Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Drug Effectiveness Review Project Summary Report – Disease-modifying Drugs for Multiple Sclerosis

Date of Review: November 2016

Date of Last Review: September 2015 (orals only)
Literature Search: Up to January 2016

Current Status of PDL Class:
See **Appendix 1**.

Research Questions:
1. What is the comparative effectiveness and safety of disease-modifying treatments for multiple sclerosis?
2. Does the relationship between neutralizing antibodies and outcomes differ by treatment?
3. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?
4. Do disease-modifying treatments for multiple sclerosis or a clinically isolated syndrome differ in harms?
5. 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?

Conclusions:
- There is low strength evidence from one small RCT that relapse rates were increased with teriflunomide 7 mg orally once daily but not 14 mg orally once daily compared to interferon beta-1a 44 mcg subcutaneously (SC)three times a week (relative risk [RR] 2.74, 95% confidence interval [CI] 1.66 to 4.53 and RR 1.52, 95% CI 0.87 to 2.67, respectively).
- An indirect comparison by network meta-analysis (NMA) showed treatment with fingolimod 0.5 mg once daily resulted in lower risk of relapse than treatment with interferon beta-1a 30 mcg intramuscularly (IM) once a week (RR 0.58, 95% CI 0.45 to 0.75). Definitive conclusions cannot be made regarding relative efficacy from indirect comparative evidence.
- From NMA data, alemtuzumab 12 mg infused once a day for 5 days followed by 12 mg infused once day for 3 days one year later is associated with the lowest risk of relapse (17.3%) and the lowest probability of study withdrawals due to adverse events (70.5%) compared with the other FDA approved MS drugs. However, since this is an indirect comparison, definitive conclusions cannot be made regarding relative efficacy.
- Ocrelizumab and daclizumab may be promising additions to current MS treatment, but additional comparative research is needed to draw definitive conclusions regarding benefits and harms. Specifically, low strength evidence from one randomized controlled trial (RCT) showed that treatment with daclizumab 150 mg SC once a month resulted in lower risk of relapse at week 144 (HR 0.59, 95% CI 0.50 to 0.69) and less disability progression at 24 weeks (HR 0.73, 95% CI 0.55 to 0.98) compared with interferon beta-1a 30 mcg IM once a week. Ocrelizumab is not yet approved by the U.S. Food and Drug Administration (FDA).
- Interferon beta-1a 30 mcg IM once a week (Avonex) appeared to have the lowest immunogenicity compared to the other interferons (interferon beta-1a 22 or 44 mcg SC and interferon beta-1b 250 mcg SC), with incidence of developing neutralizing antibodies ranging from 0% to 14% starting around 9 months

after initiation of treatment. With interferon beta-1a SC (Rebif®), antibodies also appeared around 9 months, with rates of immunogenicity ranging from 11% to 46%. With interferon beta-1b SC (Betaseron), neutralizing antibodies appeared as early as 3 months into treatment in 15% to 45% of patients. No differences in relapse were seen for any of the interferons within 2 years or less. There is insufficient evidence to determine what kind of impact the development of neutralizing antibodies has on disease progression.

- For patients with clinically isolated syndrome (CIS), there were no head-to-head trials of the drugs included in the DERP review to evaluate safety.
- Compared to interferon beta-1a (Avonex), withdrawals due to adverse events were more likely with teriflunomide 7 mg, glatiramer or interferon beta-1b (Betaseron), and less likely with teriflunomide 14 mg than with glatiramer.
- There was low strength evidence that treatment with daclizumab 150 mg SC once a month was associated with higher withdrawals due to adverse events (RR 1.57, 95% CI 1.21 to 2.03) compared with interferon beta-1a 30 mcg IM once a week, although there was similar risk of experiencing any adverse event or serious adverse event.
- One RCT provided low strength evidence of fewer early withdrawal due to adverse events with teriflunomide compared with interferon beta-1a 44 mcg (RR 0.44, 95% CI 0.25 to 0.76), although there were no differences in risk of experiencing any adverse event or serious adverse event.
- Fingolimod exposure in utero may be associated with increased risk of poor fetal outcomes.

Recommendations:

- No changes to the PDL are recommended after review of updated evidence and comparative drug costs in the executive session.
- Revise PA criteria to include assessment of lymphocyte count before initiating therapy with dimethyl fumarate.

Previous Conclusions:

- There is insufficient comparative evidence between oral disease modifying drugs for multiple sclerosis (MS) and other oral or injectable disease-modifying therapies.
- Moderate-quality evidence demonstrates the proportion of patients who experience at least one relapse over 2 years is reduced with use of dimethyl fumarate compared to placebo (relative risk [RR] 0.58; 95% CI, 0.50 to 0.67, p<0.00001) but not when compared to glatiramer acetate (RR 0.91; 95% CI, 0.72 to 1.13); however, the quality of the evidence to support benefit of dimethyl fumarate to slow worsening disability versus placebo is low (RR 0.66; 95% CI, 0.53 to 0.81).
- According to the National Institute for Health and Clinical Excellence (NICE), there is low quality evidence fampridine (i.e., dalfampridine), which is not a disease-modifying drug, may be more effective than placebo in response outcomes to different walking ability parameters are assessed; however, there is low quality evidence that there is no difference in efficacy between fampridine and placebo in time to walk 8 meters and there is insufficient evidence to determine if fampridine improves gait speed versus placebo. In addition, there is low quality evidence that there is no difference in the MS walking scale (MSWS-12) scores with fampridine compared to placebo. The NICE recommends against the use of dalfampridine due to poor cost effectiveness.
- There is low-quality evidence, based on one phase 3 trial, that a daily dose of 7 mg and 14 mg of teriflunomide may reduce time to first relapse in patients with a first clinical episode suggestive of MS (14 mg vs. placebo: hazard ratio [HR] 0.574 [95% CI, 0.379-0.869; p=0.0087] and 7 mg vs. placebo: HR 0.628 [95% CI, 0.416-0.949; p=0.0271]. It is currently FDA-approved to treat relapsing-remitting forms of multiple sclerosis (RRMS).
- A follow-up phase 3 trial of fingolimod confirms results from previous phase 3 trials, and provides moderate-quality evidence the drug significantly reduces relapse rates versus placebo in patients with RRMS (fingolimod 0.5 mg: rate ratio [RR] 0.52 (95% CI, 0.40-0.66; p<0.0001). It is currently FDA-approved to treat RRMS, to reduce the frequency of clinical exacerbations, and to delay the accumulation of physical disability in these patients.

