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Health Resources Commission
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 consisted of three Physicians, a Nurse Practitioner, a PhD, RPh 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 July of 2007, 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:


You may request more information including copies of the draft report from:

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Director, Health Resources Commission
Office for Oregon Health Policy & Research
1225 Ferry St. SE
Salem, Oregon 97301
Phone: 503-373-1629 (HRC Assistant)
Fax: 503-378-5511
Email: HRC.info@state.or.us
Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:
Alison Little, MD
Assistant Director for Health Projects
Oregon Health & Science University
Center for Evidence-based Policy
2611 SW Third Avenue, MQ280
Portland, OR 97201-4950
Phone: 503-494-2691
E-mail: littlea@ohsu.edu

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

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

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

Although more data is becoming available, the pathogenesis of MS remains elusive. Myelin-reactive T cells and B cells are present in MS.\textsuperscript{7} Environmental factors, such as infectious agents; seem to facilitate the movement of these cells from the periphery, across the blood brain barrier, and into the CNS in persons genetically susceptible to MS. The migration of T cells and antibodies across the blood brain barrier occurs because adhesion molecules, in addition to proteases that break down the endothelial cells that make up the barrier, are activated. Once within the CNS, the T cells secrete interferon $\gamma$ and interleukin 17. The antigen presenting cells (APC) and T helper cells form a complex by binding to a self-antigen, such as myelin basic protein via the major histocompatibility complex (MHC) and T cell receptor, respectively. Antigen presentation to these cells causes an enhanced immune response. Depending on other interacting molecules, the T helper cell-APC complex may cause type 1 T helper cells (Th1) to secrete pro-inflammatory cytokines, such as interferon $\gamma$, or type 2 T helper cells (Th2), to secrete anti-inflammatory cytokines, such as interleukin 4. Macrophages, cytotoxic T cells, autoantibodies secreted from B cells, and pro-inflammatory cytokines secreted from T helper cells are also activated during this process. Acute inflammatory, demyelinating plaques occur when myelin undergoes phagocytosis by macrophages when coated with antibodies for myelin basic protein and myelin oligodendrocyte glycoprotein. In addition, cytotoxic T cells and proinflammatory cytokines may directly damage the myelin. The
treatment of MS involves acute relapse treatment with corticosteroids, symptom management with appropriate agents and disease modification with DMDs. For example, when acute exacerbations occur (i.e., vision loss or loss of coordination), they are commonly treated with a short duration of high dose oral or intravenous corticosteroid; if spasticity occurs, it can be addressed with muscle relaxants; however, therapy with DMDs is designed to prevent relapses and progression of disability rather than treat specific symptoms or exacerbations of the disease. These agents modify the immune response that occurs in MS through various immunomodulatory or immunosuppressive effects. Current DMD treatments options for MS are found in Table 1.

Three of the four immunomodulatory agents are type-1 β interferons: interferon β1b SC (Betaseron®) and interferon β1a IM and SC (Avonex® and Rebif®). The fourth agent is glatiramer acetate (Copaxone®). It is currently thought that type-1 β interferons modulate the immune system by reducing T cell migration from the periphery into the CNS by decreasing the production of adhesion molecules and increasing the production of proteases on the endothelial cells that make up the blood brain barrier. 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 after three patients in the drug’s clinical trials developed progressive multifocal leukoencephalopathy (PML), a serious viral infection of the brain. FDA then put clinical trials of the drug on hold in February, 2005, allowing them to resume a year later after confirming that there were no additional cases of PML. In March, 2006, FDA consulted its Advisory Committee on drugs for peripheral and central nervous systems about the possibility of making Tysabri available to appropriate MS patients. The Advisory Committee recommended a risk-minimization program with mandatory patient registration and periodic follow-up. In response, the manufacturer, Biogen-Idec, submitted to the agency a Risk Management Plan to help ensure safe use of the product. Tysabri is available only through the Risk Management Plan, called the TOUCH Prescribing Program. In order to receive Tysabri, patients must talk to their doctor and understand the risks and benefits of Tysabri and agree to all of the instructions in the TOUCH Prescribing Program.

