Cost-Utility Analysis of Medications for Relapsing-Remitting Multiple Sclerosis: A United States Third-Party Payer Perspective

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Abstract

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Background: Many new disease-modifying therapies (DMTs) have recently been approved for relapsing-remitting multiple sclerosis (RRMS) in the United States.

Objective: To assess the values of 10 first-line therapies for RRMS, including generic glatiramer acetate, versus the natural history of disease for a newly diagnosed RRMS patient.

Perspective: United States third-party payer.

Methods: A Markov model was developed and estimates were made using data on natural history of disease progression, annual relapse rates, medication efficacy, costs, and utilities to determine incremental cost-effectiveness ratios (ICERs).

Results: Base case is a cohort of 30-year-old females at Extended Disability Status Scale (EDSS) state 0 at a 20 year time horizon versus the natural history of disease. Dimethyl fumarate demonstrates the lowest ICER at $895,073/QALY.

Conclusions: DMTs for RRMS have low value versus the natural history of disease, and would not be considered cost-effective by conventional standards.
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Background

In recent years, there has been considerable innovation and scientific progress made in the treatment of relapsing-remitting multiple sclerosis (RRMS), a subtype of multiple sclerosis (MS) that affects approximately 90% patients of MS patients\(^1\). As a result of these advancements, many new therapies have been approved by the FDA and are now available to patients, including dimethyl fumarate (Tecfidera\(^\circledR\), Biogen Idec) in 2013, and peginterferon beta-1a (Plegridy\(^\circledR\), Biogen Idec) and alemtuzumab (Lemtrada\(^\circledR\), Genzyme Corporation) in 2014. Additionally, the first generic disease-modifying treatment (DMT) for RRMS was approved by the FDA in April, 2015, for glatiramer acetate, leading to another milestone in the treatment of this challenging autoimmune inflammatory disease.

With such an increase in the number of available DTMs and a dramatic shift in the landscape of RRMS treatment, there is a need for comparative effectiveness and cost-effectiveness research to evaluate these options and determine which therapies are appropriate for patients. One method to compare across these therapies, which has not been conducted for the full range in the U.S., is a cost-utility analysis. To date, the most comprehensive cost-utility analysis from a U.S. perspective analyzed five DMTs\(^2\), yet there are now 11 DMTs on the market as of June 2015, and a 12\(^{th}\) is soon approaching with generic glatiramer acetate. Due to the substantial uncertainty regarding the comparative effectiveness of these therapies and the lack of cost-utility information for many of the new therapies, this cost-utility analysis was developed.
Methods

Model structure, base case, and scenarios

A Markov model was developed using Microsoft Excel (2010) (Microsoft Corporation, Redmond, WA) to simulate the clinical course of disease for a cohort of newly diagnosed RRMS patients who are enrolled in a health plan managed by a U.S. third-party payer. The model was structured to have patients in defined categories based on disease status and treatment status. Patients would initially start receiving treatment, but could progress to other categories such as discontinuation (no treatment benefit, still RRMS), progression to secondary progression multiple sclerosis (SPMS), and death. The model defined 19 major health states, including Expanded Disability Status Scale (EDSS)³ states from zero to six for RRMS, and within these states three degrees of relapse (no relapse; mild relapse; severe relapse), and EDSS states from two to six for SPMS and death. A full schematic of the Markov model is shown in Figure 1.

Annual relapse rate probabilities were structured so that patients within an RRMS state could only be in one state of relapse per cycle, either no relapse, mild relapse, or severe relapse. Transition probabilities were also arranged so that patients receiving treatment in an EDSS state, regardless of relapse status, could progress to only the next EDSS state or transition to the discontinuation pathway, the SPMS pathway, or death. Patients who discontinued treatment could progress to the next EDSS state or to the SPMS pathway or death. Patients in the SPMS pathway could only progress within the SPMS pathway or death. The model assumes that patients will only receive treatment from their selected DMTs in EDSS states 0 to 5, and that patients at EDSS 6, patients who discontinued treatment prior to reaching EDSS 6, and patients with SPMS will not receive DMTs. Patients who discontinued treatment were not eligible to switch to a different DMT and thus progressed with no new treatment benefit moving forward.
The Markov model was developed for recommended first-line DMTs only. In this model, the treatment options available for patients were interferon beta-1a (Avonex®, Biogen Idec; Rebif®, EMD Serono, Inc./Pfizer, Inc.), interferon beta-1b (Betaseron®, Bayer HealthCare Pharmaceuticals, Inc.; Extavia®, Novartis Pharmaceuticals Corporation), glatiramer acetate (Copaxone®, Teva Neuroscience; Glatopa®, Sandoz), dimethyl fumarate, fingolimod (Gilenya®, Novartis Pharmaceuticals Corporation), teriflunomide (Aubagio®, Genzyme Corporation), peginterferon beta-1a, and no treatment (“natural history of disease”). DMTs available for patients with RRMS that were not included in the model are natalizumab.
(Tysabri®, Biogen Idec), alemtuzumab, and mitoxantrone (various). Natalizumab and alemtuzumab were both excluded from this cost-utility analysis since distribution of both are regulated by Restricted Evaluation and Mitigation Strategy (REMS) programs due to the potential for serious adverse events. Mitoxantrone was not selected for this model since it is not recommended by the American Academy of Neurology.4

The base case presented in this paper is a cohort of 30 year old females at EDSS 0. This cohort was selected since most patients are diagnosed with MS between the ages of 25 to 35, and females are two to three times more likely than males to be diagnosed with RRMS, based on the populations of patients enrolled in DMT clinical trials. Treatment with first-line DMTs are often recommended for patients when first diagnosis of RRMS. The cycle length in this model was 1 year, and time horizon in this model was set at 20 years, with the patient receiving a treatment option in year 0. Costs and utilities were set at a discount rate of 3% each per year.