Previous Recommendations:

- Update clinical prior authorization criteria for oral MS drugs to reflect Guideline Note 95 that restricts coverage to RRMS only.
- No change to the current PDL recommended at this time.

Methods:

The May 2016 Drug Class Review on Disease-modifying Drugs for Multiple Sclerosis by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class. [1]

The final original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

The focus of the DERP update report is on disease-modifying drugs (DMDs), which are not designed to manage acute symptoms of MS but are designed to prevent relapses and slow the natural course of the disease over time. The DMDs that have been evaluated in the treatment of MS are outlined in **Table 1**. Of note, ocrelizumab received breakthrough therapy designation by the U.S. Food and Drug Administration (FDA) for treatment of PPMS in February 2016 and is included in the DERP update although it is not yet available in U.S. markets. Genentech, the manufacturer of ocrelizumab, announced in June 2016 that the FDA accepted the company's Biologic License Application (BLA) for the treatment of RRMS and PPMS. The targeted action date for FDA review is December 28, 2016.

Table 1: Disease-Modifying Drugs used to treat MS

Generic Name	Brand Name	Dose/Route/Frequency	FDA Indication
Oral Agents			
Fingolimod	Gilenya	0.5mg PO once daily	RRMS
Teriflunomide	Aubagio	7 mg or 14 mg PO once daily	RRMS
Dimethyl Fumarate	Tecfidera	240 mg PO twice a day	RRMS
Injectable Agents			
Glatiramer Acetate	Copaxone, Glatopa	20 mg SC once daily; OR 40 mg SC three times a week at least 48 hours apart	RRMS
Interferons			
Interferon beta-1a	Avonex	30 mcg IM once weekly	RRMS
Interferon beta-1a	Rebif	22 or 44 mcg SC three times a week	RRMS
Interferon beta-1b	Betaseron, Extavia	250 mcg SC every other day	RRMS
Peginterferon beta-1a	Plegridy	125 mcg SC every 14 days	RRMS

Monoclonal Antibodies			
Alemtuzumab	Lemtrada	Intravenous infusion for 2 treatment courses. (Total duration of therapy: 24 months) First course: 12 mg once a day for 5 days (total 60 mg). Second course: 12 mg once a day for 3 days (total 36 mg). Begin 12 months after the first treatment course.	RRMS Because of its safety profile, use should be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.
Daclizumab High Yield Process (HYP)	Zinbryta	150 mg SC once a month	RRMS Because of its safety profile, use should be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS
Ocrelizumab	NA	Intravenous infusion	Not FDA approved. Phase 3 trials are underway in RRMS and PPMS.

Abbreviations: FDA = U.S. Food and Drug Administration; IM = Intramuscular; MS = multiple sclerosis; NA = not applicable; PO = Oral; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SC= Subcutaneous

The DERP drug class review on DMDs for MS was the third update of the original report which was published in July 2007. The literature search was conducted through January 2016. The DERP literature search identified a total of 5,906 citations from searching electronic databases, reviews of reference lists, pharmaceutical manufacturer dossier submissions, and peer review comments. Thirty-nine head-to-head trials, 6 observational studies and 4 systematic reviews were included in the update. Most of the studies evaluated adult patients with RRMS, although patients with the other 3 forms of MS were included in the updated report. Adult patients with a clinical isolated syndrome (CIS) also known as 'first demyelinating event', 'first clinical attack suggestive of MS', or mono-symptomatic presentation were also included. The Oregon Health Evidence Review Commission (HERC) has stipulated via Guideline Note 95 that once a diagnosis of primary progressive or secondary progressive multiple sclerosis is reached, immune modifying therapies are not funded.[2] This summary report of the DERP findings will only focus on RRMS and CIS those are the only HERC funded forms of MS.

Effectiveness outcomes analyzed in the DERP update were: disability, clinical exacerbations/relapse, quality of life, functional outcomes (e.g. wheel chair use, time lost from work), and persistence (discontinuation rates). The effectiveness assessment of CIS outcomes included the same parameters for MS but added an additional outcome of progression to MS. Harms were assessed by evaluating the following: overall rate of adverse effects, withdrawals due to adverse effects or drug discontinuations due to adverse effects, serious adverse events, and specific adverse events (cardiovascular, hepatotoxicity, progressive multifocal leukoencephalopathy, secondary cancers, etc.). Comparative observational studies with 2 concurrent arms of at least 100 patients each and duration greater than 1 year were included to evaluate DMD harms.

