Disease-modifying Drugs for Multiple Sclerosis

October 2010
Based on the DERP Report of August 2010

Produced by:
The Health Resources Commission
Office for Oregon Health Policy & Research
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The State of Oregon’s Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

**Overview**

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Oregon Medical Assistance (OMAP) Department of Human Services (DHS) on this Plan.

In 2007 the Oregon Health Resources Commission (HRC) appointed a Pharmaceutical subcommittee to perform evidence-based reviews of pharmaceutical agents. The subcommittee currently consists of three Physicians, a Nurse Practitioner, and a PharmD. The subcommittee had one meeting. All meetings were held in public with appropriate notice provided. The HRC director worked with the Center for Evidence-based Policy (Center) and the Oregon Health and Science University’s (OHSU) Evidence-based...
Practice Center (EPC) to develop and finalize key questions for this drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities. Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The EPC’s report, “Disease-modifying drugs for Multiple Sclerosis” was completed in August of 2010, circulated to subcommittee members and posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings. Time was allotted for public comment, questions and testimony.

This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. The HRC, working together with the EPC, the Center for Evidence Based Policy, DMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. Approximately once per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. The “Disease-modifying drugs for Multiple Sclerosis” report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene a subcommittee.

The full OHSU Evidence-based Practice Center’s draft report, Disease-modifying drugs for Multiple Sclerosis is available via the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website: www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml
You may request more information including copies of the draft report from:
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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:
There will be a charge for copying and handling in providing documents from both the Office of Oregon Health Policy & Research and the Center for Evidence Based Policy.

**Critical Policy**

*Senate Bill 819*

− “The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price.”

*Health Resources Commission*

− “Clinical outcomes are the most important indicators of comparative effectiveness”
− “If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

**Clinical Overview**

Multiple sclerosis is a chronic, autoimmune disease of the central nervous system affecting 2.1 million people worldwide and approximately 250,000 to 400,000 people in the United States.2

Most patients are diagnosed between the ages of 20 and 50 years with women being affected to a greater degree than men by a ratio of 1.6 females to 1 male.2 The highest prevalence of multiple sclerosis is found in Caucasian women, persons of Northern European descent, and in those who live in northern latitudes. Multiple sclerosis can cause physical, mental, and emotional disability in individuals, independent of age. From a societal perspective, in 2004 multiple sclerosis costs were estimated at $47,215.00 per patient per year, including $16,050.00 (34%) spent on disease modifying drugs used in the treatment of multiple sclerosis.3

Diagnostic criteria for multiple sclerosis include a clinical presentation of 2 or more attacks and objective clinical evidence of 2 or more lesions in the myelinated regions of the central nervous system found by magnetic resonance imaging.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 multiple sclerosis may also be made in a clinically isolated syndrome with presentation of a single attack and evidence of 1 or more lesions. To maintain specificity, criteria have become stricter such that magnetic resonance imaging dissemination in space and time are critical, and cerebral spinal fluid analysis may be needed to identify oligoclonal bands or increased immunoglobulin G that are often present in multiple sclerosis.
Progression of multiple sclerosis is measured by the disability caused by the disease. The Expanded Disability Status Scale is a common measure of multiple sclerosis disability and is the primary clinical outcome in many multiple sclerosis clinical trials.5, 6 The scale ranges from 0, defined by a normal neurological examination, to 10, defined as death due to multiple sclerosis.5 An Expanded Disability Status Scale <6 indicates the patient can walk without aid for limited distances.5 An Expanded Disability Status Scale ≥6 and <8 indicates the patient is severely restricted in movement with aids or assistance.5 An Expanded Disability Status Scale >8 indicates the person is restricted to a bed, and use of arms and legs are severely restricted.5 The Multiple Sclerosis Functional Composite is also used to measure disability but has rarely been used as an outcome measure in clinical trials. Four main types of multiple sclerosis have been characterized: relapsing-remitting, secondary progressive, primary progressive, and progressive relapsing. About 85% of multiple sclerosis patients have relapsing-remitting multiple sclerosis at the onset of the disease, and about 10% have primary progressive multiple sclerosis.7 Relapsing remitting multiple sclerosis is characterized by well-defined acute relapses (attacks) of neurological symptoms followed by full or partial recovery. Relapsing-remitting multiple sclerosis rarely progresses between relapses, although the patient may never fully recover after a relapse. On the contrary, primary progressive multiple sclerosis progresses from the onset without acute attacks. Most patients with relapsing-remitting multiple sclerosis will eventually develop secondary progressive multiple sclerosis, which is a progressive form of the disease that may or may not have superimposed relapses. Progressive relapsing multiple sclerosis occurs in about 5% of the multiple sclerosis population and progresses from the onset with superimposed relapses of neurological symptoms followed by full or partial recovery.7

Multiple sclerosis causes demyelination of neuronal axons that form lesions within the white matter of the central nervous system (cerebral white matter, brain stem, cerebellar tracts, optic nerves, or spinal cord) when viewed on a magnetic resonance imaging. 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 multiple sclerosis. Indeed, the classification of symptoms as monofocal or multifocal are often associated with the location and number of lesions in the central nervous system. For example, vision loss reflects a lesion in the optic nerve.

Although more data is becoming available, the pathogenesis of multiple sclerosis remains elusive. Myelin-reactive T cells and B cells are present in multiple sclerosis.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 central nervous system in persons genetically susceptible to multiple sclerosis. 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 central nervous system, the T cells secrete interferon γ and interleukin 17.7 The antigen-presenting cells and T helper cells form a complex by binding to a self-antigen, such as myelin basic protein via the major histocompatibility complex 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-
antigen-presenting cell 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 multiple sclerosis involves acute relapse treatment with corticosteroids,
symptom management with appropriate agents, and disease modification with disease-
modifying drugs. For example, when acute exacerbations occur (such as 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 disease modifying drugs 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 multiple sclerosis
through various immunomodulatory or immunosuppressive effects. Table 1 summarizes
the pharmacology, dosing, and indications of the current disease modifying
drug treatments options for multiple sclerosis.

Four immunomodulatory agents are type-1 β interferons: interferon β1b SC
(Betaseron® and Extavia®) and interferon β1a IM and SC (Avonex® and Rebif®). Extauva (interferon beta-1b SC) is the same medicinal product and contains the same
active ingredients as Betaseron. It was approved by the US Food and Drug
Administration in August 2009 using the clinical trials in the Betaseron Prescribing
Information. The fifth 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. These agents may also inhibit the proliferation of pro-inflammatory
cytokines, such as interferon γ. 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. 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.

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. 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 due to safety concerns and reintroduced in 2006. In February 2010, the US Food and Drug Administration issued a safety announcement alerting the public that the risk of developing progressive multifocal leukoencephalopathy, associated with the use of natalizumab (Tysabri®), increases with the number of Tysabri® infusions received. This new safety information, based on reports of 31 confirmed cases of progressive multifocal leukoencephalopathy received by the US Food and Drug Administration as of January 21, 2010, will now be included in the Tysabri® drug label and patient Medication Guide. Since the US Food and Drug Administration safety announcement, the number of progressive multifocal leukoencephalopathy cases has increased, with 55 cases reported as of June 7, 2010 (http://www.reuters.com/article/idUSN1725307720100617). In addition, the US Food and Drug Administration information about the occurrence of immune reconstitution inflammatory syndrome in patients who have developed progressive multifocal leukoencephalopathy. The following is an excerpt from the US Food and Drug Administration statement about the drug’s reintroduction in 2006: “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.”