Discontinuation rates were derived from the results of an 18-year cohort study of RRMS patients starting initial DMT therapy.5 This study calculated the probability of discontinuation per year from the median time-to-discontinue for interferon betas to be 9.06% annually and glatiramer acetate to be 7.46% annually. The model applied the discontinuation rate from glatiramer acetate to oral therapies (dimethyl fumarate, fingolimod, and teriflunomide) and peginterferon beta-1a since there are no long-term studies on discontinuation rates for these therapies. The decision to apply the glatiramer acetate discontinuation rate to peginterferon beta-1a and not the interferon beta discontinuation rate is due to the low percentage of patients who discontinued treatment due to adverse events from the ADVANCE clinical trial6 and that the percentage was comparable or lower than oral therapies and glatiramer acetate from other clinical and observational trials.
A life table was calculated using the Period Life Table from 2010 from the Social Security Administration. The probability of death for RRMS patients is estimated to be about 1.5 times higher than the general population in EDSS states 7.0 or below after matching for age and sex, so the life table was adjusted to match this data\textsuperscript{7}.

**Parameters on EDSS, relapse rate, and efficacy**

Information on the natural history of disease progression, relapse rates, and efficacy of treatments was derived from the Canadian Agency for Drugs and Technologies in Health (CADTH) Therapeutic Review for RRMS\textsuperscript{8}. The parameters and probabilistic distributions were derived from the values presented, including for the hazard rates on progression within RRMS health states, the hazard rates on progression rates from RRMS to SPMS, the hazard rates on progression within SPMS health states, annual relapse rates, relative risk of disability progression across treatments, and relative risk of annual relapse across treatments. Efficacy for peginterferon beta-1a, which was not studied in the CADTH review, was obtained from the ADVANCE trial and incorporated with its own probabilistic distribution\textsuperscript{6}. The natural history of disease progression was derived from Weinshenker et al. study of a population of MS patients in Ontario, Canada between 1979 and 1984\textsuperscript{9} and modeled the clinical course of disease simulated in this model. The efficacy of medications were applied to this natural history data to simulate the effect of treatment of these patients. If patients discontinued treatment, the treatment benefit was removed and the transition probabilities for natural history were applied moving forward.
Parameters on costs

Costs were calculated for general costs per year associated with being in a specific EDSS state, costs per mild and severe relapse, and annual costs for DMTs. Annual costs for being in a specific EDSS state were obtained from Bell et al., who derived their values from Oleen-Burkey’s abstract from 2003, and adjusted for inflation\textsuperscript{10}. Costs for relapses were derived from O’Brien et al. and adjusted for inflation\textsuperscript{11}. Annual costs for medications was estimated by multiplying the June 2015 Average Wholesale Price (AWP) for each medication per day by 365 days. However, when comparing these values to the National Average Drug Acquisition Cost (NADAC), provided by Medicaid.gov, it became apparent that prices did not match. Since AWP is not an accurate measure of the true costs of a medication and since NADAC did not contain the costs for every medication evaluated in this analysis, I derived a simple equation for converting AWP to the estimated annual costs for DMTs in this model. Since the NADAC costs were generally 80% of the AWP costs for the 6 medications available, I used a consistent 80% of AWP for all DMT costs in this model. The cost of generic glatiramer acetate is not available at the time of this cost-utility analysis. The cost of generic glatiramer acetate was therefore estimated to be 70% of the cost of brand glatiramer acetate. However, it is important to note the costs and incremental cost-effectiveness ratios (ICERs) for generic glatiramer acetate in this model since it may not reflect the true costs and ICERs once a price has been finalized.

Parameters on utilities

Utilities were obtained for EDSS states 0 to 6 and disutility was obtained for mild and severe relapses. Values of utilities were derived from observational studies. The utility values for patients in specific EDSS states was derived from a cohort of 1000 RRMS patients in
The values from this study were selected since it measured the utilities of patients on DMT therapy and provided values on utilities for individual EDSS states between 0 and 6. It is important to note that there might be differences between utility values between German and American patients on DMT therapy, but this difference is likely negligible for this model.

The disutilities for relapse were derived from a health-related quality of life survey using the standard-gamble method. Since this Markov model incorporates mild and severe relapse probability and the costs associated with mild and severe relapse, the disutilities of were matched to mild and severe relapse. However, it is important to understand that the definitions between mild and severe relapse in this study and the definitions of mild and severe relapse from the other sources used to estimate relapse in this study may differ, so there is some uncertainty in how costs and disutilities link to the actual events occurring in this Markov model.

**Probabilistic sensitivity analysis**

A sensitivity analysis was constructed using the probability distributions for each parameter. Each therapy would undergo 10,000 cycles of simulations, to ensure convergence. The results of the simulations would determine the average costs per simulation and average quality-adjusted life years (QALYs) per simulation for which to compare between treatment options. ICERs were then computed using these calculated values.

A one-way sensitivity analysis was constructed for dimethyl fumarate versus natural history of disease to determine the lower bound and upper bounds of the ICER that was calculated. When available, 95% credible intervals were used to estimate lower bound and upper bound uncertainties. The transition probabilities, annual relapse rate, and utility parameters were set at ±10%, while costs were set at ±5% for this one-way sensitivity analysis.
Value of information analysis

A value of information (VOI) analysis was performed to understand the expected value of perfect information (EVPI) or expected opportunity losses associated with the current information used in this model and to assess the expected value of additional research in the treatments for RRMS. The VOI analyses were performed between the natural history of disease and all DMTs at willingness-to-pay (WTP) thresholds of $100,000/QALY, $250,000/QALY, and $500,000/QALY.
Results

The inputs, ranges, and sources for the model are provided in Tables 1–4. Table 1 displays the transition probabilities and relapse rates for the various health states within the model. The model uses these transition probabilities for both natural history and all DMT treatments. The relative risk of DMT efficacy reduces these natural history transition rates as shown by the values in Table 2. Costs for each health state, based on EDSS state, and relapse status, as well as the annual costs of each DMT, are provided in Table 3. Utilities for each health state, based on EDSS state, and relapse status, is provided in Table 4.