For this third update, DERP conducted a NMA of RCTs in patients with RRMS and a NMA in patients with CIS. The authors compared their findings to a Cochrane NMA and pointed out when the DERP findings were not consistent with the Cochrane analysis. NMA is a procedure that permits inferences into the comparative effectiveness of interventions that may or may not have been evaluated directly against each other.[3] Estimates of treatment effects from NMAs should be interpreted with caution as treatment rankings or probabilities can be misleading.[3] The DERP authors note that in the absence of head-to-head evidence, the strength of evidence generated from NMA is low for indirect comparisons.

Summary Findings

1. What is the comparative effectiveness of disease modifying treatments for multiple sclerosis?
Two systematic reviews conducted a NMA to assess the effectiveness of drugs used to treat MS. One NMA limited comparisons of interferons to other injectable medications. The other NMA included all therapies except for ocrelizumab. A third NMA by the DERP reviewers included ocrelizumab at approved doses and dosing schedules for treatment durations up to 36 months. All drug formulations were evaluated in the dosing regimens outlined in **Table 1**. Thirty two studies including 18,576 subjects were included in the DERP NMA to assess risk of relapse in RRMS patients.

Daclizumab vs. Interferon beta-1a (Avonex)

- A randomized controlled trial (RCT) conducted in 1,841 patients with RRMS found low strength evidence that treatment with daclizumab 150 mg SC every 4 weeks resulted in a lower estimated risk of relapse at week 144 than treatment with interferon beta-1a 30 mcg (33% vs 49%, HR 0.59, 95% CI 0.50 to 0.69) and less estimated confirmed disability progression at 24 weeks (13% vs 18%, HR 0.73, 95% 0.55 to 0.98), but there were no statistically significantly differences in 12 week sustained disability progression. Annualized relapse rates were also lower with daclizumab (0.22 vs. 0.39, p<0.001). However, disability progression at week 144 was not significantly different between daclizumab and interferon beta-1a 30 mcg (16% vs. 20%, HR 0.84, 95% CI 0.66 to 1.07).

Alemtuzumab vs. Interferon beta-1a (Rebif)

- Treatment with interferon beta-1a 44 mcg SC results in higher risk of relapse when compared to alemtuzumab 12 mg (RR 1.67; 95% CI 1.37 to 2.04) in the DERP NMA. Similar results were noted with the lower 22 mcg dose of interferon beta-1a (RR 2.03; 95% CI 1.51 to 2.74). These conclusions are based on low strength evidence.

Glatiramer vs Dimethyl fumarate

- In the DERP NMA, no differences were found in the risk of relapse between glatiramer 20 mg or 40 mg SC compared to oral dimethyl fumarate 240 mg twice daily (RR 1.15; 95% CI 0.89 to 1.48, and RR 0.99; 95% CI 0.68 to 1.43, respectively). In addition, no significant differences were noted in annualized relapse rates between glatiramer and dimethyl fumarate in the Cochrane NMA. These conclusions are based on low strength evidence.

Glatiramer vs Interferon beta-1a (Avonex) and Interferon beta-1b (Betaseron)

- In the DERP NMA, no differences in relapse rates were noted between treatment with glatiramer 20 mg, glatiramer 40 mg, interferon beta-1a 22 mcg, interferon beta-1a 44 mcg, or interferon beta-1b 250 mcg. Results for annualized relapse rate from the Cochrane NMA were consistent with the DERP in relation to risk of relapse. This is based on low strength evidence.

Teriflunomide vs. Interferon beta-1a (Rebif)

- One RCT (N=324) compared a minimum of 48 weeks treatment (maximum 115 weeks) with teriflunomide 7 mg, teriflunomide 14 mg, and interferon beta-1a 44 mcg SC and found no differences between treatments in time to failure, defined as confirmed relapse or permanent treatment discontinuation (36% vs 33% vs 37%, respectively) at 48 weeks. There was a higher risk of relapse with lower dose teriflunomide compared with higher dose (42% vs 23%, RR 1.80, 95% CI 1.21 to 2.69) and low strength evidence of increased relapse risk with teriflunomide 7 mg versus interferon beta-1a 44ug SC (42% vs 16%, RR 2.74, 95% CI 1.66 to 4.53). There was low strength evidence no difference in risk of relapse between higher dose teriflunomide and interferon beta-1a (RR 1.52, 95% CI 0.87 to 2.67). Adjusted annualized relapse rates were also higher with teriflunomide 7 mg compared with interferon beta-1a (0.41 vs 0.22, RR 1.90, 95% CI 1.05 to 3.43).

- In the DERP NMA, no differences in risk of relapse between treatments with teriflunomide 7 mg, teriflunomide 14 mg, and interferon beta-1a 22 mcg SC were noted (RR 0.82 to 1.10) based on low strength evidence. However, treatment with teriflunomide 7 mg was associated with increased risk of relapse compared with interferon beta-1a 44 mcg (RR 1.32; 95% CI 1.01 to 1.72). The Cochrane NMA showed no difference between teriflunomide and interferon beta-1a in annualized relapse rates, but teriflunomide doses were combined in that analysis.

Fingolimod vs Interferon beta-1a (Avonex)

- The DERP NMA included treatment with oral fingolimod 0.5 mg once daily resulted in lower risk of relapse than treatment with interferon beta-1a 30 mcg IM (RR 0.60; 95% CI 0.47 to 0.76). Fingolimod was associated with reduced annualized relapse rate compared with interferon beta-1a at 24 months but not at 12 months based on low strength evidence.

