Cost-effectiveness of disease-modifying therapy for multiple sclerosis

A population-based study

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Editorial, page 317

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ABSTRACT

Objective: To evaluate the cost-effectiveness of disease-modifying therapies (DMTs) in the United States compared to basic supportive therapy without DMT for patients with relapsing multiple sclerosis (MS).

Methods: Using data from a longitudinal MS survey, we generated 10-year disease progression paths for an MS cohort. We used first-order annual Markov models to estimate transitional probabilities. Costs associated with losses of employment were obtained from the Bureau of Labor Statistics. Medical costs were estimated using the Centers for Medicare and Medicaid Services reimbursement rates and other sources. Outcomes were measured as gains in quality-adjusted life-years (QALY) and relapse-free years. Monte Carlo simulations, resampling methods, and sensitivity analyses were conducted to evaluate model uncertainty.

Results: Using DMT for 10 years resulted in modest health gains for all DMTs compared to treatment without DMT (0.082 QALY or <1 quality-adjusted month gain for glatiramer acetate, and 0.126–0.192 QALY gain for interferons). The cost-effectiveness of all DMTs far exceeded \$800,000/QALY. Reducing the cost of DMTs had by far the greatest impact on the cost-effectiveness of these treatments (e.g., cost reduction by 67% would improve the probability of Avonex being cost-effective at \$164,000/QALY to 50%). Compared to treating patients with all levels of disease, starting DMT earlier was associated with a lower (more favorable) incremental cost-effectiveness ratio compared to initiating treatment at any disease state.

Conclusion: Use of DMT in MS results in health gains that come at a very high cost. *Neurology*® 2011;77:355–363

GLOSSARY

CE = cost-effectiveness; **CEAC** = cost-effectiveness acceptability curve; **CI** = confidence interval; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **FDA** = Food and Drug Administration; **HRQOL** = health-related quality of life; **ICER** = incremental cost-effectiveness ratio; **ICD-9-CM** = International Classification of Diseases-9-Clinical Modification; **MC** = Monte Carlo; **MEPS** = Medical Expenditure Panel Survey; **MS** = multiple sclerosis; **QALY** = quality-adjusted life-year; **RRMS** = relapsing-remitting multiple sclerosis; **RFY** = relapse-free year; **SC** = subcutaneous; **SF-36** = Short Form-36; **SPMS** = secondary progressive multiple sclerosis.

All models are wrong, but some are useful.

—George Box

Disease-modifying therapies (DMTs) were introduced in the 1990s to reduce the frequency of relapses and to slow disease progression in patients with multiple sclerosis (MS). IM interferon β -1a (Avonex[®], Biogen Idec, Weston, MA), interferon β -1b (Betaseron[®], Bayer Schering Pharma, Berlin-Wedding, Germany), glatiramer acetate (Copaxone[®], Teva Pharmaceutical Industries Ltd., Petah Tikva, Israel), subcutaneous (SC) interferon β -1a (Rebif[®], EMD Serono, Inc., Rockland, MA, and Pfizer, Inc., New York, NY), and IV natalizumab (Tysabri[®], Biogen Idec and Elan Pharmaceuticals, Inc., San Francisco, CA) are currently approved in the United States for patients with relapsing-remitting MS (RRMS) and

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secondary progressive MS (SPMS).^{1–5} In addition, mitoxantrone (Novantrone, EMD Serono, Inc.) is approved by the US Food and Drug Administration (FDA) as a DMT for progressive and relapsing MS.⁶

While evidence suggests that these drugs slow MS progression and reduce the frequency of relapses, these therapies are characterized by significant side effects and high costs, representing great economic burden to patients, as well as public and private payers. Several cost-effectiveness (CE) models of MS DMTs have been developed for different patient populations including those in the United States,^{7–10} Canada,¹¹ and various European countries.^{12–18} Published studies have produced a range of estimates from over \$2 million per quality-adjusted life-year (QALY) to being cost-saving. There is, however, a substantial body of literature indicating that evidence from CE models is not easy to transfer from one country to the other and that country-specific evidence is required for each policy decision. The 4 CE models of MS DMAs that have been developed for the US population up to date^{7–10} have limitations that restrict their application for clinical and health policy decision-making. They are based on cost and utilization estimates obtained from various, often outdated sources; use small convenience sample for utility estimates; and lack information on DMT switching and on the effect of neutralizing antibodies.