Table 1. Transition Probabilities and Relapse Rates for EDSS states

<table>
<thead>
<tr>
<th>Health state</th>
<th>Probability</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRMS EDSS 0 to 1</td>
<td>0.144</td>
<td>0.1296</td>
<td>0.1584</td>
<td>CADTH²</td>
</tr>
<tr>
<td>RRMS EDSS 1 to 2</td>
<td>0.075</td>
<td>0.0675</td>
<td>0.0825</td>
<td>CADTH²</td>
</tr>
<tr>
<td>RRMS EDSS 2 to 3</td>
<td>0.152</td>
<td>0.1368</td>
<td>0.1672</td>
<td>CADTH²</td>
</tr>
<tr>
<td>RRMS EDSS 3 to 4</td>
<td>0.272</td>
<td>0.2448</td>
<td>0.2992</td>
<td>CADTH²</td>
</tr>
<tr>
<td>RRMS EDSS 4 to 5</td>
<td>0.45</td>
<td>0.4050</td>
<td>0.4950</td>
<td>CADTH²</td>
</tr>
<tr>
<td>RRMS EDSS 5 to 6+</td>
<td>0.485</td>
<td>0.4365</td>
<td>0.5335</td>
<td>CADTH²</td>
</tr>
<tr>
<td>RRMS EDSS 0 to SPMS EDSS 2</td>
<td>0.004</td>
<td>0.0036</td>
<td>0.0044</td>
<td>CADTH²</td>
</tr>
<tr>
<td>RRMS EDSS 1 to SPMS EDSS 2</td>
<td>0.002</td>
<td>0.0018</td>
<td>0.0022</td>
<td>CADTH²</td>
</tr>
<tr>
<td>RRMS EDSS 2 to SPMS EDSS 3</td>
<td>0.029</td>
<td>0.0261</td>
<td>0.0319</td>
<td>CADTH²</td>
</tr>
<tr>
<td>RRMS EDSS 3 to SPMS EDSS 4</td>
<td>0.102</td>
<td>0.0918</td>
<td>0.1122</td>
<td>CADTH²</td>
</tr>
<tr>
<td>RRMS EDSS 4 to SPMS EDSS 5</td>
<td>0.199</td>
<td>0.1791</td>
<td>0.2189</td>
<td>CADTH²</td>
</tr>
<tr>
<td>RRMS EDSS 5 to SPMS EDSS 6+</td>
<td>0.256</td>
<td>0.2304</td>
<td>0.2816</td>
<td>CADTH²</td>
</tr>
<tr>
<td>SPMS EDSS 2 to 3</td>
<td>0.370</td>
<td>0.3330</td>
<td>0.4070</td>
<td>CADTH²</td>
</tr>
<tr>
<td>SPMS EDSS 3 to 4</td>
<td>0.385</td>
<td>0.3465</td>
<td>0.4235</td>
<td>CADTH²</td>
</tr>
<tr>
<td>SPMS EDSS 4 to 5</td>
<td>0.594</td>
<td>0.5346</td>
<td>0.6534</td>
<td>CADTH²</td>
</tr>
<tr>
<td>SPMS EDSS 5 to 6+</td>
<td>0.349</td>
<td>0.3141</td>
<td>0.3839</td>
<td>CADTH²</td>
</tr>
<tr>
<td>RR at EDSS 0 to 2.5 (5 years of MS)</td>
<td>0.712</td>
<td>0.6408</td>
<td>0.7832</td>
<td>CADTH²</td>
</tr>
<tr>
<td>RR at EDSS 0 to 2.5 (10 years of MS)</td>
<td>0.623</td>
<td>0.5607</td>
<td>0.6853</td>
<td>CADTH²</td>
</tr>
<tr>
<td>RR at EDSS 0 to 2.5 (15 years of MS)</td>
<td>0.571</td>
<td>0.5139</td>
<td>0.6281</td>
<td>CADTH²</td>
</tr>
<tr>
<td>RR at EDSS 0 to 2.5 (20 years of MS)</td>
<td>0.534</td>
<td>0.4806</td>
<td>0.5874</td>
<td>CADTH²</td>
</tr>
<tr>
<td>RR at EDSS 3 to 5.5 (5 years of MS)</td>
<td>0.506</td>
<td>0.4554</td>
<td>0.5566</td>
<td>CADTH²</td>
</tr>
<tr>
<td>RR at EDSS 3 to 5.5 (10 years of MS)</td>
<td>1.255</td>
<td>1.1295</td>
<td>1.3805</td>
<td>CADTH²</td>
</tr>
<tr>
<td>RR at EDSS 3 to 5.5 (15 years of MS)</td>
<td>1.101</td>
<td>0.9909</td>
<td>1.2111</td>
<td>CADTH²</td>
</tr>
<tr>
<td>RR at EDSS 3 to 5.5 (20 years of MS)</td>
<td>1.011</td>
<td>0.9099</td>
<td>1.1121</td>
<td>CADTH²</td>
</tr>
</tbody>
</table>

EDSS: Expanded Disability Status Scale; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progression multiple sclerosis; RR: relapse rate; MS: multiple sclerosis; CADTH: Canadian Agency for Drugs and Technologies in Health
Table 2. Relative Risks for DMT Efficacy on EDSS Progression and Relapse Rates