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. Mitoxantrone also impairs antigen presentation by causing apoptosis of APCs and other cells that associate with APCs. This drug carries a black box warning about the risk of cardiotoxicity and has a life-time cumulative dose limit of 140 mg/m2.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage and Administration</th>
<th>Black Box Warning?</th>
<th>Indication</th>
<th>Clinical Pharmacology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glatiramer Acetate Copaxone®</td>
<td>20 mg Subcutaneously qd</td>
<td>RRMS</td>
<td>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.</td>
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<tr>
<td>Interferon β 1a Avonex®</td>
<td>30 mcg Intramuscularly 1x/wk</td>
<td>RRMS</td>
<td>RRMS</td>
<td></td>
</tr>
<tr>
<td>Interferon β 1a Rebif®</td>
<td>22 or 44 mcg Subcutaneously 3x/wk</td>
<td>RRMS</td>
<td>RRMS</td>
<td></td>
</tr>
<tr>
<td>Interferon β 1b Betaseron®</td>
<td>0.25 mg Subcutaneously Every other day</td>
<td>RRMS, SPMS, CIS</td>
<td>RRMS</td>
<td></td>
</tr>
<tr>
<td>Interferon β 1b Extavia®</td>
<td>0.25 mg Subcutaneously Every other day</td>
<td>RRMS, SPMS, CIS</td>
<td>Treatment of relapsing forms of MS to reduce frequency of clinical exacerbations. Effective in patients who experienced a first clinical episode and have MRI features consistent with MS. 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. These agents may also inhibit the proliferation of proinflammatory cytokines from Th1 cells (TNFα, IFNγ, IL-12).</td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone Novantrone®</td>
<td>12 mg/m2 Intravenously Every 3 mos (Max cumulative) Y (cardiotoxicity)</td>
<td>SPMS, PRMS, or Worsening RRMS</td>
<td>SPMS, PRMS, or Worsening RRMS</td>
<td>Inhibits cell division and impairs the proliferation of T cells, B cells and macrophages by intercalating and crosslinking DNA, thus inhibiting DNA replication and</td>
</tr>
</tbody>
</table>
RNA synthesis of these cells. Impairs antigen presentation by causing apoptosis of APCs and other cells that associate with APCs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Condition</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalizumab</td>
<td>140 mg/m²</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Tysabri®</td>
<td>300 mg Intravenously</td>
<td>Every 4 wks</td>
<td>Y</td>
<td>RRMS</td>
<td>Binds to α4 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.</td>
</tr>
</tbody>
</table>

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.

**Quality of the Evidence**

For quality of evidence the EPC and subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period and the endpoints of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC’s ratings of “good, fair or poor” for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was assessed based on criteria from the United States Preventative Task Force and the national Health Service Centre for Reviews and Dissemination (UK) and included:

1) Methods used for randomization
2) Allocation concealment and blinding
3) Similarity of compared groups at baseline and maintenance of comparable groups
4) Adequate reporting of dropouts, attrition, and crossover
5) Loss to follow-up
6) Use of intention-to-treat analysis

External validity of trials was assessed based on criteria from the United States Preventative Task Force and the national Health Service Centre for Reviews and Dissemination (UK) and included:

1) Adequate description of the study population
2) Similarity of patients to other populations to whom the intervention would be applied
3) Control group receiving comparable treatment
4) Funding source that might affect publication bias.

**Weighing the Evidence**

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

**Inclusion and Exclusion Criteria**
A complete listing of inclusion and exclusion criteria can be found in the DERP report.

**Grading the Strength of Evidence**
The EPC graded strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality. Developed to grade the overall strength of a body of evidence, this approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias.

Table A describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer key questions on the comparative effectiveness, efficacy and harms of disease-modifying drugs for multiple sclerosis. Grades do not refer to the general efficacy or effectiveness of pharmaceuticals. Two reviewers independently assessed each domain for each outcome and differences were resolved by consensus. The EPC chose outcomes related to relapse and disease progression. Magnetic resonance imaging findings were considered intermediate outcomes and were not assessed.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
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<tbody>
<tr>
<td>High</td>
<td>High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.</td>
</tr>
<tr>
<td>Low</td>
<td>Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.</td>
</tr>
<tr>
<td>Insufficient</td>
<td>Evidence either is unavailable or does not permit estimation of an effect.</td>
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</table>
Scope and Key Questions

To identify relevant citations, the EPC searched Ovid MEDLINE® (1966 - December 2009), the Cochrane Database of Systematic Reviews® (4th quarter 2009), the Cochrane Central Register of Controlled Trials® (4th quarter, 2009), and the Database of Abstracts of Reviews of Effects (4th Quarter 2009).

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 participating organizations of DERP attempt to ensure that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients in their constituency. The participating organizations approved the following key questions to guide this review:

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

2. Do disease-modifying treatments for multiple sclerosis differ in their effects on the development or recurrence of interferon beta neutralizing antibodies?

3. What is the evidence that interferon beta neutralizing antibody status has an impact on clinical outcomes (relapse and disease progression) in patients with multiple sclerosis?

4. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?

5. Do disease-modifying treatments for multiple sclerosis differ in harms?

6. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), socioeconomic status, other medications, severity of disease, or comorbidities for which one disease-modifying treatment is more effective or associated with fewer adverse events?

Conclusions:

Limitations of the Evidence:
1. No study met criteria to be classified as an effectiveness study, therefore applicability of the results of this review to patients seen in usual care may be limited
2. Adverse event reporting was incomplete.
3. There was no direct evidence in patients with primary and secondary progressive multiple sclerosis and there was no evidence in patients with progressive relapsing multiple sclerosis.

Conclusions:

KQ1. What is the comparative effectiveness of disease-modifying treatments for multiple sclerosis, including use of differing routes and schedules of administration?

1. The efficacy/effectiveness outcomes studied in patients with MS were relapse prevention, disease progression and change in Expanded Disability Status Score (EDSS)

2. Direct evidence from 3 fair-quality head-to-head trials showed interferon beta-1b (Betaseron®) was more efficacious than interferon beta-1a IM (Avonex®) in relapse outcomes in patients with relapsing remitting MS.

3. For all other types of MS and measured outcomes there was insufficient evidence to determine a difference in efficacy.
KQ2. Do disease-modifying treatments for multiple sclerosis differ in their effects on the development or recurrence of interferon beta neutralizing antibodies?
   1. Subcutaneous administration of interferon appears to be more antigenic than IM administration however, 40-50% of patients who develop antibodies will become antibody negative over time and the clinical significance of antibody development is unknown.

KQ3. What is the evidence that interferon beta neutralizing antibody status has an impact on clinical outcomes (relapse and disease progression) in patients with multiple sclerosis?
   1. Evidence correlating comparative clinical outcomes to the antibody status of the individual beta interferons was incomplete and inadequate to make conclusions.

KQ4. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?
   1. There is fair evidence that glatiramer (Copaxone®), interferon beta-1a IM (Avonex®), interferon beta-1a SC (Rebif®) and interferon beta-1b (Betaseron®) are more effective than placebo at reducing the probability of converting to clinically definite MS. There were no head-to-head comparisons. There are no studies on natalizumab or mitoxantrone for this condition.

KQ5. Do disease-modifying treatments for multiple sclerosis differ in harms?
   1. Adverse event rates among the interferons were similar except; Interferon beta-1b SC (Avonex®) was associated with the lowest rates of injection site reactions (8.5%) whereas Interferon beta-1b SC (Betaseron®) and Interferon beta-1b SC (Rebif®) had similar rates (58.9% and 60.6%).
   2. Discontinuation rate due to adverse events was low and similar among the interferons.
   3. Case studies showed lipoatrophy with prolonged use of glatiramer.
   4. Observational studies showed permanent amenorrhea in older women receiving higher total doses of mitoxantrone.
   5. Case studies of mitoxantrone show rare incidence of acute leukemia and cardiotoxicity. Mitoxantrone carries a black box warning for cardiotoxicity.
   6. The incidence of Progressive Multifocal Leukoencephalopathy (PML) in patients treated with natalizumab (Tysabri®) is 1/1000. natalizumab carries a black box warning for PML.