See the following web site for more information on the TOUCH Prescribing Program: http://www.fda.gov/cder/drug/infofage/natalizumab/default.htm.
Mitoxantrone (Novantrone®) is an antineoplastic agent originally approved for adult acute myeloid leukemia and later approved for SPMS, PRMS, and worsening RRMS as an immunosuppressant drug. Mitoxantrone is thought to inhibit cell division and impair the proliferation of T cells, B cells, and macrophages by intercalating and crosslinking DNA, thus inhibiting DNA replication and RNA synthesis of these cells. 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 1. Pharmacology and dosing of included drugs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage and Administration</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>
</tr>
<tr>
<td>Interferon β 1a Avonex®</td>
<td>30 mcg Intramuscularly 1x/wk</td>
<td>RRMS</td>
<td>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 proinflammatory cytokines from Th1 cells (TNFα, IFNγ, IL-12).</td>
</tr>
<tr>
<td>Interferon β 1a Rebif®</td>
<td>22 or 44 mcg Subcutaneously 3x/wk</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></td>
</tr>
<tr>
<td>Mitoxantrone Novantrone®</td>
<td>12 mg/m² Intravenously Every 3 mos (Max cumulative dose is 140 mg/m²)</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 RNA synthesis of these cells. Impairs antigen presentation by causing apoptosis of APCs and other cells that associate with APCs.</td>
</tr>
<tr>
<td>Natalizumab Tysabri®</td>
<td>300 mg Intravenously Every 4 wks</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.

**Scope and Key Questions**
The purpose of this review is to compare the effectiveness and safety of different disease-modifying drugs for the treatment of Multiple Sclerosis (MS). The 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. What is the comparative tolerability and safety of disease-modifying treatments for multiple sclerosis?
3. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?
4. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), other medications, or co-morbidities for which one disease-modifying treatment is more effective or associated with fewer adverse events?

Results

Systematic Reviews
There were 4 systematic reviews identified that were applicable to the scope of this evaluation. Three reviews include \( \beta \) interferons, glatiramer acetate, and mitoxantrone. The best quality review is the one conducted for the National Institute for Clinical Excellence (NICE) by Clegg and Bryant and a related article that updates that review.\(^3\),\(^4\) This review assessed the general effectiveness of the interventions compared to placebo. No attempts were made to compare the drugs to one another; however the review will be used in the appropriate sections below. One additional systematic review focuses on the association of depression and \( \beta \) interferon and glatiramer acetate treatment and is discussed under Key Question 3 below.\(^5\)

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

\( \beta \) Interferons
Four fair quality trials directly compared one \( \beta \) interferon to another, ranging from 16 to 24 months in duration in patients with RRMS. The INCOMIN trial\(^6\) of Interferon \( \beta 1a \) IM (Avonex\(^\text{®}\)) and. Interferon \( \beta 1b \) SC (Betaseron\(^\text{®}\)) was open-label, while the other 3 were single blinded studies. The Etemadifar study\(^7\) was small, with only 30 patients per group. At baseline the mean or median EDSS in the groups ranged from 1.9 to 2.98, and the mean number of relapses in the 2 years prior to the study ranged from 1.38 to 3.2. Based on these parameters, the Danish Multiple Sclerosis Study Group\(^8\) patients were more severely ill compared to the other studies. In addition, while dosing for interferon \( \beta 1b \) SC (Betaseron\(^\text{®}\)) 250 \( \mu \)g every other day and interferon \( \beta 1a \) IM (Avonex\(^\text{®}\)) 30 \( \mu \)g once weekly were consistent across the studies, the dosing for interferon \( \beta 1a \) SC (Rebif\(^\text{®}\)) ranged from 22 \( \mu \)g once weekly to 44 \( \mu \)g three times a week.