<table>
<thead>
<tr>
<th>DMT Efficacy on EDSS Progression and Relapse Rates</th>
<th>DMT</th>
<th>Relative Risk</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy on EDSS progression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>interferon beta-1a (Avonex)</td>
<td></td>
<td>0.868</td>
<td>0.668</td>
<td>1.091</td>
<td>CADTH8</td>
</tr>
<tr>
<td>interferon beta-1a (Rebif)</td>
<td></td>
<td>0.836</td>
<td>0.613</td>
<td>1.083</td>
<td>CADTH8</td>
</tr>
<tr>
<td>interferon beta-1b (Betasercion)</td>
<td></td>
<td>0.744</td>
<td>0.504</td>
<td>0.967</td>
<td>CADTH8</td>
</tr>
<tr>
<td>interferon beta-1b (Extavia)</td>
<td></td>
<td>0.744</td>
<td>0.504</td>
<td>0.967</td>
<td>CADTH8</td>
</tr>
<tr>
<td>glatiramer acetate (Copaxone)</td>
<td></td>
<td>0.829</td>
<td>0.647</td>
<td>1.024</td>
<td>CADTH8</td>
</tr>
<tr>
<td>glatiramer acetate (generic)</td>
<td></td>
<td>0.829</td>
<td>0.647</td>
<td>1.024</td>
<td>CADTH8</td>
</tr>
<tr>
<td>dimethyl fumarate</td>
<td></td>
<td>0.734</td>
<td>0.528</td>
<td>0.974</td>
<td>CADTH8</td>
</tr>
<tr>
<td>finglimod</td>
<td></td>
<td>0.763</td>
<td>0.521</td>
<td>1.036</td>
<td>CADTH8</td>
</tr>
<tr>
<td>teriflunomide</td>
<td></td>
<td>0.803</td>
<td>0.499</td>
<td>1.15</td>
<td>CADTH8</td>
</tr>
<tr>
<td>peginterferon beta-1a</td>
<td></td>
<td>0.62</td>
<td>0.4</td>
<td>0.97</td>
<td>ADVANCE6</td>
</tr>
<tr>
<td>Efficacy on Relapse Rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>interferon beta-1a (Avonex)</td>
<td></td>
<td>0.864</td>
<td>0.766</td>
<td>0.974</td>
<td>CADTH8</td>
</tr>
<tr>
<td>interferon beta-1a (Rebif)</td>
<td></td>
<td>0.678</td>
<td>0.604</td>
<td>0.831</td>
<td>CADTH8</td>
</tr>
<tr>
<td>interferon beta-1b (Betasercion)</td>
<td></td>
<td>0.7</td>
<td>0.62</td>
<td>0.783</td>
<td>CADTH8</td>
</tr>
<tr>
<td>interferon beta-1b (Extavia)</td>
<td></td>
<td>0.7</td>
<td>0.62</td>
<td>0.783</td>
<td>CADTH8</td>
</tr>
<tr>
<td>glatiramer acetate (Copaxone)</td>
<td></td>
<td>0.684</td>
<td>0.612</td>
<td>0.757</td>
<td>CADTH8</td>
</tr>
<tr>
<td>glatiramer acetate (generic)</td>
<td></td>
<td>0.684</td>
<td>0.612</td>
<td>0.757</td>
<td>CADTH8</td>
</tr>
<tr>
<td>dimethyl fumarate</td>
<td></td>
<td>0.506</td>
<td>0.437</td>
<td>0.59</td>
<td>CADTH8</td>
</tr>
<tr>
<td>finglimod</td>
<td></td>
<td>0.443</td>
<td>0.375</td>
<td>0.525</td>
<td>CADTH8</td>
</tr>
<tr>
<td>teriflunomide</td>
<td></td>
<td>0.743</td>
<td>0.592</td>
<td>0.924</td>
<td>CADTH8</td>
</tr>
<tr>
<td>peginterferon beta-1a</td>
<td></td>
<td>0.644</td>
<td>0.5</td>
<td>0.831</td>
<td>ADVANCE6</td>
</tr>
</tbody>
</table>

DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; CADTH: Canadian Agency for Drugs and Technologies in Health

The base-case analysis was performed using 10,000 simulations for each therapy choice and the average costs per simulation and average QALYs per simulation were recorded and reported below in Table 5. The medications were then ordered by increasing average QALY from least (natural history of disease) to greatest (fingolimod) in a league table. The results of this analysis show that dimethyl fumarate has the lowest ICER versus natural history of disease at $895,073/QALY and that fingolimod has an ICER of $1,186,073 versus dimethyl fumarate.

A second table was created to show the relationship between each DMT and the natural history of disease to quantify the ICER for each medication evaluated. The results of this analysis are found in Table 6.
### Table 3. Cost parameters for model

<table>
<thead>
<tr>
<th>Health state or DMT costs</th>
<th>Costs ($)</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual costs for RRMS patient in EDSS 0 to 2.5</td>
<td>6685</td>
<td>6350.75</td>
<td>7019.25</td>
<td>Bell (2007)(^{10})</td>
</tr>
<tr>
<td>Annual costs for RRMS patient in EDSS 3 to 5.5</td>
<td>12943</td>
<td>12295.85</td>
<td>13590.15</td>
<td>Bell (2007)(^{10})</td>
</tr>
<tr>
<td>Annual costs for RRMS patient in EDSS 6+</td>
<td>30707</td>
<td>29171.65</td>
<td>32242.35</td>
<td>Bell (2007)(^{10})</td>
</tr>
<tr>
<td>Costs of mild relapse</td>
<td>2375</td>
<td>2256.25</td>
<td>2493.75</td>
<td>O'Brien (2003)(^{11})</td>
</tr>
<tr>
<td>Costs of severe relapse</td>
<td>16549</td>
<td>15721.55</td>
<td>17376.45</td>
<td>O'Brien (2003)(^{11})</td>
</tr>
<tr>
<td>Annual costs of interferon beta-1a (Avonex)</td>
<td>62997</td>
<td>59847.15</td>
<td>66146.85</td>
<td>UpToDate</td>
</tr>
<tr>
<td>Annual costs of interferon beta-1a (Rebif)</td>
<td>67999</td>
<td>64599.05</td>
<td>71398.95</td>
<td>UpToDate</td>
</tr>
<tr>
<td>Annual costs of interferon beta-1b (Betaseron)</td>
<td>66804</td>
<td>63463.8</td>
<td>70144.2</td>
<td>UpToDate</td>
</tr>
<tr>
<td>Annual costs of interferon beta-1b (Extavia)</td>
<td>56158</td>
<td>53350.1</td>
<td>58965.9</td>
<td>UpToDate</td>
</tr>
<tr>
<td>Annual costs of glatiramer acetate (Copaxone)</td>
<td>71370</td>
<td>67801.5</td>
<td>74938.5</td>
<td>UpToDate</td>
</tr>
<tr>
<td>Annual costs of glatiramer acetate (generic)</td>
<td>49959</td>
<td>47461.05</td>
<td>52456.95</td>
<td>Assumption</td>
</tr>
<tr>
<td>Annual costs of dimethyl fumarate</td>
<td>63773</td>
<td>60584.35</td>
<td>66961.65</td>
<td>UpToDate</td>
</tr>
<tr>
<td>Annual costs of finglomid</td>
<td>68109</td>
<td>64703.55</td>
<td>71514.45</td>
<td>UpToDate</td>
</tr>
<tr>
<td>Annual costs of teriflunomide</td>
<td>63550</td>
<td>60372.5</td>
<td>66727.5</td>
<td>UpToDate</td>
</tr>
<tr>
<td>Annual costs of peginterferon beta-1a</td>
<td>62997</td>
<td>59847.15</td>
<td>66146.85</td>
<td>UpToDate</td>
</tr>
</tbody>
</table>