Here we present a new model that evaluates CE of MS DMT for the US patient population with RRMS and SPMS by incorporating the lessons learned from the existing models and by using nationally representative data from the Sonya Slifka Longitudinal MS Survey.¹⁹ We also used aggregated data from multiple sources to estimate the model parameters and to evaluate uncertainty of the modeling results and its implications for clinical practice, health policy, and research.

METHODS Primary data source. The CE and treatment policy model was developed based on the 2000–2005 Sonya Slifka Longitudinal Multiple Sclerosis study. The data for this study are gathered from an ongoing mail-in survey of a nationally representative panel of over 2,000 people with MS, funded by the National Multiple Sclerosis Society.^{19–21} The sample represents the US population with MS and contains patients with MS with all durations and courses of illness, all degrees of severity, and all types and extents of disability,^{22,23} from all regions of the United States.

All demographics were reported at baseline only except for family and disability income, insurance type, and work status,

which were updated annually. Epidemiologic and clinical characteristics and health services utilization were collected semianually. The study was approved by the University of Rochester Research Subject Review Board.

Analytic datasets. Figure 1 illustrates a process flow diagram of the overall simulation model.

Simulation cohort. The initial simulation cohort was based on 1,121 out of 1,271 survey participants who completed information on disease duration and progression at their baseline interview. This cohort is representative of the US MS population with RRMS and SPMS types. Table 1 shows the descriptive statistics for the simulation cohort.

Estimation sample for disease progression. Disease-related information was taken from the baseline and annual interviews (e.g., age, date of diagnosis, disability-based disease state, number of relapses) and supplemented by semiannual interviews (number of relapses). After excluding people with only one complete interview, those with missing information, and those treated with mitoxantrone, the sample for disease progression estimation included annual records for 844 people with MS.

Estimation sample for health care utilization. In the Slifka survey, health care utilization was reported in the semiannual interviews. Similar to the estimation sample above, we excluded 256 people who completed only baseline interviews or had incomplete data on disease duration and progression from the estimation cohort. As a result, the health care utilization sample consists of longitudinal records for 910 people with RRMS or SPMS.

Overview of the model. The purpose of the simulation is to estimate expected costs and health outcomes for an MS cohort for each DMT, to calculate incremental cost-effectiveness ratios (ICERs), and to evaluate statistical uncertainty (figure 1). The model consists of 2 components: a series of estimation procedures (for transition probabilities, health utilization, and health-related quality of life [HRQOL]) and a cohort Monte Carlo (MC) simulation of disease progression and associated costs and health outcomes. Estimation and simulation were performed using STATA 9.²⁴

First we performed MC simulation for the cohort of patients with MS. We generated a random 10-year disease progression path for each individual from the simulation cohort for each treatment strategy (4 DMTs and no DMT). Disease states from the simulation cohort were considered initial states at time zero. Patients progressed to another state annually according to the estimated progression probabilities. This “disease progression” was repeated 10 times, representing 10 years.

Next, using the results of the estimation models, we assigned utility and health care utilization to each annual cycle, by treatment. For each person, we calculated 10-year total costs (using category-specific unit costs) (table 2), QALYs (using state-specific utility), and relapse-free years (RFYs). Finally, we calculated cohort means for the costs and health outcomes and repeated the process to obtain MC estimates of their expected values. We calculated ICERs as functions of expected costs and outcomes.

We obtained bootstrap distribution and confidence intervals for these values by resampling from the estimation samples and repeating MC simulation for each resample.

