, et al. Autoantibodies in multiple sclerosis patients before and during IFN-beta 1b treatment: are they correlated with the occurrence of autoimmune diseases?[erratum appears in J Interferon Cytokine Res 2002 Apr;22(4):504]. *Journal of Interferon & Cytokine Research.* Feb 2002;22(2):245-255.	Study design did not meet inclusion criteria
Vermersch P, de Seze J, Delisse B, Lemaire S, Stojkovic T. Quality of life in multiple sclerosis: influence of interferon-beta1 a (Avonex) treatment. *Multiple Sclerosis.* Oct 2002;8(5):377-381.	Study design did not meet inclusion criteria
Vermersch P, de Seze J, Stojkovic T, Hautecoeur P, G SEP. Interferon beta1a (Avonex) treatment in multiple sclerosis: similarity of effect on progression of disability in patients with mild and moderate disability. *Journal of Neurology.* Feb 2002;249(2):184-187.	Study design did not meet inclusion criteria
Waubant E, Vukusic S, Gignoux L, et al. Clinical characteristics of responders to interferon therapy for relapsing MS.[see comment]. *Neurology.* Jul 22 2003;61(2):184-189.	Study design did not meet inclusion criteria
Weinstein A, Schwid SR, Schiffer RB, et al. Neuropsychologic status in multiple sclerosis after treatment with glatiramer. *Archives of neurology.* 1999;56(3):319-324.	Outcome did not meet inclusion criteria
Wolinsky JS, Narayana PA, Johnson KP, et al. United States open-label glatiramer acetate extension trial for relapsing multiple sclerosis: MRI and clinical correlates. *Multiple Sclerosis.* 2001;7(1):33-41.	Study design did not meet inclusion criteria
Wroe SJ. Effects of dose titration on tolerability and efficacy of interferon beta-1b in people with multiple sclerosis. *The Journal of international medical research.* 2005;33(3):309-318.	Study design did not meet inclusion criteria
Zingler VC, Nabauer M, Jahn K, et al. Assessment of potential cardiotoxic side effects of mitoxantrone in patients with multiple sclerosis. *European Neurology.* 2005;54(1):28-33.	Intervention did not meet inclusion criteria
Zivadinov R, Zorzon M, Tommasi MA, et al. A longitudinal study of quality of life and side effects in patients with multiple sclerosis treated with interferon beta-1a. *Journal of the Neurological Sciences.* Dec 15 2003;216(1):113-118.	Outcome did not meet inclusion criteria

* In addition, there are 74 articles which did not have any original data (e.g., letter, editorial and systematic review).

Appendix D. Results of literature search