DMT: disease-modifying therapy; RRMS: relapsing-remitting multiple sclerosis; EDSS: Expanded Disability Status Scale

### Table 4. Utility parameters for model

<table>
<thead>
<tr>
<th>Health state utilities</th>
<th>Value</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utility of being in EDSS 0</td>
<td>0.87</td>
<td>0.783</td>
<td>0.957</td>
<td>Putzki(^{12})</td>
</tr>
<tr>
<td>Utility of being in EDSS 1</td>
<td>0.84</td>
<td>0.756</td>
<td>0.924</td>
<td>Putzki(^{12})</td>
</tr>
<tr>
<td>Utility of being in EDSS 2</td>
<td>0.77</td>
<td>0.693</td>
<td>0.847</td>
<td>Putzki(^{12})</td>
</tr>
<tr>
<td>Utility of being in EDSS 3</td>
<td>0.68</td>
<td>0.612</td>
<td>0.748</td>
<td>Putzki(^{12})</td>
</tr>
<tr>
<td>Utility of being in EDSS 4</td>
<td>0.65</td>
<td>0.585</td>
<td>0.715</td>
<td>Putzki(^{12})</td>
</tr>
<tr>
<td>Utility of being in EDSS 5</td>
<td>0.59</td>
<td>0.531</td>
<td>0.649</td>
<td>Putzki(^{12})</td>
</tr>
<tr>
<td>Utility of being in EDSS 6+</td>
<td>0.51</td>
<td>0.459</td>
<td>0.561</td>
<td>Putzki(^{12})</td>
</tr>
<tr>
<td>Disutility of a mild relapse</td>
<td>-0.091</td>
<td>-0.063</td>
<td>-0.119</td>
<td>Prosser (2003)(^{13})</td>
</tr>
<tr>
<td>Disutility of a severe relapse</td>
<td>-0.302</td>
<td>-0.238</td>
<td>-0.366</td>
<td>Prosser (2003)(^{13})</td>
</tr>
</tbody>
</table>

EDSS: Expanded Disability Status Scale
Table 5. League Table of ICERs for DMTs

<table>
<thead>
<tr>
<th>Natural History (no treatment)</th>
<th>Interferon beta-1a (Avonex)</th>
<th>Teriflunomide</th>
<th>Interferon beta-1a (Rebif)</th>
<th>Glatiramer Acetate (Copaxone)</th>
<th>Interferon beta-1b (Betaseron)</th>
<th>Glatiramer Acetate (Generic)</th>
<th>Interferon beta-1b (Extavia)</th>
<th>Peginterferon beta-1a</th>
<th>DMT: Disease-Modifying Therapy</th>
<th>Glatiramer Acetate (Generic)</th>
<th>Interferon beta-1b (Extavia)</th>
<th>DMT: Disease-Modifying Therapy</th>
<th>Finglimod</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Costs per Simulation ($)</td>
<td>185,415</td>
<td>648,890</td>
<td>700,537</td>
<td>681,502</td>
<td>674,327</td>
<td>586,057</td>
<td>594,975</td>
<td>697,006</td>
<td>Teriflunomide</td>
<td>763,589</td>
<td>Peginterferon beta-1a</td>
<td>DMT: Disease-Modifying Therapy</td>
<td>731,079</td>
</tr>
<tr>
<td>Average QALYs per Simulation</td>
<td>11.35</td>
<td>11.53</td>
<td>11.67</td>
<td>11.68</td>
<td>11.72</td>
<td>11.72</td>
<td>11.73</td>
<td>11.88</td>
<td>Glatiramer Acetate (Copaxone)</td>
<td>11.71</td>
<td>Glatiramer Acetate (Generic)</td>
<td>DMT: Disease-Modifying Therapy</td>
<td>11.95</td>
</tr>
<tr>
<td>ICER ($/QALY)</td>
<td>-</td>
<td>2,621,882</td>
<td>Dominated</td>
<td>Dominated</td>
<td>Dominated</td>
<td>Dominated by extension</td>
<td>Dominated by extension</td>
<td>Dominated by extension</td>
<td>Interferon beta-1b (Betaseron)</td>
<td>1,341,641</td>
<td>Interferon beta-1b (Extavia)</td>
<td>Peginterferon beta-1a</td>
<td>DMT: Disease-Modifying Therapy</td>
</tr>
</tbody>
</table>

ICER: incremental cost-effectiveness ratio; DMT: disease-modifying therapy; QALY: quality-adjusted life year