Estimation. Estimating probabilities of disease progression and relapse probability. We modeled probabilities of disease state transitions using a first-order annual Markov model that adjusted for demographics, disease duration, recent relapse rates, prior states, and the specific DMT. We developed an iterative multino-

Figure 1 Overview of the simulation model

We draw and redraw multiple samples of patients with multiple sclerosis (MS) from the Slifka survey cohort to estimate health care utilization, health utility, and disease progression probabilities. Using Monte Carlo simulations, we modeled 10-year MS progression paths for treatment and untreated individuals. ICER = incremental cost-effectiveness ratio.

mial logistic regression algorithm to estimate transition probabilities for each treatment regimen by translating the relative risks from RCT data into restrictions on treatment effect coefficients within a multinomial logistic regression. We modeled probability of having relapses depending on patient and disease characteristics, but unconditional on having relapses in the previous cycle.

Estimating health care utilization. Because the assignment of treatment in the Slifka survey was not randomized, we used adjusted rather than observed utilization rates for our simulation model. We estimated predicted rates of utilization (number of hospital admissions, outpatient treatments, emergency room visits, office visits, mental health visits, home health provider visits, home personal care use, and blood tests and MRI procedures) to control for the differences in utilization attributable to patient characteristics. Respondents reported the number of health care services they received during the prior 6-month period, up to 4 observations per person.

We used log-linear negative binomial or Poisson count models for health care utilization with the exception of estimating the number of health care provider visits, for which we used a log transformed model, and home personal care, which required a 2-part

model. The estimated utilization rates were adjusted to account for disease state and duration, age at diagnosis, presence of relapses, region, marital status, and living situation. All models included robust standard errors to control for potential nonindependence among multiple observations contributed by the same person.

Estimating unit medical costs and lost productivity costs. *Unit medical costs.* To assign values to the health utilization estimates, we used cost estimates from the Medical Expenditure Panel Survey (MEPS) and average Medicare reimbursement rates (2005 Medicare claim from the Medicare Current Beneficiary Survey) (table 2). Using claims data, patients with MS were identified by International Classification of Diseases–9–Clinical Modification (ICD-9-CM) diagnosis code 340. Finally, the costs of home provider and health aid visits were estimated using published rates (table 2).

Opportunity/productivity costs. Opportunity costs are defined as the value of lost time due to MS. Opportunity costs were broken down into costs of unemployment spells, part-time labor, interruptions in schooling, and short-term absences from work or school due to MS. Short-term absences from work and school were valued for both individuals with MS and their care-

Table 1 Demographic and health characteristics of the study cohort

	No. of individuals	Proportion (SE) ^a
All	1,121	
Male	182	0.17 (0.01)
Race		
White	1,023	0.91 (0.01)
Black	46	0.04 (0.01)
Hispanic	52	0.05 (0.01)
Region		
Northeast	279	0.25 (0.01)
Midwest	279	0.25 (0.01)
South	302	0.27 (0.02)
West	261	0.23 (0.01)
Rural	185	0.16 (0.01)
Education		
High school or lower	259	0.23 (0.01)
Some college	206	0.20 (0.01)
Associate degree	129	0.12 (0.01)
College graduate	322	0.27 (0.02)
Graduate degree	205	0.19 (0.01)
Marital status		
Married	749	0.68 (0.02)
Previously married	227	0.22 (0.01)
Never married	145	0.10 (0.01)
Marital status/living situation interactions		
Married and household size ≥3	464	0.41 (0.02)
Not married and living with somebody	191	0.16 (0.01)
Disability-based disease states		
1: No MS symptoms (EDSS 0–1.5)	0	0 (—)
2: Mild symptoms, not limiting (EDSS 2–2.5)	328	0.26 (0.01)
3: Mild symptoms, not affecting walking (EDSS 3–4)	384	0.32 (0.02)
4: Problem with walking, do not use aid or cane walk 25 ft without cane or aid (EDSS 4.5–5.5)	203	0.19 (0.01)
5: One-side cane or aid for 25 ft (EDSS 6)	105	0.11 (0.01)
6: Two-side cane or aid for 25 ft (EDSS 6.5–7)	40	0.05 (0.01)
7: Only wheelchair/scooter (EDSS 7.5–8.5)	61	0.07 (0.01)
8: Bedridden (EDSS 9–9.5)	0	0 (—)
Had one or more relapses during the last 12 mo	542	0.60 (0.02)
Age at time of diagnosis, mean (SE)		36.52 (0.293)
Time from diagnosis, mean (SE)		10.11 (0.25)

Abbreviations: EDSS = Expanded Disability Status Scale; MS = multiple sclerosis.