Interferon \( \beta 1b \) SC (Betaseron\(^\text{®}\)) vs. Interferon \( \beta 1a \) SC (Rebif\(^\text{®}\))
Neither the small study by Etemadifar nor the Danish study by Koch-Henriksen found a significant benefit of interferon \( \beta 1b \) SC (Betaseron\(^\text{®}\)) over interferon \( \beta 1a \) SC (Rebif\(^\text{®}\)) at 2 years. While the smaller trial by Etemadifar found interferon \( \beta 1b \) SC (Betaseron\(^\text{®}\)) numerically superior to interferon \( \beta 1a \) SC (Rebif\(^\text{®}\)) for outcomes related to disease progression (EDSS at endpoint and mean change in EDSS), the difference was not statistically significant. Koch-Henrikson enrolled a somewhat more severely ill population, but also did not find significant differences in annualized relapse rates, rate of
steroid use, or the proportion with disease progression at 2 years. Other outcomes reported in the Koch-Henriksen trial also were unable to identify a difference between the 2 β interferons, including exacerbations requiring hospitalization and time to confirmed progression.

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

Disability-related outcomes were reported differently in the 2 trials, but statistically significant differences between the drugs were not found.

Interferon β1b SC (Betaseron®) vs. Interferon β1a IM (Avonex®)
Two trials evaluated the comparison of interferon β1b SC (Betaseron®) and interferon β1a IM (Avonex®) and found higher rates of patients who were relapse free at 2 years with interferon β1b SC (Betaseron®); pooled RR 1.51, 95% CI 1.11-2.07.43, 44 Data for disease progression is somewhat conflicting. The mean change in the EDSS was greater with interferon β1a IM (Avonex®) in the Durelli trial (INCOMIN), but larger with interferon β1b SC (Betaseron®) in the small trial by Etemadifar. Both trials reported a lower final EDSS with interferon β1b SC (Betaseron®) compared to interferon β1a IM (Avonex®); pooled difference 0.46 (95% CI 0.20-0.71; p=0.0005). In addition, the INCOMIN trial found the rate of disease progression to be significantly lower in the interferon β1b SC (Betaseron®) group compared to the interferon β1a IM (Avonex®) group. Of the 4 head to head trials, these 2 represent the lowest quality evidence such that these findings should be interpreted with caution.

Neutralizing Antibodies
Neutralizing antibodies are known to develop in some patients taking β interferons, potentially interfering with effectiveness. Two recent reviews of neutralizing antibodies summarize the current state of understanding about the impact of these antibodies on relapse and disease progression, and how the products differ. Because there is no standardized universal assay, making comparisons across studies of the β interferons is fraught with uncertainty. In addition, the duration of many studies is not adequate to assess the impact of antibody status on progression clearly. To date, evidence correlating comparative clinical outcomes to the antibody status of the individual β interferons is incomplete and inadequate to make conclusions.

Post-Marketing Studies
Three non-randomized controlled studies were identified. 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\textsuperscript{12}. Eighty-four percent of these patients were exposed to the interferon as their first DMD. The group receiving Interferon $\beta_1$b (Betaseron®) was older, had MS longer and had higher baseline EDSS scores compared to the other groups, and the group receiving interferon $\beta_1$a 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 $\beta_1$a IM (Avonex®) was found superior to interferon $\beta_1$b (Betaseron®) (83.4\% vs. 76.2\%, $p=0.001$), and compared to the interferon $\beta_1$a SC 44 mcg (Rebif®) group (83.4\% vs. 69.4\%, $p<0.001$), but not significantly different to interferon $\beta_1$a 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 $\beta$ 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\textsuperscript{13} conducted for the Cochrane Collaboration pooled all interferons together, including interferon $\alpha$, while the review by Clegg and Bryant\textsuperscript{3} considered data on the 2 interferon $\beta_1$a products together. These reviews are based on the 5 trials of $\beta$ interferons; a pilot study and a multicenter trial of interferon $\beta_1$b SC (Betaseron®), 1 multicenter trial of 2 doses of interferon $\beta_1$a IM (Avonex®) and 2 trials of interferon $\beta_1$a 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 $\beta_1$b SC (Betaseron®) and the early discontinuation and lack of intention-to-treat analysis in the trial of interferon $\beta_1$a IM (Avonex®).