Table 6. ICERs for DMTs versus natural history

| Natural History (no treatment) | Interferon beta-1a (Avonex) | Teriflunomide | Interferon beta-1a (Rebif) | Glatiramer Acetate (Copaxone) | Interferon beta-1b (Betaseron) | Glatiramer Acetate (Generic) | Interferon beta-1b (Extavia) | Peginterferon beta-1a | DMT: Disease-Modifying Therapy | Glatiramer Acetate (Generic) | Interferon beta-1b (Extavia) | Peginterferon beta-1a | DMT: Disease-Modifying Therapy | Finglimod |
|-------------------------------|-----------------------------|---------------|---------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------|-------------------------------|-------------------------------|-------------------------------| Peginterferon beta-1a | DMT: Disease-Modifying Therapy | 68,109 |
| Average Costs per Simulation ($) | 185,415              | 648,890       | 700,537                   | 681,502                       | 674,327                       | 586,057                       | 594,975                       | 697,006          | Teriflunomide               | 763,589                       | Peginterferon beta-1a       | DMT: Disease-Modifying Therapy | 731,079 |
| Average QALYs per Simulation | 11.35                      | 11.53         | 11.67                     | 11.68                         | 11.72                         | 11.72                         | 11.73                         | 11.88             | Glatiramer Acetate (Copaxone)| 11.71                         | Glatiramer Acetate (Generic)| DMT: Disease-Modifying Therapy | 11.95 |
| ICER ($/QALY)                | -                          | 2,621,882     | Dominated                 | Dominated                     | Dominated                     | Dominated by extension         | Dominated by extension        | Dominated by extension | Interferon beta-1b (Betaseron)| 1,341,641                     | Interferon beta-1b (Extavia)| Peginterferon beta-1a | DMT: Disease-Modifying Therapy | 1,186,073 |

ICER: incremental cost-effectiveness ratio; DMT: disease-modifying therapy; QALY: quality-adjusted life year
The ICERs for all DMTs were organized on a scatter plot to show how the ICER of each DMT compared to each other. Figure 2 shows the average ICER for all DMTs versus natural history. An ICER threshold of $895,073/QALY was added between the origin and dimethyl fumarate, and an ICER threshold of $1,186,073/QALY between dimethyl fumarate and finglimod. Figure 3 shows the overall distribution of every simulated ICERs calculated for each DMT, with each icon representing the calculated ICER versus natural history of disease.

**Figure 2. Scatter Plot of ICERs for all DMTs versus natural history**

ICER: incremental cost-effectiveness ratio; DMT: disease-modifying therapy; QALY: quality-adjusted life year
**Figure 3.** Scatter Plot of all simulated ICERs for all DMTs versus natural history

ICER: incremental cost-effectiveness ratio; DMT: disease-modifying therapy; QALY: quality-adjusted life year

Cost-effectiveness curves were also developed to demonstrate the probability that a therapy is the most cost-effective choice at a certain WTP threshold. The results of this analysis demonstrate the lack of cost-effectiveness at typical WTP thresholds and that no therapy achieves a 20% probability of being cost-effective on average. The full results can be found in Figure 4 below.
The one-way sensitivity analysis produced a wide range for lower bound and upper bound values around the ICER for dimethyl fumarate against natural history. It was determined through the one-way sensitivity analysis that the parameter of greatest effect on the results was the relative risk of dimethyl fumarate on disease progression, which creates an ICER range from $724,824/QALY at the lower bound to $1,259,152/QALY at the upper bound. However, many of the ten most influential parameters are related to relapse, including the efficacy of dimethyl fumarate on relapse rate, the disutilities of mild and server relapse, and the rate ratio of relapses between EDSS 0 to 2.5 in the first 5 years of RRMS. It is also worth noting that utility values at
EDSS states 0, 1, 2, and 6 are also influential in this model. The full results of the one-way sensitivity analysis can be found in Table 7.

**Table 7. One-way sensitivity analysis for dimethyl fumarate versus natural history**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lower Bound ($/QALY)</th>
<th>Upper Bound ($/QALY)</th>
<th>Range ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy of dimethyl fumarate on progression</td>
<td>724,824</td>
<td>1,259,152</td>
<td>534,328</td>
</tr>
<tr>
<td>Utility of being in EDSS 0</td>
<td>778,825</td>
<td>1,051,996</td>
<td>273,171</td>
</tr>
<tr>
<td>Efficacy of dimethyl fumarate on relapse rate</td>
<td>813,768</td>
<td>1,017,624</td>
<td>203,856</td>
</tr>
<tr>
<td>Disutility of a mild relapse</td>
<td>814,850</td>
<td>992,772</td>
<td>177,922</td>
</tr>
<tr>
<td>Disutility of a severe relapse</td>
<td>838,702</td>
<td>959,548</td>
<td>120,847</td>
</tr>
<tr>
<td>Annual costs of dimethyl fumarate</td>
<td>848,138</td>
<td>942,008</td>
<td>93,871</td>
</tr>
<tr>
<td>RR at EDSS 0 to 2.5 (5 years of MS)</td>
<td>859,619</td>
<td>933,429</td>
<td>73,810</td>
</tr>
<tr>
<td>Utility of being in EDSS 2</td>
<td>869,195</td>
<td>922,536</td>
<td>53,341</td>
</tr>
<tr>
<td>Utility of being in EDSS 6</td>
<td>871,980</td>
<td>919,419</td>
<td>47,739</td>
</tr>
<tr>
<td>Utility of being in EDSS 1</td>
<td>878,303</td>
<td>912,495</td>
<td>34,192</td>
</tr>
</tbody>
</table>

QALY: quality-adjusted life year; EDSS: Expanded Disability Status Scale; RR: relapse rate; MS: multiple sclerosis

The value of information analysis yielded an EVPI of $0 at a WTP threshold of $100,000/QALY, meaning there is no expected opportunity loss for making the wrong decision at that threshold. When the threshold is increased to $250,000/QALY, the EVPI becomes $27 per patient, with peginterferon beta-1a as the highest at $10 per patient. When the threshold is increased to $500,000/QALY, the EVPI becomes $11,162 per patient, with generic glatiramer acetate as the highest at $1,893 per patient, followed by peginterferon beta-1a at $1,885 per patient, dimethyl fumarate at $1,857 per patient, and interferon beta-1b (Extavia) at $1,642 per patient. The most recent estimate of prevalence of MS in the United States, from 2002, predicts 400,000 patients currently are living with the disease. If we estimate that 87.6% of the total MS population has RRMS, as reported by Tremlett et al. in British Columbia, Canada in 2003, then
we can estimate that there are approximately 350,000 RRMS patients that count benefit from additional research in DMTs. By multiplying the EVPI per patient by the total patient population, we obtain a population EVPI of $9,450,000 at a WTP threshold of $250,000/QALY.
Discussion