KQ6. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), socioeconomic status, other medications, severity of disease, or co-morbidities for which one disease-modifying treatment is more effective or associated with fewer adverse events?
   1. There is insufficient evidence to determine a comparative difference in subgroups.

Supporting Evidence
Systematic Reviews
We found 6 systematic reviews that assessed multiple drugs for the treatment of multiple sclerosis.31-37 One of these reviews was updated in 2009 but without new evidence of the outcomes of interest this review was not analyzed further.38 One review focused on treatment of symptoms rather than disease modification and will not be discussed here.33 Another focused on the association of depression with beta interferon and glatiramer acetate treatment and is discussed under Key Question 3 below.34 The 4 remaining reviews included beta interferons, glatiramer acetate, and mitoxantrone. The best quality review was the one conducted for the National Institute for Clinical Excellence by Clegg and Bryant and a related article that updated that review.31, 32 This review assessed the general effectiveness of the interventions compared with 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.

Key Question 1. What is the comparative effectiveness of disease-modifying treatments for multiple sclerosis, including use of differing routes and schedules of administration?

RRMS
Direct Evidence

β Interferons
Five fair quality trials directly compared one β interferon to another, ranging from 16 to 24 months in duration in patients with RRMS. The INCOMIN trial1 of Interferon β1a IM (Avonex®) and Interferon β1b SC (Betaseron®) was open-label, while the other 3 were single blinded studies. The EVIDENCE trial compared the 2 beta-1a interferons to each other and original data was published in 2002.44 A crossover phase followed in which all patients were either switched to or continued on interferon beta-1a SC (Rebif®). Given the lack of comparative data on this crossover phase, it will only be included in the discussion of harms that follows.45 The 2 Etemadifar trials compared all 3 beta interferons to another, and in the most recent trial, also to azathioprine. This later study did not report relapse related outcomes.43 Both Etemadifar studies were small, ≤30 patients per group and as low as 13 in the second trial. In the first trial, the baseline mean or median Expanded Disability Status Scale 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. In the second trial the mean baseline Expanded Disability Status Scale score was 1.55 and although the authors provide data on the mean Expanded Disability Status Scale score for each drug, it was not designed to compare the 3 drugs to each other.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. Additionally, the Danish Multiple Sclerosis Study Group patients were more severely ill compared with the other studies, and the studies differed in terms of whether the endpoint reported was primary or secondary.
The EPC limited the pooling of data to the 44 μg dose of interferon beta-1a SC (Rebif®) only. Overall, these studies supported the use of the beta interferons for improving relapse-related outcomes, with less effect on the disability-related outcomes.

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

One small study by Etemadifar (2007) showed a statistically significant improvement in Expanded Disability Status Scale scores with interferon beta-1a SC (Rebif®) compared with interferon beta-1b SC (Betaseron®), whereas an earlier trial by Etemadifar found interferon beta-1b SC (Betaseron®) numerically superior to interferon beta-1a SC (Rebif®) for outcomes related to disease progression (endpoint and mean change in Expanded Disability Status Scale.41, 43 Due to the significant heterogeneity between the 2 studies, the results could not be combined (I2 = 83.1%). In both trials, the difference between the scores was small, most likely were not clinically important, and given the discrepant results, conclusions could not be made. Only the earlier Etemadifar study evaluated relapse related outcomes and found no difference between interferon beta-1a SC (Rebif®) compared with interferon beta-1b SC (Betaseron®).

Koch-Henriksen enrolled a somewhat more severely ill population and used a lower dose of interferon beta-1a SC (Rebif®) dosed once weekly. They 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 beta interferons, including exacerbations requiring hospitalization and time to confirmed progression. The lower dose and dosing frequency in this trial limits our ability to draw conclusions from this trial.

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

Three trials compared the 2 forms of interferon beta-1a SC (Rebif®) and IM (Avonex®).39, 41, 43 Two 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 trial9 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 trials did not report these outcomes, but 1 trial 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 trials39,41,43, but statistically significant differences between the drugs were not found.

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

Three trials evaluated the comparison of interferon beta-1b SC (Betaseron®) and interferon beta-1a IM (Avonex®) with only 2 reporting relapse-related outcomes. They found higher rates of patients who were relapse-free at 2 years with interferon beta-1b SC (Betaseron®) (pooled relative risk, 1.51; 95% CI, 1.11 to 2.07).41, 42 However, data for disease progression were conflicting. The mean change in the Expanded Disability Status
Scale was greater with interferon beta-1a IM (Avonex®) in the Durelli trial (INCOMIN) and the second Etemadifar trial, but larger with interferon beta-1b SC (Betaseron®) in the first trial by Etemadifar. The combined weighted mean difference was $-0.330$ (95% CI, $-0.686$ to $+0.025$; I²=59.5%), indicating no significant difference. The INCOMIN trial was the only 1 of the 3 that measured disease progression and found it to be significantly lower in the interferon beta-1b SC (Betaseron®) group compared with the interferon beta-1a IM (Avonex®) group. Of the 5 head-to-head trials, these 3 represented the lowest-quality evidence such that these findings should be interpreted with caution.

Post-Marketing Studies

Of 5 published observational studies, 3 met inclusion criteria. 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. 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. 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. 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.

Indirect evidence

Two good quality and comprehensive reviews include all the studies relevant to this review. 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®), 1 multicenter trial of 2 doses of interferon β1a IM (Avonex®) 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). 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®).

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.). 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.). 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.

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.

**Synthesis of Direct and Indirect Evidence**

Comparison of direct and indirect results yield contradictory results. Because there is only a small amount of evidence available from which to make these comparisons, the EPC 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. The dose of interferon beta-1a SC (Rebif®) 22 μg 3 times weekly was used in this analysis and resulted in no statistically significant differences for the comparison of interferon beta-1a SC (Rebif®) and interferon beta-1b SC (Betaseron®). For the comparison of interferon beta-1a IM (Avonex®) with either interferon beta-1b SC (Betaseron®) or interferon beta-1a SC (Rebif®) the results of our exploratory analysis was consistent with the findings of our direct and indirect analyses with both interferon beta-1a SC (Rebif®) and interferon beta-1b SC (Betaseron®) being superior to interferon beta-1a IM (Avonex®) in percent relapse-free, and with interferon beta-1b SC (Betaseron®) being superior to interferon beta-1a IM (Avonex®) in progression rates (see Table 2). Inadequate data were available to conduct this analysis with annualized relapse rates.