Overall, the data indicate that both interferon $\beta_1$a products result in reductions in the proportions of patients having progressed at 2 years, while interferon $\beta_1$b 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. This analysis resulted in no statistically significant differences for the comparison of interferon β1a SC (Rebif®) and interferon β1b SC (Betaseron®). For the comparison of interferon β1a IM (Avonex®) with either interferon β1b SC (Betaseron®) or interferon β1a SC (Rebif®) the results of our exploratory analysis is consistent with the findings of our direct and indirect analyses (see Table 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</th>
<th>Betaseron vs Avonex</th>
<th>Rebif 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>-0.19 (-0.51, 0.14)</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**
No trials directly comparing glatiramer acetate (Copaxone®) to another disease modifying drug were identified.

**Indirect evidence: Placebo-controlled trials**
One fair-quality meta-analysis\textsuperscript{14} and one good-quality systematic review\textsuperscript{15} 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 three relevant trials\textsuperscript{16,17,18} and pooled results where possible. The mean difference in relapse rate between glatiramer and placebo was statistically significant (-0.64 [-1.19, -0.09] \(p=0.02\)) when results from the three trials were pooled. Since the absolute difference in relapse rate between glatiramer acetate and placebo was considerably higher in the Bornstein\textsuperscript{14} study, a sensitivity analysis was conducted for this outcome. That analysis found the difference in mean relapse rate to be much smaller, but still statistically significant (-0.31 [-0.5227; -0.106], \(p=0.0031\).) When results from the
three trials were pooled, there was no statistically significant difference in the percentage of relapse-free patients between glatiramer acetate and placebo groups (RR 1.23; p=0.086.) Again, the Bornstein study had a much higher absolute rate difference compared to the two larger studies: 30.0% vs. 6.3% and 6.6% respectively.

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)\textsuperscript{15}

\textbf{β interferons vs. glatiramer acetate}

\textit{Direct evidence}

In a study using data obtained through a prospectively designed clinical database, Haas, et al.\textsuperscript{19} 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 \(\leq 3.5\). 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.

\textbf{Natalizumab}

\textit{Direct evidence}

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

\textit{Indirect evidence}

Two well-conducted trials compared natalizumab to placebo in patients with RRMS.\textsuperscript{20,21} Patient population, natalizumab dose, and study duration were similar in the two trials, however in one of these trials\textsuperscript{19}, 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.

**Mitoxantrone**

*Direct evidence*

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

*Indirect evidence*

One small trial compared mitoxantrone to placebo in 51 patients with RRMS.22 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 IMPACT23 (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/m2) of interferon β1b SC (Betaseron®) was generally less effective than the 250 μg dose. Health related quality of life was measured in 2 studies using different tools, both finding a benefit of the respective β interferon used.58

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

PPMS

β Interferons
The only evidence of the effectiveness of drug treatment in PPMS comes from a single, small (n = 50) trial of interferon β1a IM (Avonex®) at doses of 30 μg, 60 μg ,or placebo once a week for 2 years.24 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.

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

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.25 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 RRMS and SPMS patients. While there were some similarities in patient characteristics across the trials, the size and quality of the trials varied and relevant baseline data was not uniformly reported across
all trials. Natalizumab doses were weight-based in all three trials, although the only dosage that was common amongst the trials was 3 mg/kg. Two of the trials reported effectiveness outcomes, although these were not the primary outcomes in either trial. The longest trial, Miller, et al.,26 had a duration of 12 months, while the other trial was considerably shorter at 24 weeks (Tubridy27). There was no significant difference in change in EDSS between the natalizumab and placebo groups at the final timepoint in both trials that reported this as an outcome, although trials of longer duration are needed to confirm this finding. The total number of relapses reported in each study arm varied considerably between the two trials. Possible reasons for this discrepancy include trial duration (12 months of follow-up vs. 24 weeks of follow-up), total natalizumab dose (up to 18 mg/kg vs. 9 mg/kg), and criteria used to assess relapse.