Pegylated interferon beta-1a vs. Placebo

- In one placebo-controlled RCT, 1512 RRMS patients were treated with pegylated interferon beta-1a 125 mcg SC administered every 2 or 4 weeks. There was moderate strength of evidence that risk of relapse was reduced with peginterferon compared with placebo (18% vs. 29%; HR 0.61; 95% CI 0.47 to 0.80: 22% vs. 29%; RR 0.74; 95% CI 0.59 to 0.92, respectively). Annualized relapse rates were 0.26 and 0.29 for peginterferon compared with 0.40 for placebo ($p<0.05$). Disability progression also favored peginterferon versus placebo (7% vs. 11%, HR 0.62, 95% CI 0.40 to 0.97) for both treatment regimens.

Interferons

- The DERP NMA showed that interferon beta-1a 44 mcg SC (Rebif) and interferon beta-1b 250 mcg SC (Betaseron) are associated with a relative lower risk of relapse compared with interferon beta-1a 30 mcg (Avonex) by 19% and 29% (RR 0.81; 95% CI 0.68 to 0.96, and RR 0.71; 95% CI 0.59 to 0.86, respectively). Pegylated interferon beta-1a is also associated with lower relapse risk versus interferon beta-1a 30 mcg (RR 0.67; 95% CI 0.47 to 0.95). Other treatment comparisons between interferons were not significantly different. The Cochrane NMA showed no differences in annualized relapse rates between interferons at 12 or 24 months, although point estimates favored interferon beta-1a 44 mcg SC (at 12 and 24 months) and beta-1b 250 mcg SC (at 24 months) over interferon beta-1a 30 mcg IM. An additional systematic review compared pegylated interferon beta-1a with the other interferons, and although peginterferon was numerically superior to the other interferons in annualized relapse rates, no comparison achieved statistical significance.

Ocrelizumab compared to interferon beta-1a (Avonex and Rebif)

- One published RCT compared ocrelizumab with interferon beta-1a 30 mcg and placebo. The trial included 220 patients from North America, east-central Europe and Asia, western Europe, and Latin America, although most patients were white (96%), female (65%), and had 2 or 3 relapses in the past 3 years (83%). There were 32 patients who experienced relapses within 24 weeks of treatment. Compared to interferon beta-1a 30 mcg IM, treatment with ocrelizumab 600 mg and 2000 mg resulted in a similar risk of relapse (5% vs. 17%, RR 0.33, 95% CI 0.09 to 1.14; 7% vs. 17%, RR 0.44, 95% CI 0.14 to 1.33, respectively), although annualized relapse rates versus interferon beta-1a 30 mcg were significantly lower for ocrelizumab 600 mg (0.13 vs. 0.36, $p=0.03$). When the two doses of ocrelizumab were combined (the relapse rate for ocrelizumab 2000 mg was higher than the rate for 600 mg), there was low strength evidence that ocrelizumab was associated with lower relapse rates than interferon beta-1a, 6% vs 17%, RR 0.38, 95% CI 0.15 to 0.97. Annualized relapse rates by week 24 were 0.13 to 0.17 with ocrelizumab, 0.36 with interferon, and 0.64 for placebo.

- In the DERP NMA, treatment with ocrelizumab 600 mg IV is associated with lower risk of relapse when compared to interferon beta-1a 30 mcg IM (Avonex) [RR 0.24; 95% CI 0.07 to 0.76] and interferon beta-1a 22 mcg SC (Rebif) [RR 0.27; 95% CI 0.08 to 0.89] but not interferon beta-1a 44 mcg SC (RR 0.33; 95% CI 0.10 to 1.07). Treatment with ocrelizumab 2000 mg IV is associated with lower risk of relapse compared to interferon beta-1a 30 mcg IM (RR 0.31; 95% CI 0.11 to 0.87). These conclusions are based on low strength evidence.

2. Does the relationship between neutralizing antibodies and outcomes differ by treatment?

- Neutralizing antibodies are known to develop in some patients taking beta interferons, potentially interfering with effectiveness. One systematic review focused solely on interferon therapy and analyzed 9 comparative observational studies that reported the presence of neutralizing antibodies in patients taking interferons. Interferon beta-1a IM (Avonex®) appeared to have the lowest immunogenicity, with rates of development of neutralizing antibodies of 0% to 14% reported, starting around 9 months of treatment. With interferon beta-1a SC (Rebif®), antibodies also appeared around 9 months, with rates of immunogenicity from 11% to 46%; with interferon beta-1b SC (Betaseron®), neutralizing antibodies appeared as early as 3 months into treatment in 15% to 45% of patients. No difference in relapse is seen for any of the interferons in trials with short follow-up (2 years or less) and there is inadequate evidence to conclude there is an impact on disease progression.

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

- There were no head-to-head trials of included drugs in patients with clinically isolated syndrome (CIS). The DERP NMA of the comparative effectiveness of the 3 interferons and 2 doses of teriflunomide found no statistically significant differences in rates of progression to MS through indirect analysis.

4. Do disease-modifying treatments for multiple sclerosis or a clinically isolated syndrome differ in harms?

To evaluate study drug tolerance/safety, the DERP reviewers conducted an NMA with withdrawals due to adverse events/study drug discontinuations as the outcome. Thirty three trials (n=19,191) evaluated study withdrawal due to adverse events. There were few significant differences between treatments. A sensitivity analysis for study withdrawal due to adverse events was not conducted. Moderate strength evidence showed that alemtuzumab 12 mg had the highest probability of being the best treatment with lower rates of study withdrawals due to adverse events (70.5%) followed by placebo (13.1%), which is consistent with the Cochrane NMA.