**Table 2. Exploratory Bayesian analysis of direct and indirect evidence in RRMS**

<table>
<thead>
<tr>
<th></th>
<th>Betaseron vs Rebif 22 μg</th>
<th>Betaseron vs Avonex</th>
<th>Rebif® 22 μg vs. Avonex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression rates*</td>
<td>1.18 (0.80, 1.71)</td>
<td>0.48 (0.27, 0.86)</td>
<td>1.05 (0.93, 1.22)</td>
</tr>
<tr>
<td>EDSS change**</td>
<td>−0.30 (−0.60 to +0.015)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Relapse free*</td>
<td>0.85 (0.56, 1.25)</td>
<td>1.48 (1.11, 2.02)</td>
<td>1.22 (1.06, 1.41)</td>
</tr>
</tbody>
</table>

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

*Direct evidence*

Three trials directly comparing glatiramer acetate (Copaxone®) to another disease-modifying drug were identified, 2 comparing to interferon beta-1b (Betaseron®) and 1 comparing to interferon beta-1a (Rebif®).57-59 The BEYOND trial comparing glatiramer acetate (Copaxone®) to interferon beta-1b (Betaseron®) was a good-quality study59 while the other 2 trials were fair quality. The BECOME trial was small with a mixed population of patients with relapsing remitting multiple sclerosis and clinically isolated syndrome and will be discussed under mixed populations. In both the double-blinded BEYOND trial, which lasted up to 3.5 years, and the single-blinded REGARD trial, no significant differences were found at 96 weeks between the drugs in relapse-related or disease progression outcomes. The primary outcome in the REGARD trial was time to first relapse, however there were fewer relapses than expected which meant that the study was under-powered to show a significant difference. The results however are consistent with the BEYOND trial.

The effectiveness results of the head-to-head trials were contrary to 2 observational studies that analyzed clinical databases to compare glatiramer acetate (Copaxone®) to the interferons: One compared with all 3 beta interferons (interferon beta-1a SC [Rebif®] 22 μg dose)60 and the other to interferon beta-1a SC (Rebif®), dose not reported.61 Castelli-Haley et al included both an intention-to-treat cohort of 845 patients as well as a continuous use cohort of 410 for which no other disease-modifying therapy was used during the 2-year period after the index date. There were limitations to both studies including differences in the baseline demographics with the interferon groups having a more severely ill population, use of only 22 μg dosing of interferon beta-1a SC (Rebif®) in the Haas et al study, and the fact that glatiramer acetate (Copaxone®) was only available in exceptional circumstances for at least some portion of the study period. Both analyses attempted to control for these potential confounders.60, 61 They both found a significantly greater reduction in relapse rate at 2 years with glatiramer acetate. The Haas et al study also evaluated the percentage of patient progression free but found no difference in this outcome.60 While these data appeared to support the superiority of glatiramer acetate in relapse over interferon, the fact that no difference was found in the direct comparison studies and the limitations of the observational studies raises the concern that potentially important differences may have contributed to these results. Further good-quality direct comparison studies are needed to confirm the findings.

*Indirect evidence: Placebo-controlled trials*

One fair-quality meta-analysis4 and one good-quality systematic review5 analyzed trials of glatiramer acetate versus placebo. The two reviews used different meta-analytic methods and drew different conclusions regarding the effectiveness of glatiramer acetate. Due to the conflicting nature of these conclusions, the EPC conducted a separate analysis of the 3 relevant trials64-66 and found a small but significant difference in mean relapse rate between glatiramer acetate and placebo (−0.64; 95% CI, −1.19 to −0.09), no difference in the percentage of relapse-free patients (relative risk, 1.23; P=0.086), and inadequate data to pool annualized relapse rates although rates were lower for glatiramer acetate in the trials that reported this outcome.
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).

**β interferons vs. glatiramer acetate**

**Direct evidence**

In a study using data obtained through a prospectively designed clinical database, Haas, et al. 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. 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.

**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. Patient population, natalizumab dose, and study duration were similar in the two trials, however in one of these trials, 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.

Post-hoc analysis of 2-year data in the AFFIRM trial found a significantly higher number of patients in the natalizumab group with no relapse at 2 years (absolute difference, 27.3%; 95% CI, 20.6 to 34.0) and had no disease progression by Expanded Disability Status Scale.
Status Scale at 2 years (absolute difference, 12.0%; 95% CI, 5.9 to 17.9).69 Additionally, the number with the composite outcome “free of clinical disease activity” (a combination of no relapse and no progression) was significantly higher in the natalizumab group (absolute difference, 25.4%; 95% CI, 18.7 to 32.1%).69

Two studies evaluated the secondary outcome results of the AFFIRM and SENTINEL trials, 1 assessing the efficacy of natalizumab on health-related quality of life, and 1 assessing the efficacy on prevention of visual loss.70, 71 Natalizumab offered a significant improvement in the physical component scale of the short-form-36 health-related quality of life questionnaire at week 104 (AFFIRM: odds ratio, 1.54; 95% CI, 1.06 to 2.23; SENTINEL: odds ratio, 1.47; 95% CI, 1.08 to 2.03).71 Vision testing, including low-contrast testing using a Sloan chart which is known to best identify visual dysfunction in multiple sclerosis cohorts, was performed in both trials as a predefined tertiary outcome. Post hoc analysis found that clinically significant visual loss (2 line worsening of acuity sustained over 12 weeks) was seen in the natalizumab group in the AFFIRM trial at the 2.5% contrast level (absolute difference, 47%; hazard ratio, 0.53%; 95% CI, 0.36 to 0.76; P<0.001), and at the 1.25% contrast level (absolute difference, 35%; hazard ratio, 0.65; 95% CI, 0.47 to 0.90; P=0.008).70 In the SENTINEL trial where patients received interferon beta-1a IM (Avonex®) +/- natalizumab, there was a significant reduction in visual acuity only at the 1.25% contrast level (hazard ratio, 0.72; 95% CI, 0.54 to 0.98; P=0.038).70

Mitoxantrone

Direct evidence

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

Indirect evidence

One small trial compared mitoxantrone to placebo in 51 patients with RRMS9. 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.

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. These include 1 study of interferon β1a IM (Avonex®), 2 studies of interferon β1a SC (Rebif®), 2 studies of interferon β1b SC (Betaseron®), and one combined analysis of these 2 trials. 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. Only 2 studies found a significant benefit of β interferons in slowing progression. In IMPACT\textsuperscript{10} (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. 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 2 studies of interferon β1b SC (Betaseron®) used the same outcome measure and report conflicting results. Pooled results indicate an overall benefit, 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.

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\textsuperscript{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.\textsuperscript{58, 60, 61, 62}

**Glatiramer acetate, Natalizumab or Mitoxantrone**

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

**PPMS**

**β Interferons**

The primary 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.\textsuperscript{11} 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.

While a pilot trial of interferon beta-1b SC (Betaseron®) has been done, it has only been partially reported to date.\textsuperscript{66} Details in this publication were inadequate for inclusion here. One systematic review by Rojas et al of the Cochrane collaboration reviewed data from both of these trials including unpublished data from the pilot trial by Montalban.\textsuperscript{36} This
trial data found a no significant differences between interferon beta-1b SC (Betaseron®) and placebo in sustained progression of disease and mean Expanded Disability Status Scale change over a 2 year period. The review pooled data from both interferons, which did not allow interpretation for comparative effectiveness, however, they found no difference in relapse related and disease progression outcomes when the data was pooled. These results were limited by the small number (N=143).

Glatiramer Acetate
One indirect fair quality study, N=943, compared glatiramer acetate to placebo in patients with primary progressive multiple sclerosis. The duration of the study was intended to be 36 months but was stopped early due to lack of efficacy. At that time 60% of patients randomized to Glatiramer and 59% of those randomized to placebo had received the study drug for 24 months, and 18% and 15% respectively had received the study drug for 36 months. The study found no significant difference in delay to sustained disability (hazard ratio, 0.87; 95% CI, 0.71 to 1.07).

Natalizumab and Mitoxantrone
No studies of natalizumab or mitoxantrone in patients with PPMS were found.