Mitoxantrone
Indirect Evidence
A well-conducted systematic review compared mitoxantrone (Novantrone®) to placebo using data from four trials.28 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 patients20 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.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 ≥2 and ≤6.5, and exhibiting progression in a pre-trial period).29 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 1 Consensus:
**Medications Included in this report:** Glatiramer Acetate Copaxone®, Mitoxantrone Novantrone®, Natalizumab Tysabri®, Interferon β 1a Avonex®, Interferon β 1a Rebif®, Interferon β 1b Betaseron®

1. All included drugs are modestly effective compared to placebo in relapse prevention and disease progression.
2. There is no evidence of clinical superiority of any of the studied drugs.
3. Limited data suggests that neutralizing antibodies (in β-interferon therapy) may negatively affect relapse rate 3-4 years after treatment.

KQ 2. What is the comparative tolerability and safety of disease-modifying treatments for multiple sclerosis?

RRMS
*Direct Evidence*

**β Interferons**

**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 study\(^9\) found statistically significant differences in the rates of specific adverse events between the 2 interferon β1a’s. Significantly more patients taking interferon β1a IM (Avonex®) experienced flu-like symptoms (53% vs. 45%; $p=0.031$). However, significantly more patients taking interferon β1a SC (Rebif®) experienced injection site reactions (85% vs. 33%; $p<0.001$), abnormal liver function tests (18% vs. 10%, $P=0.003$), and white blood cell dysfunction (14% vs. 5%; $p<0.001$). Differences in withdrawal or early discontinuation overall or due to adverse events were not found. Data on compliance or patient satisfaction with treatment were not recorded.

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

<table>
<thead>
<tr>
<th>Data source</th>
<th>Adverse event</th>
<th>Rate</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 trials</td>
<td>Injection-site reactions</td>
<td>Itching: 43% vs. 7% Swelling: 37% vs. 19% Redness/erythema: 59% vs. 19% Pain: 39% vs. 20%</td>
<td>&lt;0.0001 for all comparisons</td>
</tr>
<tr>
<td>Total n=251</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 trials</td>
<td>Immediate postinjection reactions/ systemic reactions*</td>
<td>33% vs. 8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total n=540</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 trials</td>
<td>Palpitations</td>
<td>9% vs. 2%</td>
<td>0.0178</td>
</tr>
<tr>
<td>Total n=301</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*consisting of transient flushing, chest tightness, sweating, palpitations and anxiety*
One of the glatiramer acetate placebo-controlled trials, Johnson, et al.,\textsuperscript{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**

In the study by Haas, et al.\textsuperscript{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.

**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.\textsuperscript{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.\textsuperscript{19} This led to early cessation of the SENTINEL trial; no cases of PML were reported in the AFFIRM trial.\textsuperscript{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). 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% CI1.41-13.7). No differences were seen between the groups in reporting of other adverse events. Withdrawals due to adverse events are not discussed in detail.

**Additional Evidence of Safety**

**β Interferons**

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. 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.31 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.32 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 β1a treated RRMS patients33. 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. 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®) 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**

Only one additional adverse effect in addition to those already mentioned was found. A small, retrospective study that assessed the risk of potentially permanently disfiguring lipoatrophy with glatiramer acetate use. That study found that 34/76 (45%) of patients identified through chart review had evidence of lipoatrophy. Five of these cases were identified as severe, all cases occurred in women, and four withdrawals were attributed to lipoatrophy.

**Depression**

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

**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...
was undertaken. 37389 patients were followed up, using neurological exam, brain MRI, and cerebrospinal fluid samples. 44 patients (1.3%) had findings of possible PML. Data were then examined by an expert panel; 43 potential cases were ruled out, and one patient refused further follow-up. The authors then estimate the incidence of PML at 1.0 per 1000 treated patients (95% CI 0.2 to 2.8 per 1000) based on the 3 original cases. Because these 3 patients had also been receiving immunomodulators or immunosuppressants, it is recommended that natalizumab be used only as monotherapy.

**Mitoxantrone**
Small (n= 7 to 31) before-after studies of patients with various categories of MS have been reported.144-146 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.38 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 Boneschi39 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).