Comparative harms of DMDs in multiple sclerosis

Fingolimod

- In the DERP NMA, no difference was noted between fingolimod 0.5 mg and interferon beta-1a 30 mcg IM (Avonex) in study withdrawals due to adverse events (RR 1.16; 95% CI 0.65 to 2.08).

Teriflunomide

- One head-to-head trial (n=324) provided low strength evidence of fewer study withdrawals with teriflunomide (pooled data from 7 mg and 14 mg doses) compared with interferon beta-1a 44 mcg SC (Rebif) [10% vs. 22%, RR 0.44; 95% CI 0.25 to 0.76], although there was no difference between treatments in serious adverse events (8% vs 7%, RR 1.18; 95% CI 0.51 to 2.74) or in risk of experiencing any adverse event (93% vs. 96%, RR 0.97; 95% CI 0.92 to 1.02). Gastrointestinal disorders were more common in the groups receiving oral teriflunomide compared to injectable interferon (40% vs. 27%, RR 1.51; 95% CI 1.06 to 2.17) while influenza-like illness was less likely with teriflunomide (3% vs. 53%, RR 0.06; 95% CI 0.03 to 0.13).
- Treatment with teriflunomide 7 mg and 14 mg was associated with no difference in withdrawals due to adverse events when compared with interferon beta-1a 44 mcg SC (RR 0.57; 95% CI 0.32 to 1.02, and RR 0.72; 95% CI 0.42 to 1.25, respectively) based on the DERP meta-analysis, although point estimates favored teriflunomide. The NMA conducted by Cochrane found no difference at 24 months but found interferon beta-1a all doses associated

with lower risk of withdrawal compared with teriflunomide all doses (RR 0.46; 95% CI 0.28 to 0.78). However, confidence limits for all comparisons lack precision.

Glatiramer acetate

- One placebo-controlled trial provided low quality evidence that glatiramer 40 mg given three times weekly was associated with a borderline increase in withdrawals due to adverse events compared with placebo (3% vs. 1%, RR 2.36; 95% CI 0.99 to 5.65).
- A fair-quality observational study analyzed patients treated for 2 years or more with glatiramer or an interferon. Ninety percent of included patients had RRMS and 10% had CIS. Rates of any adverse event were similar across the three interferon formulations (range 53% to 56%), and lower in patients given glatiramer (38.6%), though differences across all groups did not reach statistical significance (p=0.052). Flu-like symptoms did differ across treatments, as did injection-site reactions (both p<0.001).
- The DERP meta-analysis found no differences between oral dimethyl fumarate 240 mg twice daily and either glatiramer 20 mg SC (RR 0.85; 95% CI 0.49 to 1.48) or glatiramer 40 mg SC (RR 0.69; 95% CI 0.26 to 1.85) in study withdrawal due to adverse events. No differences in early withdrawal due to adverse events were noted between glatiramer 20 mg or 40 mg and any of the interferons (beta-1a 44 mcg SC, 22 mcg SC, 30 mcg IM, and beta-1b 250 mcg), including pegylated interferon, as well.

Interferons

- One trial (n=1512) compared pegylated interferon beta-1a 125 mcg SC (Plegridy) administered every 2 weeks or every 4 weeks to placebo. The study found that interferon beta-1a 125 mcg SC every 2 weeks (the approved dose) was associated with increased withdrawals due to adverse events and severe adverse events compared with placebo (5% vs. 1%, RR 3.49; 95% CI 1.52 to 7.99, and 18% vs. 11%, RR 1.66; 95% CI 1.21 to 2.28, respectively). There was little difference between the two dosing schedules of pegylated interferon on frequency of adverse events.
- In one head-to-head trial, alanine and aspartate aminotransferase levels (ALT/AST) were increased with interferon beta-1a 44 mcg SC (Rebif) (12% vs. 2%, RR 7.88; 95% CI 1.01 to 61) compared with interferon beta-1b 250 mcg SC (Betaseron). Injection site reactions were also twice as high with interferon beta-1a (28% vs. 14%, RR 1.97; 95% CI 0.96 to 4.05) compared with interferon beta-1b, whereas fatigue (14% vs. 7%, RR 3.05; 95% CI 0.86 to 11) and depression were twice as common with interferon beta-1b (13% vs. 6%, RR 2.03; 95% CI 0.64 to 6.41), although none of these differences were statistically significant. There was no difference between treatment with interferon beta-1a and interferon beta-1b in withdrawals due to adverse events (14% vs. 11%, RR 1.27, 95% CI 0.50 to 3.19).
- In one small head-to-head trial (n=188), there was no difference in withdrawal due to adverse events between interferon beta-1b 250 mcg SC (Betaseron) and interferon beta-1a 30 mcg (Avonex) IM (5% vs. 1%, RR 4.79; 95% CI 0.57 to 40).
- The DERP NM indicated no difference between either treatment with interferon beta-1a 44 mcg SC or interferon beta-1a 22 mcg SC (Rebif) and interferon beta-1b 250 mcg SC (Betaseron) in study withdrawals due to adverse events (RR 0.96; 95% CI 0.48 to 1.92, and RR 0.72; 95% CI 0.20 to 2.57, respectively). Similar results were seen between interferon beta-1a 30 mcg IM (Avonex) and interferon beta-1a 44 mcg SC or interferon beta-1a 22 mcg (Rebif) SC in study withdrawals due to adverse events (RR 0.59; 95% CI 0.33 to 1.05, and RR 0.78; 95% CI 0.23 to 2.63, respectively). Furthermore, no difference in risk of study withdrawal due to adverse events between interferon beta-1b 250 mcg SC (Betaseron) and interferon beta-1a 30 mcg (Avonex) IM (RR 1.77; 95% CI 0.80 to 3.91) was found.
- A pooled analysis of the risk of malignancy in patients treated with interferon beta-1a SC (Rebif) included evidence from 5 placebo-controlled trials. The analysis of placebo-controlled trials showed a lower incidence of cancer in patients treated with interferon than in those receiving placebo; however, the