Mixed populations: Clinically isolated syndrome and relapsing-remitting multiple sclerosis
One small single-blinded head-to-head trial (N=75) comparing interferon beta-1b (Betaseron®) to glatiramer acetate evaluated clinical exacerbations over 2 years as a secondary outcome. Randomization was stratified by clinical site and presence of enhancement on screening magnetic resonance imaging, which introduced bias to the results. There was no specific criterion for defining relapse, including change in Expanded Disability Status Scale and/or a decrease in the Scripps Neurological Rating Scale of at least 7 points, and a neurological examination was performed by a blinded examining neurologist. Most of the patients had relapsing-remitting multiple sclerosis (79%) with a baseline median annualized relapse rate and Expanded Disability Status Scale score of 1.85 (0-7.5) and 2.0 (0-5.5) respectively. No difference was found in the annualized relapse rate (interferon beta-1b [Betaseron®] 0.37, glatiramer acetate 0.33, P=0.68) or percent relapse-free at 18 months (interferon beta-1b [Betaseron®] 62%, glatiramer acetate 70%). Because these were secondary outcomes, the study may not have had an adequate sample size (statistical power) to identify a statistically significant difference if one exists. It did, however, agree with findings from 2 other trials where the population was restricted to relapsing-remitting multiple sclerosis, both of which found no difference in clinical measures including relapse rate between the interferon studied and glatiramer acetate (see section on relapsing-remitting multiple sclerosis, above).

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.12 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. While these data suggest that baseline disease severity has an 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.

**Natalizumab**

*Indirect Evidence*

Three trials compared natalizumab (Tysabri®) to placebo in relapsing-remitting and secondary progressive multiple sclerosis patients.89-91 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. Natalizumab doses were weight-based in 2 of the trials whereas in the O’Connor et al trial, the patients were randomized to placebo, a 1 mg/kg dose, or a 3 mg/kg dose and received only 1 infusion at study entry.90 The only infusing dosage that was common amongst the trials was 3 mg/kg but the total accumulated dose varied considerably from 1 mg/kg to 18 mg/kg. All of the trials reported effectiveness outcomes.89-91 The longest trial, Miller et al,89 had a duration of 12 months, while the other trials were considerably shorter (14 weeks for O’Connor and 24 weeks for Tubridy91).

For data comparing the same infusion dose of 3 mg/kg, the EPC pooled the data to find the combined mean difference in Expanded Disability Status Scale score and found no significant difference between the natalizumab and placebo groups at the final time point (−0.049; 95% CI, −0.301 to +0.204),89-91 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 trials. Miller et al reported a 4% relapse rate, O’Connor a 2% relapse rate, and Tubridy reported a 39% relapse rate. Relapse rates for placebo were 21%, 5%, and 44% respectively, resulting in a significant difference between natalizumab and placebo in only 1 of the trials.89 Possible reasons for this discrepancy include total natalizumab dose (18 mg/kg compared with 1 or 3 mg/kg compared with 9 mg/kg respectively), trial duration (12 months compared with 14 weeks compared with 24 weeks of follow-up), and criteria used to assess relapse. Miller et al used a more restrictive criterion 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).16 Due to the heterogeneity of the 3 trials (I²=79.3%), we did not combine the relapse outcome data. Due to these discrepant findings, it is difficult to draw a definitive conclusion regarding the effect of natalizumab on relapse rate.

**Mitoxantrone**

*Indirect Evidence*

A well-conducted systematic review compared mitoxantrone (Novantrone®) to placebo using data from four trials.13 A second review included the same four trials, and preliminary and unpublished data from an ongoing study. 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 while the remaining study enrolled only RRMS patients\(^\text{20}\) and had a lower a mean baseline EDSS score. 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.\(^\text{26}\) 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.

**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 \(\geq 2\) and \(\leq 6.5\), and exhibiting progression in a pre-trial period).\(^\text{14}\) 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 \(\geq 1\) if baseline \(\geq 5\), 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%, \(p = 0.03\)).

**KQ 2. Do disease-modifying treatments for multiple sclerosis differ in their effects on the development or recurrence of interferon beta neutralizing antibodies?**
Neutralizing antibodies are known to develop in some patients taking beta interferons, potentially interfering with effectiveness. Two systematic reviews summarized the current state of understanding about the impact of these antibodies on relapse and disease progression, and how the products differ.\(^\text{98, 99}\) There were 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 (subcutaneous more antigenic than intramuscular). Because there is no standardized universal assay, comparisons across studies of the beta interferons is fraught with uncertainty. It appears that the rate of antibody development occurs earlier and in greater frequency with interferon beta-1b SC (Betaseron®), appearing as early as 3 months into treatment in approximately 30% to 40% of patients. Evidence reported in the Namaka review99 indicated that antibodies occur somewhat later (9 months) with interferon beta-1a SC (Rebif®), with rates as low as 12% and as high as 46%. Interferon beta-1a IM (Avonex®) appeared to have the lowest immunogenicity with rates of 2% to 8.5% reported, starting around 9 months of treatment. Importantly, 40% to 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. Data from 9 comparative observational studies reporting the presence of neutralizing antibodies in patients taking beta interferons are included.100-108 The proportion of patients developing antibodies was lower for interferon beta-1a IM (Avonex®), 0% to 14%, compared with 11% to 44% with interferon beta-1a SC (Rebif®) and 15% to 44% with interferon beta-1b SC (Betaseron®), consistent with findings from the Namaka systematic review. The usefulness of these studies in making comparisons across drugs was limited because most did not study patients on therapy for more than 2 years.

KQ 3. What is the evidence that interferon beta neutralizing antibody status has an impact on clinical outcomes (relapse and disease progression) in patients with multiple sclerosis?

The duration of many studies was not adequate to assess the impact of antibody status on progression clearly. Namaka et al found that in the first 2 years of treatment a difference in outcome based on antibody status could not be identified, but that relapse rates were lower in years 3 and 4 among patients who were antibody-positive. The review by Goodin et al98 also found that relapse rates were 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 was less compelling, with only 2 of 8 studies showing a significant increase in progression among those with neutralizing antibodies. Two trials published subsequent to the Goodin and Namaka systematic reviews reported rates of interferon beta neutralizing antibodies occurring in enrolled patients. Most of these may not have been of sufficient duration to show clinical effects of antibody development, however. In the EVIDENCE trial, which compared interferon high-dose, high-frequency interferon beta-1a (Rebif®) 44 mcg to low-dose interferon beta-1a IM (Avonex®) 30 mcg over 2 years, neutralizing antibodies were detected at least once in 26% of patients receiving high-dose Rebif® and in 3% of those receiving low dose Avonex® (P<0.001). Neutralizing antibodies developed earlier with high-dose treatment (58% by week 24, compared with 14% in the low-dose group). Relapse rates were similar in antibody-positive and antibody-negative patients.45 The proportion of patients developing neutralizing antibodies was reported in the REGARD study of interferon beta-1a (Rebif®). The rate was 60/138 (16%) at 24 weeks, 93/355 (26%) at 48 weeks, 91/319 (29%) at 72 weeks, and 102/374 (27%) at 96 weeks or last observation carried...
Neutralizing antibodies had no effect on clinical efficacy: there was no difference in time to first relapse for those positive at any time and those negative (hazard ratio, 1.24; 95% CI, 0.86 to 1.77), although the study may not have been long enough to show clinical effects.

Eight observational studies reported clinical outcomes based on antibody status. Although there was an association between neutralizing antibody status and clinical outcome shown in several studies, none found the detrimental effect of positive antibody status to be greater with one of the beta interferons than another. The conclusions that could be drawn from these studies were limited for several reasons: most were not of sufficient duration to show an effect of neutralizing antibodies on clinical status, the numbers of patients taking each drug may not have been sufficient to show a difference between treatments, and lack of control for confounding factors limited the validity of their results.

Evidence correlating comparative clinical outcomes to the antibody status of the individual beta interferons was incomplete and inadequate to make conclusions. 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.