**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).40 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.
KQ 2 Consensus:

1. There was no difference in withdrawal rates among studied drugs noted, however adverse event reporting was poor.
2. For β-interferons:
   a) There is insufficient evidence to determine a comparative difference between the β-interferons for flu-like symptoms
   b) There is insufficient evidence to determine a relative difference in ALT elevations for the β-interferons.
3. Interferon β1a IM (Avonex®) appears to have a lower injection site reaction compared to the other β-interferons and glatiramer acetate.
4. There is insufficient evidence to determine a relative difference between the β-interferons and glatiramer acetate for depression.
5. Therapy related acute leukemia was reported in 2/1620 patients (both were women) taking minoxantrone.
6. Estimates of progressive multifocal leukoencephalopathy (PML) incidence with natalizumab (Tysabri®) use is 1.0/1000 patients based on three known cases. Because of concerns regarding this the company instituted a risk management plan in cooperation with the FDA known as the TOUCH prescribing program. Patients may only get this medication through this program. See pages 6-7 for details.

KQ 3. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?

The evidence on the use of disease-modifying drugs in patients with a CIS to ultimately prevent progression to MS is limited to 3 trials (7 publications) involving the β interferons. No evidence was found for glatiramer acetate, natalizumab or mitoxantrone.

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

Indirect evidence
Three placebo-controlled trials have been conducted, one with each of the interferon products versus placebo. All 3 trials show a statistically significant reduction in the proportion of patients and the time to converting to clinically definite MS compared to placebo with relative risks or hazard ratios in the 0.5 to 0.65 range and NNT of 6 for interferon β 1b (Betaseron®), 7 for interferon β 1a (Avonex®), and 10 for interferon β 1a (Rebif®).

Evidence suggests that all three β interferon products reduce the probability of converting from CIS to clinically definite MS over 2 to 5 year periods. At 3 years, Avonex® was superior to placebo with a rate ratio of 0.56 (95% CI 0.38-0.81). At 2 years, both Betaseron® and Rebif® were also superior to placebo: rate ratios 0.50 (95% CI 0.36-0.70) and 0.65 (95% CI 0.45 to 0.94) respectively.
KQ 3 Consensus:

1. β-interferons were felt to be more effective than placebo at reducing the probability of converting to clinically definite MS in studies of 2-3 years duration.
2. There is insufficient evidence to determine a comparative difference between the β-interferons in reducing the probability of converting from clinically isolated syndrome (CIS) to clinically definite MS.
3. No data on prevention of CIS from converting to clinically definite MS was found for any of the other included drugs.

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

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

KQ 4 Consensus:

1. A meta-analysis of a small (n=69) population with in-utero exposure to interferon β1a yielded a 29% pregnancy loss vs. 0% in placebo or previous exposure (greater than two weeks).
2. There is insufficient evidence to determine a relative difference between disease-modifying drugs for MS in subpopulations.
Conclusions:

1. There is no evidence of clinical superiority of any of the studied drugs.
2. Limited data suggests that neutralizing antibodies (in β-interferon therapy) may negatively affect relapse rate 3-4 years after treatment.
3. In general adverse event reporting was poor.
4. For β-interferons:
   a) There is insufficient evidence to determine a comparative difference between the β-interferons for flu-like symptoms
   b) There is insufficient evidence to determine a relative difference in ALT elevations for the β-interferons.
5. Interferon β1a IM (Avonex®) appears to have a lower injection site reaction compared to the other β-interferons and glatiramer acetate.
6. Therapy related acute leukemia was reported in 2/1620 patients (both were women) taking minoxantrone.
7. Estimates of progressive multifocal leukoencephalopathy (PML) incidence with natalizumab (Tysabri®) use is 1.0/1000 patients based on three known cases. Because of concerns regarding this the company instituted a risk management plan in cooperation with the FDA known as the TOUCH prescribing program. Patients may only get this medication through this program. See pages 6-7 for details.
8. There is insufficient evidence to determine a comparative difference between the β-interferons in reducing the probability of converting from clinically isolated syndrome (CIS) to clinically definite MS. There is no data on prevention of conversion for any of the other included drugs.
9. A meta-analysis of a small (n=69) population with in-utero exposure to interferon β1a yielded a 29% pregnancy loss vs. 0% in placebo or previous exposure (greater than two weeks).
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