difference was not statistically significant (incidence 2.5 neoplasms per 1000 patient-years, 95% CI 0.9 to 5.4 for interferon vs. 6.3, 95% CI 2.9 to 11.9 for placebo).

Alemtuzumab

- In a publication detailing thyroid dysfunction, 42 out of 108 patients (39%) treated with alemtuzumab 12 mg and 31 out of 108 patients (29%) treated with alemtuzumab 24 mg developed thyroid dysfunction as compared with 7 out of 107 patients treated with interferon beta-1a 44 mcg SC (7%). Types of thyroid dysfunction ranged from hyperthyroidism to hypothyroidism.
- The DERP NMA found increased study withdrawals due to adverse events with interferon beta-1a 44 mcg SC (RR 3.35; 95% CI 1.76 to 6.36), but not interferon beta-1a 22 mcg SC (RR 2.51; 95% CI 0.71 to 8.89), compared with alemtuzumab 12 mg.

Ocrelizumab

- Three fair-quality trials provided safety and tolerability evidence for ocrelizumab. One placebo-controlled trial (n=218) compared ocrelizumab treatment with interferon beta-1a 30 mcg IM and found no difference between ocrelizumab 600 mg or 2000 mg compared with interferon beta-1a 30 mcg IM in withdrawals due to adverse events (4% vs. 2%, RR 1.97; 95% CI 0.18 to 21, and 2% vs. 2%, RR 0.98; 95% CI 0.06 to 15, respectively) or in serious adverse events (2% vs. 4%, RR 0.49; 95% CI 0.05 to 5.26, and 6% vs. 4%, RR 1.47; 95% CI 0.26 to 8.47, respectively). However, one patient who was treated with ocrelizumab 2000 mg died after she developed thrombocytopenia followed by disseminated intravascular coagulopathy and multi-organ-dysfunction; she suffered brain edema and died on day 15 of hospitalization from transcranial herniation. The relation to ocrelizumab is unknown. Additionally, treatment with ocrelizumab was associated with mild to moderate infusion-related reactions, especially with the initial dose which affected 39% of subjects on the first day of treatment.
- Two unpublished randomized trials (Opera I and Opera II) treated 1651 total patients with ocrelizumab 600 mg or interferon beta-1a 44 mcg SC. Opera 1 was shared at an international conference and Opera II data was shared by Genentech, the manufacturer of ocrelizumab. Withdrawals due to adverse events were similar for both trials and were lower in the ocrelizumab arms (4% vs. 6%, RR 0.58; 95% CI 0.37 to 0.91) although the same percentage of patients experienced at least one adverse event (83%) in both treatment groups. Serious adverse events were not different between groups (7% vs. 9%, RR 0.79; 95% CI 0.57 to 1.11). There was one death due to suicide in the ocrelizumab 600 mg group and two deaths in the interferon beta-1a 44 mcg SC group due to suicide and mechanical ileus (RR 0.50; 95% CI 0.05 to 5.51). The most common adverse events were infusion-related reactions in the ocrelizumab groups resulting in 11 study withdrawals (1%) during the first ocrelizumab treatment.
- Estimates of withdrawals due to adverse events from the DERP NMA are consistent with trials outlined above which indicates no difference between ocrelizumab 600 mg and either interferon beta-1a 30 mcg IM (Betaseron) or interferon beta-1a 44 mcg SC (Rebif).
- A fair-quality placebo-controlled trial of ocrelizumab in PPMS patients (n=732) provided insufficient evidence to compare all-cause mortality between the two treatment groups (RR 2.0, 95% CI 0.30 to 13; 5 deaths occurred; 4/486 in ocrelizumab group; 1/239 in placebo group). There was low-strength evidence that rates of serious adverse events did not differ between groups (RR 0.92, 95% CI 0.69 to 1.2). Overall, withdrawals were less likely with ocrelizumab (RR 0.59, 95% CI 0.46 to 0.76), but withdrawals due to adverse events were not reported. Rates of infection did not differ between treatment arms (RR 1.0, 95% CI 0.93 to 1.1). More malignancies (2.3% vs. 0.8%) occurred in patients given ocrelizumab than in those receiving placebo, but the difference was not statistically significant (RR 2.7, 95% CI 0.68 to 11).

Daclizumab

- Treatment with daclizumab 150 mg SC every 4 weeks was compared with treatment with interferon beta-1a 30 mcg IM weekly for up to 144 weeks in a RCT of 1841 RRMS patients. While almost all patients experienced at least one adverse event (91% both groups), there was low strength evidence that patients who received daclizumab were more likely to withdraw from the study due to adverse events, excluding relapse compared with patients treated with interferon beta-1a (14% vs. 9%, RR 1.57; 95% CI 1.21 to 2.03). However, there was low strength evidence that the risk of having a serious adverse event was similar between study treatments (24% vs. 21%, RR 1.14; 95% CI 0.96 to 1.35). Both infections and serious infections were more likely with daclizumab (65% vs. 57%, RR 1.14; 95% CI 1.06 to 1.23, and 4% vs. 2%, RR 2.68; 95% CI 1.49 to 4.81). Additionally, there were 5 deaths during the study, although none were considered treatment-related by investigators blinded to treatment allocation--1 death in the daclizumab group vs. 4 in the group receiving interferon (RR 0.25; 95% CI 0.03 to 2.24).
- In a randomized trial of daclizumab 150 mg and 300 mg compared with placebo, most patients experienced at least one adverse event (daclizumab doses pooled 74% vs. 79%; RR 0.94; 95% CI 0.86 to 1.03) and there were no differences between treatment in risk of experiencing any serious adverse event, excluding relapse (8% vs. 6%; RR 1.39; 95% CI 0.73 to 2.62).
- The DERP N found no difference in withdrawals due to adverse events between daclizumab 150 mg or 300 mg and interferon beta-1a 30 mcg IM (RR 1.62; 95% CI 0.94 to 2.79, and RR 2.62; 95% CI 0.85 to 8.12, respectively) but confidence intervals are imprecise.

Comparative harms of DMDs in Clinically Isolated Syndrome

- No head to head evidence in patients with CIS evaluated harms of DMDs. The DERP reviewers completed a NMA of the comparative harms of glatiramer, the 3 interferons, and 2 doses of teriflunomide in CIS. For withdrawals due to adverse events, confidence intervals for many comparisons were wide; however, available evidence suggested that withdrawal rates were higher with teriflunomide 7 mg, glatiramer, or interferon beta-1b (Betaseron), each compared with interferon beta-1a IM (Avonex). Indirect analysis showed there was also a statistically significant difference in withdrawals due to adverse events between teriflunomide 14 mg and glatiramer 20 mg (RR 0.24, 95% CI 0.07 to 0.86).

5. 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?

- There were no differences found in annualized relapse rate between fingolimod 0.5 mg and interferon beta-1a 30 mcg IM when patients were stratified based on gender, age, treatment history, and number of relapses in the past 1 to 2 years. Although the treatment effect with fingolimod on annualized relapse rates were greatest in females and those under 40 years of age, confidence intervals overlapped.
- There was no difference in effect on annualized relapse rates of daclizumab 150 mg compared with interferon beta-1a 30 mcg IM based on gender (Male: ARR 0.46, 95% CI 0.35 to 0.62; Female: ARR 0.59, 95% CI 0.49 to 0.72).
- Fingolimod exposure in utero may be associated with increased risk of poor fetal outcomes. The results of 74 pregnancies (66 pregnancies with in utero exposure to fingolimod) resulted in 35 deliveries with 1 congenital unilateral posteromedial bowing of the tibia and 1 infant with acrania (both were exposed in utero). There were 25 elective abortions with 1 Tetrology of Fallot, 1 ectopic pregnancy, 1 intrauterine death, and 1 pregnancy not developing normally.

References:

1. Selph S, Holmes R, Thakurta S, et al. Disease-Modifying Drugs for Multiple Sclerosis Drug Class Review: Final Update 3 Report, May 2016. Drug Effectiveness Review Project at the Pacific Northwest Evidence Practice Center, Portland, Oregon.

2. Health Evidence Review Commission Prioritized List Overview. https://www.oregon.gov/oha/herc/Pages/Prioritized-List-Overview.aspx. Accessed August 26, 2016.

3. Mills EJ, Thorlund K, Ioannidis JPA. Demystifying trial networks and network meta-analysis. *BMJ*. 2013;346:f2914. doi:10.1136/bmj.f2914.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
SUB-Q	SYRINGE	COPAXONE	GLATIRAMER ACETATE	Y
SUB-Q	SYRINGE	GLATOPA	GLATIRAMER ACETATE	Y
INTRAMUSC	KIT	AVONEX ADMINISTRATION PACK	INTERFERON BETA-1A/ALBUMIN	Y
SUB-Q	SYRINGE	REBIF	INTERFERON BETA-1A/ALBUMIN	Y
SUB-Q	PEN INJCTR	REBIF REBIDOSE	INTERFERON BETA-1A/ALBUMIN	Y
INTRAMUSC	PEN IJ KIT	AVONEX PEN	INTERFERON BETA-1A	Y
INTRAMUSC	SYRINGE	AVONEX	INTERFERON BETA-1A	Y
INTRAMUSC	SYRINGEKIT	AVONEX	INTERFERON BETA-1A	Y
SUB-Q	KIT	BETASERON	INTERFERON BETA-1B	Y
SUB-Q	KIT	EXTAVIA	INTERFERON BETA-1B	Y
INTRAVEN	VIAL	LEMTRADA	ALEMTUZUMAB	N
ORAL	TAB ER 12H	AMPYRA	DALFAMPRIDINE	N
ORAL	CAPSULE DR	TECFIDERA	DIMETHYL FUMARATE	N
ORAL	CAPSULE	GILENYA	FINGOLIMOD HCL	N
SUB-Q	SYRINGE	COPAXONE	GLATIRAMER ACETATE	N
INTRAMUSC	PEN INJCTR	AVONEX PEN	INTERFERON BETA-1A	N
SUB-Q	VIAL	EXTAVIA	INTERFERON BETA-1B	N
INTRAVEN	VIAL	MITOXANTRONE HCL	MITOXANTRONE HCL	N
SUB-Q	SYRINGE	PLEGRIDY	PEGINTERFERON BETA-1A	N
SUB-Q	PEN INJCTR	PLEGRIDY PEN	PEGINTERFERON BETA-1A	N
ORAL	TABLET	AUBAGIO	TERIFLUNOMIDE	N

Oral Multiple Sclerosis Drugs

Goal(s):
- Promote safe and effective use of oral disease-modifying multiple sclerosis drugs
- Promote use of preferred multiple sclerosis drugs.

Length of Authorization:
- Up to 12 months

Requires PA:
- Fingolimod
- Teriflunomide
- Dimethyl Fumarate

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does the patient have a diagnosis of primary or secondary progressive multiple sclerosis?	**Yes:** Pass to RPh. Deny; not funded by the OHP. See Guideline Note 95 in the Prioritized List of Health Services.	**No:** Go to #3

Approval Criteria		
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #4
4. Has the patient failed or cannot tolerate a trial of interferon beta 1a or interferon beta 1b, and glatiramer?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the patient on concurrent treatment with a disease modifying drug (i.e. interferon beta 1B, glatiramer acetate, interferon beta 1A, natalizumab, mitoxantrone)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #7
7. Is the prescription for teriflunomide?	**Yes:** Go to #8	**No:** Go to #10
8. Is the patient of childbearing potential?	**Yes:** Go to #9	**No:** Approve for up to 1 year.
9. Is the patient currently on a documented use of reliable contraception and is there documentation of a negative pregnancy test prior to initiation of teriflunomide?	**Yes:** Approve for up to 1 year.	**No:** Pass to RPh. Deny; medical appropriateness.
10. Is the prescription fingolimod?	**Yes:** Go to #11	**No:** Go to #14
11. Does the patient have evidence of macular edema?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #12

Approval Criteria		
12. Does the patient have preexisting cardiac disease, risk factors for bradycardia, or is on anti-arrhythmic, beta-blockers, or calcium channel blockers?	**Yes:** Go to #13	**No:** Approve up to 1 year.
13. Has the patient had a cardiology consultation before initiation (see clinical notes)?	**Yes:** Approve up to 1 year.	**No:** Pass to RPh. Deny; medical appropriateness.
14. Is the prescription for dimethyl fumarate?	**Yes:** Go to # 15	**No:** Pass to RPh. Deny; medical appropriateness.
15. Does patient have a baseline CBC with lymphocyte count greater than 500/µL?	**Yes:** Approve for up to 1 year	**No:** Pass to RPh. Deny; medical appropriateness.

Fingolimod Clinical Notes:

- Because of bradycardia and atrioventricular conduction, patients must be observed for 6 hours after initial dose in a clinically appropriate area.
- Patients on antiarrhythmics, beta-blockers or calcium channel blockers or with risk factors for bradycardia (h/o MI, age >70 yrs., electrolyte disorder, hypothyroidism) may be more prone to development of symptomatic bradycardia and should be initiated on fingolimod with caution. A cardiology evaluation should be performed before considering treatment.
- Injectable disease modifying treatments remain first-line agents in MS therapy.
- An ophthalmology evaluation should be repeated 3-4 months after fingolimod initiation with subsequent evaluations based on clinical symptoms.

Teriflunomide Clinical Notes:

- Before starting teriflunomide, screen patients for latent tuberculosis infection with a TB skin test, exclude pregnancy, confirm use of reliable contraception in women of childbearing potential, check blood pressure, and obtain a complete blood cell count within the 6 months prior to starting therapy. Instruct patients to report symptoms of infection and obtain serum transaminase and bilirubin levels within the 6 months prior to starting therapy.
- After starting feriflunomide, monitor ALT levels at least monthly for 6 months. Consider additional ALT monitoring when feriflunomide is given with other potentially hepatotoxic drugs. Consider stopping feriflunomide if serum transaminase levels increase (>3-times the ULN). Monitor serum transaminase and bilirubin particularly in patients who develop symptoms suggestive of hepatic dysfunction. Discontinue teriflunomide and start accelerated elimination in those with suspected teriflunomide-induced liver injury and monitor liver tests weekly until normalized. Check blood pressure periodically and manage hypertension. Check serum potassium level in teriflunomide-treated patients with hyperkalemia symptoms or acute renal failure. Monitor for signs and symptoms of infection.
- Monitor for hematologic toxicity when switching from teriflunomide to another agent with a known potential for hematologic suppression because systemic exposure to both agents will overlap.

Dimethyl Fumarate Clinical Notes:

- Dimethyl fumarate may decrease a patient's white blood cell count. In the clinical trials the mean lymphocyte counts decreased by approximately 30% during the first year of treatment with dimethyl fumarate and then remained stable. The incidence of infections (60% vs. 58%) and serious infections (2%

vs. 2%) was similar in patients treated with dimethyl fumurate or placebo, respectively. There was no increased incidence of serious infections observed in patients with lymphocyte counts <0.8 $x10^3$ cells/mm^3. A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.

- Dimethyl fumarate should be held if the WBC falls below 2 $x10^3$ cells/mm^3 or the lymphocyte count is below 0.5 $x10^3$ cells/mm^3 and permanently discontinued if the WBC did not increase to over 2 $x10^3$ cells/mm^3 or lymphocyte count increased to over 0.5 $x10^3$ cells/mm^3 after 4 weeks of withholding therapy.
- Patients should have a CBC with differential monitored on a quarterly basis

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P&T Review: *11/16 (DM); 9/15; 9/13; 5/13; 3/12*
Implementation: *TBD; 1/1/14; 6/21/2012*