**Development of antibodies to natalizumab**

An analysis of the AFFIRM and SENTINEL trials reported the incidence and clinical effects of antibodies to natalizumab that developed over 2 years of therapy. In AFFIRM, 57 of 625 patients (9%) tested positive for antibodies at any time during the study; 3% were transiently positive and 6% were persistently positive throughout the study. Most (88%) patients developed antibodies by week 12 of treatment. Results were similar in SENTINEL, in which natalizumab was added to interferon beta-1a therapy, with 12% of patients testing positive for antibodies to natalizumab during the 2-year study, 5% transiently positive, and 96% showing antibodies by week 12 of treatment. In AFFIRM, 34% of patients who were persistently antibody-positive had sustained disability progression, compared with 17% of patients who were antibody-negative. The proportion of patients with sustained disability progression who were transiently antibody positive was identical to that of patients who were antibody-negative. In contrast, in the SENTINEL study, patients who were persistently antibody-positive did not show a reduced effect of natalizumab on disability progression compared with those who were antibody-negative ($P=0.503$). The cumulative proportion of patients with sustained disability progression over 2 years was 24% in antibody-negative patients, 19% in transiently-positive patients, and 20% in persistently positive patients.

**KQ 4. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?**

**Previous systematic review**

A Cochrane systematic review evaluated the efficacy and safety of treatment with beta interferons on the proportion of patients delayed to convert from clinically isolated syndrome to clinically definite multiple sclerosis. Three trials were included in the review: CHAMPS, ETOMS, and BENEFIT. Searches were conducted through June 2007. This review did not include a comparison of interferon beta-1a to
interferon beta-1b; it combined the interferons and considered them as a group for analysis. Overall, meta-analysis showed that fewer patients converted to CDMS with beta interferon treatment compared with placebo after 1 year (pooled odds ratio, 0.53; 95% CI, 0.40 to 0.71) and after 2 years (pooled odds ratio, 0.52; 95% CI, 0.38 to 0.70).

Direct evidence
No head-to-head trials have been conducted.

Indirect evidence
Five placebo-controlled trials (in 12 publications) assessed disease-modifying drugs in patients with a clinically isolated syndrome.119-130 One trial was rated good quality121 and the rest were fair. All 5 trials showed a statistically significant reduction in the proportion of patients and the time to converting to clinically definite multiple sclerosis compared with placebo with relative risks or hazard ratios in the 0.50 to 0.65 range and numbers needed to treat ranging from 5 (glatiramer acetate and Avonex®) to 10 (Rebif®). Because there were apparent clinical differences in the populations enrolled, an indirect meta-analysis of these data was not undertaken.

The 3 trials of interferon beta-1a products were low dose with weekly injections, while the study of interferon beta-1b (Betaseron®), the BENEFIT study, used every other day dosing. The dose of interferon beta-1a SC (Rebif®) in the ETOMS study was 22 mcg. The dose of glatiramer acetate in the PreCIS study was 20 mg daily, the standard dose for treatment of multiple sclerosis. The patient populations enrolled in the studies were somewhat different, with the study of interferon beta-1a SC (Rebif®)120 enrolling patients with multifocal presentation, a higher percentage with gadolinium enhancing brain lesions, and lesions with larger median volume compared with the other studies.121, 126 All patients enrolled in CHAMPS received standardized corticosteroid treatment for the initial episode and were enrolled within 2 weeks of initial symptom presentation, while patients in the other studies were enrolled within 2 or 3 months of initial presentation and treatment of the episode was not standardized. Only patients with monofocal lesions were enrolled in the trial of glatiramer acetate.127 In contrast, the BENEFIT study of interferon beta-1b (Betaseron®) and 1 of the studies of interferon beta-1a (Avonex®)130 enrolled patients with at least 2 silent magnetic resonance imaging lesions, and may represent patients at higher risk for progressing to multiple sclerosis.131 While the primary endpoint of conversion to clinically definite multiple sclerosis was defined slightly differently in the studies, they were based primarily on a relapse of the initial or new symptoms. The BENEFIT trial also used the McDonald criteria, which incorporate magnetic resonance imaging findings. All of the studies reported a 3-year follow-up, with the exception of ETOMS, which followed patients for 2 years.120 The CHAMPS trial was stopped early after a planned interim analysis indicated a significant difference in benefit between the groups.126 Patients enrolled in the CHAMPS who had not converted to multiple sclerosis at the end of the 3-year trial were offered enrollment in CHAMPIONS, a 5-year open-label, investigator-initiated extension study.123 Fifty-three percent (203 of 383) of patients who had participated in CHAMPS enrolled in CHAMPIONS. Patients who had been assigned to interferon beta-1a during the trial were considered the immediate treatment group and those assigned to placebo and given interferon beta-1a 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% compared with 49% in the delayed treatment group (adjusted hazard ratio 0.57; 95% CI, 0.38 to 0.86). Multivariate analysis indicated that the factors associated with conversion to multiple sclerosis were randomization to the delayed treatment group and younger age at enrollment in the CHAMPS.

The BENEFIT trial included a 5-year follow-up phase. Patients were eligible to enter the follow-up phase after 2 years in the placebo-controlled phase, and were offered treatment with interferon beta-1b (Betaseron®) 250 mcg SC every other day for up to 5 years.129 Patients initially randomized to interferon beta-1b (Betaseron®) were considered the early treatment group and those initially randomized to placebo were considered the delayed treatment group. Eighty-nine percent (418 of 468) of patients who participated in the placebo-controlled phase entered the follow-up phase. After 5 years, the risk for clinically definite multiple sclerosis was lower in the early treatment group (46%) than the delayed treatment group (57%) (hazard ratio, 0.63; 95% CI, 0.48 to 0.83; number needed to treat, 9).

In a post hoc analysis of the CHAMPS data, only patients considered at high risk of conversion to multiple sclerosis (≥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). The relative risk of conversion to multiple sclerosis was found to be 0.34 (95% CI, 0.17 to 0.70; P=0.002). This compared with a relative risk of 0.56 (95% CI, 0.38 to 0.81; P=0.002) in the total population. In the BENEFIT study of interferon beta-1b (Betaseron®), multiple subgroup analyses were undertaken, examining the effects in monofocal compared with 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 for conversion to multiple sclerosis ranging from 0.40 in patients with <9 T2 lesions to 0.63 in patients with multifocal presentation (compared with a hazard ratio of 0.50; 95% CI, 0.36 to 0.70 in the overall study group). In the trial of glatiramer acetate, post hoc subgroup analyses showed a better response in women (hazard ratio, 0.52; 95% CI, 0.34 to 0.81), in patients younger than age 30 years (hazard ratio, 0.47; 95% CI, 0.27 to 0.80), and in patients with 1 or more gadolinium enhancing lesions at baseline (0.29; 95% CI, 0.16 to 0.54).127 In patients with 9 or more T2 lesions at baseline, the hazard ratio was 0.42 (95% CI, 0.27 to 0.64) compared with placebo. Because these were subgroup analyses, with relatively small numbers of patients in each group, these results should be interpreted with caution.

KQ 5. Do disease-modifying treatments for multiple sclerosis differ in harms?

RRMS

Direct Evidence

The Cochrane systematic review of placebo-controlled trials in patients with relapsing remitting multiple sclerosis evaluated the frequency of adverse events, reporting only on the 44 μg dosing of interferon beta-1a (Rebif®) however they did include data from a once weekly dosing schedule from the OWIMS trial. Only 3 times weekly interferon beta-1a 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 3 times weekly interferon beta-1a SC (Rebif®), while interferon beta-1b SC (Betaseron®) and interferon beta-1a IM (Avonex®) were not. Comparing the 2 dosing
regimens of interferon beta-1a SC (Rebif®), dosing once weekly resulted in statistically significantly greater rates of flu-like syndrome, fever, and headache while dosing 3 times weekly did not. Of note, standard dosing for (Rebif®) is 3 times weekly.