^a We used cross-sectional weights from the Slifka dataset to extrapolate to the US population with MS. Nonresponse adjustment weights were also used. Persons who left the study ($n = 353$ at 6 months and $n = 537$ at 24 months) were more disabled, were more likely to have fair or poor health, had a more progressive form of the disease, and lacked health insurance.

takers using age- and gender-specific wages reported by the Bureau of Labor Statistics.²⁵ All other opportunity costs were valued only for individuals with MS (table 2).

Estimating utility. The Slifka dataset collected health status information on all subjects at baseline using the Medical Outcomes Study Short Form–36 (SF-36) questionnaire.^{26,27} We used

the same cohort as for the simulation. We calculated HRQOL for each patient by translating the SF-36 into preference scores using the additional scoring mechanism, SF-6D.²⁸ Mean utility values were estimated conditional on disease state and on the presence of relapses (table e-1 on the *Neurology*[®] Web site at www.neurology.org).

The main reason for differences in the sample size across different cohorts is exclusion of subjects who had missing data on key model parameters. The main difference among the cohorts was in the distribution of patients by MS severity (up to 2%). The differences in time from diagnosis and age at diagnosis across the cohorts were not significant. The estimation sample had fewer people with advanced MS (consistently with attrition information in Slifka) that resulted in less precision and wider confidence intervals for the estimates of probabilities and utilization for these DSs. We included as many people as possible in the simulation cohort because it is supposed to resemble the whole MS population.

Health outcomes. The primary outcome of the model is the number of QALYs each DMT produces over 10 years. This is a generic health outcome that could be used to compare benefits of any health intervention for any condition. The other, MS-specific outcome measure was the number of relapse-free years. In the Slifka survey, relapses are defined as a period of at least 24 hours in which new symptoms develop, or existing ones deteriorate. We estimated the cost of having a relapse-free year.

Cost-utility analysis. The primary outcome of the model was the incremental cost-utility ratio measured in terms of the incremental cost associated with each DMT strategy compared to basic supportive treatment (i.e., no use of glatiramer acetate or β -interferon) per QALY gain.

For the base case analysis, we assessed whether it is cost-effective to provide DMT for any category of patients with MS in the United States using current prescribing patterns (table e-2). Using bootstrapping and MC simulation, we conducted sensitivity analyses to examine the robustness of our model to medication pricing and discounting rate. Finally, by modifying the characteristics of the simulation cohort, we modeled several distinct scenarios: 1) initiating DMT early (DS 2 or Expanded Disability Status Scale [EDSS] 2–2.5); 2) initiating DMT after mild/moderate disability (DS 3 or EDSS 3–4); 3) modeling advanced MS progression through DS 8 (EDSS 9); and 4) using a payer perspective analysis (excluding any costs associated with lost productivity).

Since there were very few patients with EDSS 8+ in the Slifka cohort, we extrapolated patient health outcomes and utilization beyond the survey data using published estimates. We assumed probability 0.5 of advancing to DS = 8 from DS = 7 during a cycle; when a person advances to DS = 8 he or she stays in this state indefinitely (absorbing state). We assumed that an individual in DS = 8 incurs the same expenses as was incurred in DS = 7 except for home health care. The cost of a custodial NH stay of \$65,000 per year was added for each year in DS 8. All-cause mortality is unchanged compared to the main analyses. We generated CE acceptability curves (CEAC)²⁹ to graphically demonstrate the tradeoff between modeling uncertainty and societal willingness to pay for a gain in health.