The base case results of the cost-utility analysis project that all current DMTs for RRMS are of low value, i.e., have very high cost-utility ratios. The medication having the highest projected value from this model was dimethyl fumarate at a mean of $895,073 per QALY gained, which would be considered far above conventional willingness-to-pay thresholds in the U.S. The one-way sensitivity analysis shows that there is considerable variability, and thus uncertainty, around this ICER, too, so there is a good margin of error to consider in comparing dimethyl fumarate with other therapies, such as ginfolimod and peginterferon beta-1a, which have similarly high ICERs compared to the natural history of RRMS. Additionally, since the price of generic glatiramer acetate has not yet been established, there is the strong possibility that its price could be low enough to yield a much lower ICER. However, this analysis does determine that, at current prices, all current DMTs for RRMS from a United States third-party payer are of low value.

Given that this is a chronic condition with no predicted survival benefits, a simple calculation can provide a validity check for the result for this one medication by using directly what was observed in the phase III clinical trials for dimethyl fumarate. The pooled odds ratios from the DEFINE\textsuperscript{14} and CONFIRM\textsuperscript{15} clinical trials are 0.685 for EDSS progression and 0.630 for annualized relapse rate. The two trials measured patients through an intent-to-treat analysis over a two year period with the median patient entering the trial at EDSS 2. Assuming an initial annual relapse rate of 0.712 in the placebo arm, with 23\% of those relapses being severe, dimethyl fumarate would produce a gain of 0.077 QALYs and savings $3097 during the two year trial period based on relapse data alone. If we assume patients start around EDSS 2, then we would expect 7.50\% of all patients would not progress to EDSS 3 or EDSS 4 due to dimethyl
fumarate. This translates into a QALY gain of 0.051 and a savings of $970 during the two-year trial period. Together, this produces a total gain of 0.127 QALYs and a savings of $4067. Assuming the cost of dimethyl fumarate is $63,773 per year, then the cost over two years would be $127,546 on the medication alone. With the cost offset, this would imply a total cost of $123,479 and a total gain of 0.127 QALYs during the two-year period. This translates to an ICER of $970,250/QALY of dimethyl fumarate versus placebo, which is comparable to the calculated ICER from the full Markov model of $895,073/QALY.

The implications of this cost-utility analysis should bring attention to the first-line therapies for RRMS patients. As shown by this cost-utility analysis, many of the newer therapies dominate older therapies by producing more QALYs at lower total costs. This may signal a shift in what is prescribed as first-line therapies in newly diagnosed RRMS patients or alternatives to consider for patients who develop adverse events or lack clinical response with other DMTs. Additionally, there may be value with these newer medications that is not captured adequately by this model. For example, patient adherence and satisfaction may be higher with oral therapies as opposed to injectable therapies due to the ease in administration. Since this model assumed the glatiramer acetate discontinuation rate from the Zhornitsky et al. study for oral therapies, and measured utility values for EDSS states for patients currently taking injectable therapy, our projections may underestimate the value of oral therapies. However, in order to receive this difference in value, patients would need to remain on these medications in order to achieve improved patient outcomes and decreased costs. If patients will be treated with any of these agents, then this analysis suggests that the newer DMTs should be made available.

The results of this cost-utility analysis are not strictly comparable to results of other cost-utility analyses assessing DMTs for RRMS for a variety of reasons, but some aspects can be
compared. Of the cost-utility analyses publically available, only the CADTH model\textsuperscript{8} assesses the economic impact of the three new oral DMTs – dimethyl fumarate, fingolimod, and teriflunomide – in comparison with the older injectable therapies. The results of this analysis and the CADTH analysis show similar ordering in league tables based on QALYs: this is not overly surprising since this model was designed to be similar to the CADTH model and used many of its inputs. The biggest difference between the two models is the differences in costs (U.S., vs. Canada). For example, glatiramer acetate was found to be the least costly therapy in the CADTH model\textsuperscript{8} while glatiramer acetate was determined to be the most expensive in this model. However, this significant difference can be explained by the differences in annuals costs for glatiramer acetate, with the CADTH model assuming $16,286 per year\textsuperscript{8} and this model assuming $71,370 per year.

The results of other cost-utility analyses were examined, too, as a means to validate the results and to understand the differences between this model and other models\textsuperscript{10,16,17,18,19,20,21}. Although upon initial examination, the results are sometimes vastly different, it is important to note that the different models use different patient populations, therapies, disease transition probabilities, relapse probabilities, clinical efficacies, costs, utilities, and time horizons. The results, however, generally reach the same conclusions that DMTs are usually low value relative to no treatment. Although there are differences to the magnitude to which these medications show value, the general conclusion is that DMTs are of low value, especially in the U.S.

Guo et al. published a review of modeling approaches for cost-effectiveness analyses for multiple sclerosis and provided critiques on the models available in the literature\textsuperscript{2}. They would criticize this model for (a) using natural history data from the 1980s to model the natural history of disease and (b) not considering switching to other DMTs after discontinuation of the initial
DMT. Nonetheless, this model does address some of their other criticisms. This model has a similar structure to other RRMS models which have been validated to simulate the clinical course of disease; the comparative efficacy data was derived from a network meta-analysis performed by CADTH for their therapeutic review of RRMS medications; and information regarding the model’s validation are provided. However, while this model attempted to address the criticisms by Guo et al., some limitations remain. One challenge is to find appropriate natural history of disease data for which to simulate the clinical course of disease. Thus, this model used one of the most commonly cited sources for history of disease. Additionally, this model did not incorporate the decision to select another specific DMT after discontinuing the initial DMT. While it is assumed that patients will switch to other DMTs after discontinuing the initial treatment option, data are needed to determine why patients are discontinuing therapy, which may influence the options available to a patient. Since patients could either discontinue the therapy due to adverse reactions (secondary therapy may have normal efficacy), lack of efficacy (secondary therapy may have diminished efficacy), or other reasons (unknown effect on efficacy), it is difficult to incorporate this decision without adequate information on what is causing the discontinuations and what therapies are appropriate choices for patients.

Prior to using these results, other limitations of this study need to be considered. First, the parameters in this model are derived from many different sources from many different times and from many different geographies. Markov models are highly dependent on the structure and inputs, so altering these parameters can have a profound effect on how these therapies compare to each other, as was demonstrated by the one-way sensitivity analysis between dimethyl fumarate and natural history of disease. Of particular note is the lack of real world data and longitudinal data on the safety and efficacy of these medications. Many of the inputs used in this
model are based on clinical trial data which may not provide the best evidence for which to determine cost-effectiveness in a theoretical, but more general cohort population. However, since many of these medications have been new to the market, approved in the last few years, utilization is low, and it may be many years before there is sufficient evidence to determine differences in clinical effectiveness and long-term safety. With this more accurate information, a more accurate model could be constructed to better estimate the economic impact of DMTs.

Additionally, there is a lack of recent evidence on the natural history of disease, which explains why models use decades-old data from the Weinshenker et al. study in Ontario, Canada. A more recent study conducted by Tremlett et al. in British Columbia, Canada surveyed MS patients in 2003 and found that disability progression occurred slower than in the Weinshenker et al. study\(^1\). This difference in disease progression between these studies does raise the question of whether the parameters used in this model are accurate for a population of MS patients in 2015. Additionally, the natural history of disease is characterized by this information, and the standard of care is surely different between Canada in the early 1980s and the United States in 2015. This raises the question of how quickly disease progression would occur in this theoretical population.

Another limitation with this study is the potential of value that is not captured by this model. Without evidence on how medications are different, such as in disutility of treatment or discontinuation rates, assumptions must be made in this model based on generalized information. For example, since the data is lacking of oral DMTs, assumptions were made using data from injectable DMTs for disutilities of administration and discontinuation of treatment. Moreover, there could also be long-term benefits associated with adherence to oral therapies over injectable that could provide value not captured in the available clinical trial data. Thus, it could be that the value of the oral therapies may be underestimated in this model. This may result in
underestimating the utilities and ICERs of oral therapies, which may be greater if we include the utilities associated with oral administration versus injectable administration. However, there are no data on the difference in utilities between injectable therapies, oral therapies, and no therapy for RRMS at this time. Without that information, this model used the assumption that there is no difference in disutility of treatment between DMTs.

Likewise, the model made an assumption on constant discontinuation rates between therapies. The assumption of a constant discontinuation rate for interferon betas and all other therapies, as was derived from glatiramer acetate, was incorporated since there is a lack of information on the discontinuation rates for all therapies beyond 2 years of treatment. It would be reasonable to assume the discontinuation rate would be lower among oral therapies than injectable therapies and in peginterferon beta-1a, which requires injections every two weeks, compared to other injectable therapies, so this assumption may not capture some of the advantages associated with certain therapies. Nonetheless, without robust evidence of appropriate discontinuation rates for these therapies in an RRMS population, it is difficult to quantify these differences.

Another limitation with this model is the assumption of when to stop therapy for patients. The assumption that treatment would be discontinued at SPMS is based on the recommendation from the Association of British Neurologists\textsuperscript{22}. The Association of British Neurologists also suggests discontinuing therapy at EDSS 7: this model discontinues therapy at EDSS 6 due to the lack of information on efficacy for therapies at EDSS 6 or above. Since most clinical trials recruit patients at low EDSS states, this raises the question whether the efficacy in these populations is accurate for patients at EDSS 6 or above. Additionally, the instruments that were evaluated for measuring the validity and reliability for the utility values of EDSS states usually
grouped patients by EDSS 0 to 2.5, EDSS 3 to 5.5, and EDSS 6.0 or greater\textsuperscript{13,23}, and there was
considerable variability in utility scores for patients EDSS 6.0 or greater\textsuperscript{12}. Due to this increased
uncertainty and lack of data at EDSS 6, the model assumed stopping at EDSS 6.

A final limitation with this study is the selected patient population. The population
assumes a cohort of 30-year-old females who are newly diagnosed with RRMS at EDSS 0.
However, this may not be the case for most patients starting DMTs, as patients may be of
different ages, different sexes, and different EDSS states. One of the rationales for selecting 30
is that it is a common age for first diagnosis of RRMS and that being 30 years old or above is
associated with greater adherence to DMTs than 18-29 year olds\textsuperscript{5}. A cohort of women was
selected for this study since women are a majority of patients who develop RRMS. However, it
is worth noting that men with RRMS progress more quickly than women at the onset of disease\textsuperscript{1},
raising the question whether these therapies might be slightly more efficacious and cost-effective
in men than women. Lastly, many clinical trials enroll patients at higher EDSS states than 0,
with many showing a median EDSS state of 2 at the time of therapy. Not all patients start DMTs
at EDSS 0 and many may wait until EDSS 1 or 2 before starting a DMT. If patients start DMTs
at different EDSS states, it may lead to different ICERs due to how the efficacy of medications
reduces progression and relapses at other EDSS states.
Conclusions

The results of this model demonstrate that DMTs for RRMS are typically of low value when compared to the natural history of disease. Dimethyl fumarate was projected to have the lowest ICER for DMTs at $895,073/QALY, which would not be considered cost-effective at conventional willingness-to-pay thresholds. Indeed, it is far above conventional thresholds cited in the U.S. of $150,000 to $250,000 per QALY gained. Additionally, there is considerable uncertainty around this ICER as shown by the one-way sensitivity analysis, specifically on the efficacy of dimethyl fumarate and utilities. More research is needed on longitudinal outcomes, long-term efficacy of treatments, and utilities associated with RRMS in order to better determine the long-term value of DMTs for RRMS in the U.S.
REFERENCES