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

Adverse events were not well reported. 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®)**

The Panitch study9 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. This study then had a crossover phase in which patients initially receiving weekly interferon beta-1a IM (Avonex®) once weekly were switched to interferon beta-1a SC (Rebif®) 3 times weekly while those taking interferon beta-1a SC (Rebif®) continued to do so.45 For those transitioning to the interferon beta-1a SC (Rebif®) there was a significant increase in injection site reactions (10% compared with 23%), liver function abnormalities (3% to 6%), and white blood cell abnormality (1.5% compared with 4.5%). Similarly, there was a significant decrease in flu-like symptoms with the interferon beta-1a SC (Rebif®) (16% to 4%).

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

Differences between the drugs were not found in the Durelli (INCOMIN) trial. Data on compliance or patient satisfaction with treatment were not recorded. None of the other studies reported adverse events.

**Post Marketing Studies**

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.

**Indirect Evidence**

Adverse events occurred significantly more frequently in the β interferon groups compared to the placebo groups. Looking across the results from 4 trials 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®), doses once weekly resulted in statistically significantly greater rates of flu-like syndrome, fever and headache while dosing three times weekly did not.

**Glatiramer acetate**
Direct evidence
No trials directly comparing glatiramer acetate (Copaxone®) to another disease modifying drug were identified.

Indirect Evidence
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 3) 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 3. Adverse event rates: glatiramer acetate vs. placebo

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<tr>
<th>Data source</th>
<th>Adverse event</th>
<th>Rate</th>
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| 2 trials70, 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 trials70-72 Total n=540 | Immediate postinjection reactions/ systemic reactions* | 33% vs. 8%  | <0.0001   |
| 2 trials70, 72 Total n=301 | Palpitations | 9% vs. 2%  | 0.0178     |

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

One of the glatiramer acetate placebo-controlled trials, Johnson, et al.,16 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. 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. 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
Two head-to-head trials in patients with relapsing-remitting multiple sclerosis compared
Glatiramer acetate to a beta interferon and reported adverse events.58, 59 The BEYOND trial (N=2244), comparing daily glatiramer acetate (Copaxone®) 20 mg SC to interferon beta-1b (Betaseron®) 250 μg or 500 μg SC every other day in patients with relapsing-remitting multiple sclerosis, lasted 3.5 years and was a good-quality study,59 while the REGARD trial (N=764) compared daily glatiramer acetate (Copaxone®) 20 mg SC to interferon beta-1a (Rebif®) 44 μg SC 3 times per week, lasted 96 weeks, and was of fair quality.58, 59 Adverse events from these 2 trials suggested that both drugs have similar tolerability, with severe adverse events being reported by 11% of patients taking interferon beta-1b (Betaseron®) 250 μg and 13% of patients taking glatiramer acetate in the BEYOND trial, and no significant differences in withdrawal due to adverse events noted in the REGARD trial.58, 59 Overall, the interferons had higher frequency of influenza-like illness (P<0.001), elevated liver enzymes (P<0.0001), and fever (P=0.003) in the BEYOND trial, with similar findings as well as headache and myalgia in the REGARD trial.58 Glatiramer acetate had higher frequency of injection site reactions and post-injection systemic response (which may include dyspnea, chest pain, flushing, or post-procedural complication).58, 59 Lipoatrophy was only reported in patients receiving glatiramer acetate.58, 59

In the study by Haas, et al.17 comparing all 3 β interferons and glatiramer acetate; at 2 years, glatiramer acetate had significantly fewer patients discontinuing treatment after 6 months of treatment. While these data appear to support the superiority of glatiramer acetate in 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.

Data from multiple open label studies appear to support the superiority of glatiramer acetate in tolerability over interferon, the fact that no difference was found in the direct comparison studies raises the concern that potentially important differences among the population treated with glatiramer acetate compared with the others may have contributed to these results. Further good-quality direct comparison studies are needed to confirm the findings.

A study by Tremlett and Oger reviewed the adverse drug reactions reported to the Canadian Adverse Drug Reaction Monitoring Program between 1995 and March 2006. A total of 888 reports were extracted concerning the interferons and glatiramer acetate (Copaxone®).171 The average age of the patients was 45 years, with 74% being female. Of the events reported, 92.2% were considered serious. There were 49 deaths with no clear pattern to the underlying reasons. There were 16 adverse reactions related to pregnancy involving interferon beta-1b (Betaseron®) and glatiramer acetate with the majority due to miscarriage or congenital malformations.

**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.18,19 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. 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.19 This led to early cessation of the SENTINEL trial; no cases of PML were reported in the AFFIRM trial.18 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*

In the one small placebo controlled trial (n=51) 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*

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. 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. 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.

**Glatiramer acetate, Natalizumab or Mitoxantrone**

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

**PPMS**

*β Interferons*

The only study identified for this category is a 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 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.

**Glatiramer Acetate, Natalizumab and Mitoxantrone**

No studies of natalizumab or mitoxantrone in patients with PPMS were found.

**Mixed Populations: RRMS and SPMS**

### β Interferons

No studies were identified that addressed adverse events in this population.

### Natalizumab

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. 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.

### Mitoxantrone

**Indirect Evidence**

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 nonserious 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.

**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 This study utilized a non standard dosing schedule and used a form of the drug that is not the same as the now commercially available drug. 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% CI 1.41-13.7). 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
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 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.

Thyroid Function
The effect of β interferons on thyroid function in RRMS patients was assessed in two observational studies.12,15 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. 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. 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.16 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.17 No cases of liver failure have been reported with Interferon β1b SC (Betaseron®).

ALT elevations
ALT elevations, are the most commonly reported hepatic outcome. 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

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 β1atreated RRMS patients.18 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). 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.

**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 unfortunately there were significant baseline differences in the patients involved. There were no statistically significant differences in between-group comparisons.

**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.19 While these studies were primarily of interferon β1a SC (Rebif®), one trial of interferon β1a IM (Avonex®) was also included.

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, as well as withdrawal rates due to depression were not significantly different between interferon β1a and placebo groups.

The EPC’s own analysis of the all published trials reporting rates of depression indicates a nonsignificant increase in risk for both interferon β1a products and a non-significant decrease in risk with interferon β1b SC (Betaseron®). Our (EPC) adjusted indirect analysis 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®) 44 μ g 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.

**Glatiramer acetate**

**Lipoatrophy**
Evidence on the safety of glatiramer acetate (Copaxone®) from 5 non-comparative, nonrandomized studies was consistent with that from previously discussed trials.178-181 No additional serious adverse events were reported in any of these studies, with the exception of the risk of potentially permanently disfiguring lipoatrophy with glatiramer acetate use.182 One long-term follow-up study and 1 small retrospective study found evidence of lipoatrophy.170, 182 The small retrospective study found that 34 of 76 (45%) patients identified through chart review had evidence of lipoatrophy. Five of these cases were identified as severe, all cases occurred in women, and 4 withdrawals were attributed to lipoatrophy. The Miller study, which had the longest follow-up of up to 22 years, found 33% of 18 patients had developed lipoatrophy.170 Overall, the observational studies agreed with the direct and placebo-controlled trials. Most patients experience at least 1 adverse event with the most common being injection site reactions and post-injection systemic reactions, however, treatment was generally well tolerated for years and treatment discontinuation due to an adverse event was uncommon. Lipoatrophy did appear to be a concern with long-term use.

**Depression**
A small (n=163) cohort study by Patten, et al.20 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. 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.