RESULTS Health outcomes. Being on DMT for 10 years resulted in modest QALY gains (for example, patients on interferon β -1a IM on average would gain 0.192 QALYs over 10 years or about 2 quality-adjusted months) (table 3). In addition, use of DMTs was associated with a reduction in the frequency of re-

Table 2 Estimated average (per person) 10-year costs, by type and treatment (no discounting)

Type	Source	Unit cost	Average 10-year cost									
			Basic supportive		Interferon β -1a IM		Interferon β -1b		Glatiramer acetate		Interferon β -1a SC	
			\$	%	\$	%	\$	%	\$	%	\$	%
Hospital admission	MEPS	\$11,143	\$26,290	9.8	\$22,230	10.1	\$21,060	9.5	\$22,610	9.3	\$21,940	9.5
Emergency room visit	MEPS	\$887	\$3,930	1.5	\$3,540	1.6	\$3,380	1.5	\$3,530	1.5	\$3,470	1.5
Hospital day treatment	MEPS	\$540	\$3,150	1.2	\$2,710	1.2	\$2,600	1.2	\$2,760	1.1	\$2,690	1.2
Therapy visit ^a	MEPS	\$142	\$9,280	3.5	\$7,420	3.4	\$7,320	3.3	\$8,080	3.3	\$7,700	3.3
Mental health visit	MCBS	\$67	\$1,470	0.5	\$1,420	0.6	\$1,400	0.6	\$1,420	0.6	\$1,410	0.6
Physician office visit	MEPS	\$175	\$16,160	6.0	\$15,130	6.9	\$14,890	6.7	\$15,330	6.3	\$15,130	6.6
Home health	^b	\$70/h	\$3,430	1.3	\$2,380	1.1	\$2,500	1.1	\$2,950	1.2	\$2,680	1.2
Home personal care visit	^c	\$18/h	\$23,860	8.9	\$16,770	7.6	\$17,360	7.8	\$20,330	8.4	\$18,720	8.1
Blood test	MCBS	\$12	\$310	0.1	\$290	0.1	\$280	0.1	\$290	0.1	\$290	0.1
MRI	MCBS	\$295	\$740	0.3	\$730	0.3	\$700	0.3	\$700	0.3	\$700	0.3
Productivity losses	BLS	—	\$179,090	66.9	\$147,720	67.0	\$149,620	67.7	\$163,970	67.8	\$156,200	67.6
Total costs, no DMT			\$267,710	100	\$220,340	100	\$221,110	100	\$241,970	100	\$230,920	100
DMT cost	Red Book ^d	—			\$247,372		\$271,200		\$234,258		\$254,912	
Total costs			\$267,710		\$467,712		\$492,310		\$476,228		\$485,832	

Abbreviations: BLS = Bureau of Labor Statistics²⁵; DMT = disease-modifying therapy; MCBS = Medicare Current Beneficiary Survey & Medicare claims (<https://www.cms.gov/MCBS/>); MEPS = Medical Expenditures Panel Survey (<http://www.meps.ahrq.gov/mepsweb/>).

^a Physical/occupational therapy visit.

^b Using the CMS rate for short office visits.

^c <http://www.disabled-world.com/artman/publish/health-care-cost.shtm>.

^d The Red Book Drug Topics. Montvale, NJ: Medical Economics Company Inc.; 2008.

lapses that in turn resulted in a gain in the number of relapse-free years (e.g., patients on interferon β -1b on average spent 6.074 out of 10 years without relapses compared to 5.051 years for untreated patients). Over time, average cohort health utilities declined for all treatment strategies, but they declined more quickly in untreated patients (figure e-1).

Health care costs. Ten-year disease-related costs were similar across the DMTs (\$467,712 including the cost of the medication vs \$220,340 excluding medication costs over 10 years on interferon β -1a IM) (table 2). Together with the cost of DMT, the next 3 most expensive categories in this population, productivity losses (up to \$180,000 over 10 years), inpatient admissions (up to \$26,300), and in-home nonmedical care (up to \$24,000), constituted over 90% of total costs.

Base case ICER. Based on the ICER estimates alone, all interferons had similar cost-effectiveness (e.g., \$901,319/QALY [95% confidence interval (CI) \$807,884–\$1,157,624] for interferon β -1a

IM, \$1,123,162/QALY [\$944,463–\$1,422,342] for interferon β -1b, and \$1,487,306 [\$1,209,560–\$1,914,390] for interferon β -1a SC). This was true for both cost per QALY and cost per RFY measure (table 3). However, the ICER for GA was statistically different from the ICER for any of the interferons (\$2,178,555/QALY [\$1,591,107–\$2,876,617]) (table 3).

Sensitivity and uncertainty analyses. We estimated uncertainty due to sampling (via bootstrapping), disease progression (via MC simulation), as well as modeling assumptions (e.g., by varying the discounting rate, CE threshold value, and outcome measures). Overall, the base case ICERs in our model have narrow 95% CIs indicating good precision (table 3). In order for the probability of the CE to be at least 50% or higher, the payer has to be willing to spend more than \$900,000/QALY for DMT (figure 2).

However, a substantial price reduction, analogous to bringing the current cost of DMT in the United States in line with the cost in the United Kingdom, could make DMTs nearly cost-effective. For in-

Table 3 Incremental cost-effectiveness ratios and health outcomes: Cumulative measures for the entire cohort over 10-year period, 3% discount

Measure (average per person)	Basic supportive treatment	Interferon β -1a IM	Interferon β -1b	Glatiramer acetate	Interferon β -1a SC
Health outcomes					
QALYs	6.500 (6.419–6.588)	6.692 (6.608–6.760)	6.673 (6.587–6.748)	6.582 (6.505–6.666)	6.626 (6.550–6.706)
Δ QALY		0.192 (0.148–0.209)	0.173 (0.137–0.202)	0.082 (0.062–0.113)	0.126 (0.098–0.155)
RFYs	5.051 (4.788–5.322)	5.620 (5.409–5.858)	6.074 (5.874–6.282)	5.879 (5.676–6.099)	5.918 (5.694–6.125)
Δ FRY		0.569 (0.507–0.649)	1.023 (0.945–1.110)	0.828 (0.773–0.889)	0.867 (0.789–0.917)
ICER^a					
Base case (simulation cohort starts at DS 2–DS 7)					
Cost/QALY		\$901,319 (807,884–1,157,624)	\$1,123,162 (944,463–1,422,342)	\$2,178,555 (1,591,107–2,876,617)	\$1,487,306 (1,209,560–1,914,390)
Cost/RFY		\$303,339 (264,567–346,052)	\$188,973 (173,181–208,044)	\$216,094 (198,078–234,104)	\$216,426 (202,186–241,696)
SA 1: Payer perspective (no productivity losses)		\$1,035,140 (938,175–1,329,469)	\$1,263,207 (1,066,647–1,591,004)	\$2,329,739 (1,698,518–3,049,534)	\$1,635,299 (1,326,498–2,090,528)
SA 2: included progression to advanced MS (DS = 8, bedridden)		\$428,120 (381,120–561,873)	\$539,406 (474,317–699,682)	\$1,010,359 (838,271–1,302,651)	\$704,509 (606,092–889,276)
Simulation cohort starts at DS = 2					
Cost/QALY		\$730,123 (616,352–840,935)	\$878,044 (767,228–1,055,937)	\$1,534,144 (1,311,623–2,129,312)	\$1,159,575 (969,722–369,482)
Cost/RFY		\$249,106 (228,351–283,685)	\$177,549 (168,387–195,889)	211,172 (198,755–231,290)	210,780 (197,656–228,854)
Simulation cohort starts at DS = 3					
Cost/QALY		\$898,169 (727,423–1,044,003)	\$958,738 (832,797–1,219,595)	\$1,763,036 (1,396,586–2,420,077)	\$1,255,088 (1,040,287–1,636,218)
Cost/RFY		\$294,697 (251,022–324,686)	\$183,177 (167,647–196,421)	\$206,290 (192,903–222,774)	\$215,466 (195,688–231,022)

Abbreviations: DS = disease steps multiple sclerosis disability scale; ICER = incremental cost-effectiveness ratio; MS = multiple sclerosis; QALY = quality-adjusted life-year; RFY = relapse-free year; SA = sensitivity analysis.

^a Compared to basic supportive treatment.

Figure 2 Cost-effectiveness acceptability curves: Current drug prices (A) and 67% price reduction (B)

We plotted probability of being cost-effective (vertical axes) vs cost-effectiveness threshold value (willingness to pay) (horizontal axes) for the cost of 1 year in perfect health (\$/quality-adjusted life-year) using current disease-modifying therapy medication prices (A) as well as reduced prices (B).

stance, if we reduce the cost of interferon β -1a IM by 67%, to about \$8,000/year, the chance of ICER for interferon β -1a IM being below \$700,000/QALY would be near 100% (figure 2).

Initiating DMT earlier (EDSS 2–2.5) was shown to improve the CE of all DMTs (e.g., for interferon β -1a IM \$730,123/QALY) compared to waiting to start DMT after patients reach noticeable disability (EDSS 3–4) (\$745,046/QALY for interferon β -1a IM) or compared to the base case, that is, initiating treatment at any disease state (\$898,169/QALY).

DISCUSSION This study presents an analysis of the CE of DMT use by patients with MS that is based solely on evidence from the United States, including data on drug effectiveness, patient health preferences, health care utilization, lost productivity, and cost information. Our estimates of the ICERs for all 4 examined DMTs were on the order of a million dollars per QALY. While there is no formal CE threshold in the United States, these estimates are an order of magnitude greater than the CE of many commonly accepted therapies for chronic illness.³⁰ Hence, our study indicates

that it is very unlikely that under current prescribing and pricing patterns, DMTs may be considered cost-effective for patients with RRMS and SPMS in the United States. The DMT cost-reduction analysis suggested that the probability that the ICER of DMT could be below \$700,000/QALY is near 0.

Our results indicate that the cost of DMT represents a substantial fraction of total health-related costs for patients with MS in the United States amounting to about 50% of 10-year cumulative costs. Lowering the prices of the DMTs by 67% to match prices in other industrialized countries³¹ would improve the CE of these therapies. Indeed, we demonstrate that when DMT costs in our model were reduced by 2-thirds, the CE of DMTs became comparable to the CE of other accepted interventions.³⁰ For instance, the annual cost of interferon β -1a IM in the United Kingdom is about £8,000 (\$12,000) compared to ~\$25,000 (\$34,000 in 2010) in the United States.³²

Our sensitivity analyses reemphasize the need for early DMT initiation and suggest that starting DMT earlier, at EDSS 2 or before, could be more cost-effective than starting DMT for patients with MS at later stages of the disease. One potential reason for this result is that starting DMT earlier may defer the substantial costs associated with late-stage MS and disability.

Inpatient utilization was low (0.18 hospitalizations per person per year) and contributed about 30% (\$22,000–\$26,000 per person in hospitalization costs over 10-year period) of medical costs in DMT medication costs of patients with MS. One reason for this is that the vast majority of relapses, which used to significantly contribute to the rate of hospitalization, are now managed in outpatient or home-based settings.

While the US models presented important evidence on cost-effectiveness of MS DMTs in the United States,^{7–10} these models have weaknesses that limit their current use for health policy and clinical practice decisions that we discussed earlier. Our model addresses these major concerns, mainly by using newly data collected after the DMTs were introduced to the US market. Our results are consistent with results reported in other studies conducted by independent academic groups,^{7,12} but are substantially less favorable than the results of industry-sponsored investigations.^{8,16,33,34} This is likely due to the funding effect and the conflict of interest bias that may enter into the model design, estimating parameters, and interpretation of CE study results.³⁵

We also recognize potential sample selection issues. Because healthier patients may be more likely to enroll in a registry or a study, our estimates of effec-

tiveness may be overestimated while the cost estimates are likely to be underestimated. Finally, the composition of patients in the “support therapy” arm is fairly heterogeneous and may include patients who choose to receive no therapy, as well as those who do not have access to therapy.

AUTHOR CONTRIBUTIONS

Dr. Noyes: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision, obtaining funding. A. Bajorska: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis. A. Chappel: drafting/revising the manuscript, analysis or interpretation of data, statistical analysis. Dr. Schwid: drafting/revising the manuscript. Dr. Mehta: drafting/revising the manuscript, analysis or interpretation of data, study supervision. Dr. Weinstock-Guttman: drafting/revising the manuscript. Dr. Holloway: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Dick: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis, study supervision, obtaining funding.

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DISCLOSURE

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