**Natalizumab**
Data from 2 post-marketing observational studies of patients with relapsing-remitting multiple sclerosis in Europe, 1 in Italy with 909 cases and 1 in Denmark with 234 cases, provide additional safety data.184, 185 Both were of relatively short duration, 15 months by the Italian Drug Agency and a median period of 11.3 months (range 3.0-21.5) in the Danish nationwide study. There were no cases of progressive multifocal leukoencephalopathy. There were a high percentage of infections in the Danish study, 58%, although none severe. Neutralizing antibodies were found in 4% of the Danish group.185 There were allergic reactions in 5% of the Italian group, none serious, whereas 4% in the Danish study, 2 cases of which were serious anaphylactic reactions.

**Progressive Multifocal Leukoencephalopathy (PML)**
Two patients with MS and one with Crohn’s disease treated with natalizumab (Tysabri®) were reported to have developed PML. 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.21 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. Since that time, additional cases have been reported in patients on monotherapy as well. The risk appeared to increase with greater time on therapy. According to the US Food and Drug Administration who have reviewed all the cases of progressive multifocal leukoencephalopathy, there have been no reports of progressive multifocal leukoencephalopathy in patients treated for less than 12 months since the remarketing of natalizumab (Tysabri®) in 2006. In patients treated with 24 to 36 infusions, the overall worldwide rate and the rate in the United States of developing progressive multifocal leukoencephalopathy is similar to the rate seen during clinical trials (1 case per 1000 patients treated). For unknown reasons, the rate outside of the United States is approximately 2 cases per 1000 patients. As of June 2010, 55 cases of progressive multifocal leukoencephalopathy associated with natalizumab use have been reported worldwide. At the first signs of progressive multifocal leukoencephalopathy, patients are to receive plasma exchange or immunoadsorption to decrease circulating natalizumab (Tysabri®) levels which can lead to the development of immune reconstitution inflammatory syndrome. Immune reconstitution inflammatory syndrome is characterized by a severe inflammatory response as the immune system recovers and can cause a profound decline in a patient’s condition.

**Mitoxantrone**

Small (n= 7 to 31) before-after studies of patients with various categories of MS have been reported.144-146 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**

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.22 The meta-analysis was based on patient data (n=1378) from one phase-III trial and two open-label, non-comparative studies available in abstract form only. The full results of the trial were included in the Martinelli Boneschi23 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/m2 had a lower incidence of asymptomatic LVEF <50% than those patients receiving ≥100mg/m2, although this did not reach statistical significance (incidence of 1.8% vs. 5.0%; p=0.06).

Observational studies have reported a reduction in left ventricular ejection fraction in the 3-5 % range.196, 197 One small study of 18 patients monitored cardiac function with repeat transthoracic echocardiograms every 3 months before each infusion and found 4 cases in 18 patients (22%).198 Further monitoring found that these were transient in 2 of these cases, bringing their percentage to 11%, but they do suggest that more frequent cardiac monitoring might influence the infusion regimen and minimize risk of non-reversible cardiotoxicity. Long-term randomized trials would help to better appreciate whether these transient changes have any long term associated harm.
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). There were two reports of t-AL, both in young women who had received 70 mg/m2 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.

Amenorrhea
Amenorrhea has been reported as a frequent side effect in the placebo-control trials of mitoxantrone but the degree of permanent amenorrhea affecting fertility remains unclear. The FEMIMS study assessed the frequency and risk factors of mitoxantrone-induced amenorrhea in multiple sclerosis. It was a retrospective observational study of 189 Italian female patients with relapsing-remitting (57%), secondary progressive (41%), and primary progressive multiple sclerosis (2%) who had received at least 3 cycles of mitoxantrone before the age of 45. The mean age of the patients was 37 years with a median follow-up of 26 months after discontinuing the drug. The median cumulative dose of mitoxantrone was 100 mg/m2 (range 30-140 mg/m2) over a median period of 15 months (range 3-55 months). Their findings suggested that older age (odds ratio, 1.18; 95% CI, 1.10 to 1.27; \( P=0.01 \)) and higher cumulative dose (odds ratio, 1.02; 95% CI, 1.01 to 1.04; \( P=0.01 \)) were associated with increase risk of permanent amenorrhea whereas concomitant use of estrogen-progesterone therapies was associated with a decreased risk (odds ratio, 0.31; 95% CI, 0.13 to 0.7; \( P=0.01 \)).

KQ 6. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), socioeconomic status, other medications, severity of disease, or co-morbidities for which one disease-modifying treatment is more effective or associated with fewer adverse events?

Race
A post hoc subgroup analysis of EVIDENCE, a head-to-head trial of interferon beta-1a products (Avonex® and Rebif® 44 mcg) compared the response to treatment in African-American and white patients. The proportion of African-American patients in the EVIDENCE trial was small (6%). The subgroup analysis found that although the 2 groups were similar at baseline, the African-American patients experienced more exacerbations and were less likely to be exacerbation-free compared with the white patients over the course of the study. The small number of patients in the African-American group meant 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 with 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 beta-1a SC (Rebif®) or IM (Avonex®), including open-label extension phase studies and involving
patients with relapsing-remitting or secondary progressive multiple sclerosis or clinically isolated syndrome, 41 pregnancies occurred with in utero exposure to interferon. Twenty-two pregnancies occurred in women with previous exposure (discontinued interferon more than 2 weeks prior to conception) and only 6 occurred in women receiving placebo. In the group with in utero exposure to interferon beta-1a, pregnancy loss occurred in 29%, compared with 0 in either the placebo or prior exposure groups. The authors indicated that the rate of pregnancy loss with in utero exposure was greater than the average reported in the overall population, although they reported 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% of 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.

In a prospective cohort study conducted in Germany between 1996 and 2007, pregnancy outcomes for women who were exposed to beta interferons (n=69) or glatiramer (n=31) during pregnancy were compared with 2 control groups: pregnant women with multiple sclerosis who had not taken beta interferons or glatiramer (n=64), and pregnant women without multiple sclerosis (n=1557). Overall, the miscarriage rate in all 4 cohorts was within normal range and did not differ among the cohorts. Among interferon-exposed pregnancies, however, there was a significantly higher rate of miscarriage in the interferon beta-1b group (27.8%; 5 of 18) compared with the interferon beta-1a group (4.8%; 2 of 42; \( P = 0.02 \)), the non-multiple sclerosis control group (9.1%; \( P = 0.02 \)), and the glatiramer group (3.9%; \( P = 0.03 \)). Two major birth defects (club feet and atrioventricular canal) occurred in the glatiramer group, but the rate was not significantly different from the comparison cohorts. Birth weight was within normal range in all groups, but was significantly lower in the (combined) interferon group. Birth weight was also lower in the subgroup of women who relapsed during pregnancy, regardless of drug exposure.

**Men**

Two studies analyzed the association of gender with response to glatiramer or beta interferons. In the PROMISE trial of glatiramer (Copaxone®) in primary progressive multiple sclerosis, there was no effect of glatiramer on progression of disability in the total group, but a post hoc subgroup analysis showed a delayed time to progression of disability in the subgroup of men randomized to glatiramer (hazard ratio, 0.71; 95% CI, 0.53 to 0.95). An observational study of 2570 patients with relapsing remitting multiple sclerosis treated with beta interferon and followed for up to 7 years found a lower risk of relapse in men compared with women, especially in the subgroup of patients with lower pre-treatment disease activity (less than 1 relapse in the year before treatment initiation). Although these studies suggested that men with multiple sclerosis may respond differently than women to treatment, they did not provide evidence to make conclusions about comparative effectiveness or safety of the different products in men.
References: