How effective are disease-modifying drugs in delaying progression in relapsing-onset MS?

M.G. Brown, PhD
S. Kirby, FRCPC
C. Skedgel, MDE
J.D. Fisk, PhD
T.J. Murray, FRCPC
V. Bhan, FRCPC
I.S. Sketris, PharmD

Address correspondence and reprint requests to Dr. Murray G. Brown, Centre for Clinical Research, 5890 University Avenue, Halifax, NS, Canada B3H 1V7
murray.brown@dal.ca

ABSTRACT

Objective: Our objective was to estimate the effectiveness of disease-modifying drugs (DMDs) in delaying multiple sclerosis (MS) disability progression in relapsing-onset (R-onset) definite MS patients under "real-world" conditions.

Methods: Treatment effect size, for DMDs as a class, was estimated in absolute terms and relative to MS natural history. A basic model estimated annual Expanded Disability Status Scale (EDSS) change before and after treatment. An expanded model estimated annual EDSS change in pretreatment years, treatment years on first drug, treatment years after drugs were switched, and in years after treatment stopped. Models were populated with 1980 through 2004 clinical data, including 1988 through 2004 data for all Nova Scotians treated with DMDs. Estimates were made for relapsing–remitting MS (RRMS), secondary progressive MS (SPMS), and R-onset groups.

Results: Estimated pretreatment annual EDSS increases were approximately 0.10 of one EDSS point for the RRMS group, 0.31 for the SPMS group, and 0.16 for the R-onset group. Estimates of EDSS increase avoided per treatment year on the first drug were significant for the RRMS group (−0.103, 0.000), the SPMS group (−0.065, 0.011), and the R-onset group (−0.162, 0.000); relative effect size estimates were 112%, 21%, and 105%. Estimated EDSS progression was faster in years after drug switches and treatment stops.

Conclusions: Our estimates of disease-modifying drug (DMD) relative treatment effect size, in the context of "real-world" clinical practice, are similar to DMD treatment efficacy estimates in pivotal trials, though our findings attained statistical significance. DMDs, as a class, are effective in delaying Expanded Disability Status Scale progression in patients with relapsing-onset definite multiple sclerosis (MS) (90%), although effectiveness is much better for relapsing–remitting MS than for secondary progressive MS groups. ***Neurology*® 2007;69:1498–1507**

Randomized clinical trials (RCTs) have demonstrated the efficacy of disease-modifying drugs (DMDs)—interferon β-1a, interferon β-1b, and glatiramer acetate—in relapsing-onset (R-onset) multiple sclerosis (MS). Thus far, efficacy has been demonstrated by reductions in relapse frequency, relapse severity, and MRI indices of gadolinium enhancing lesions and T2 lesion burden.[1-10] Evidence for preventing or delaying long-term neurologic disability is less convincing, incomplete, and controversial.[11-22] Although RCT results collectively show a trend toward slower disability progression, significant delays in progression by one Expanded Disability Status Scale (EDSS)[23] point or slower mean

Editorial, see page 1478

e-Pub ahead of print on August 15, 2007, at www.neurology.org.

From the Health Outcomes Research Unit (M.G.B.) and Department of Medicine, Neurology (S.K., T.J.M., V.B.) and Department of Medicine (C.S.), Department of Psychiatry (J.D.F.), and Department of Community Health and Epidemiology (M.G.B., T.J.M., I.S.S.), Capital Health District, Nova Scotia; College of Pharmacy (I.S.S.), Dalhousie University, Halifax, Nova Scotia, Canada.

Supported by Health Research and Policy Program, Health Canada; Multiple Sclerosis Society of Canada; Nova Scotia Health Research Foundation; Capital Health, Nova Scotia Health. Ingrid Sketris holds a CIHR/CHSRF Chair in Health Services Research, which is cosponsored by the Nova Scotia Health Research Foundation.

Disclosure: M.G. Brown has done consulting research and/or workshops from Serono, AstraZeneca, Aventis Pharma, and Biogen-Idec. J.D. Fisk has received honoraria for lecturing and workshop participation, and providing outcomes research consultation services for AstraZeneca, Bayer, Biogen-Idec, Bristol-Myers Squibb, Novartis, Sanofi-Aventis, and TEVA Neuroscience. T.J. Murray has received honoraria for advisory councils and travel expenses for attending meetings from Biogen-Idec, Serono, Teva, and Berlex. V. Bhan has received honoraria for advisory councils and travel expenses for attending meetings from Biogen-Idec, Serono, Teva, and Berlex. No other authors reported competing interests.

EDSS progression of treated vs untreated groups have not been demonstrated. Delayed progression to selected EDSS endpoints has been reported in only one study.[6] If DMD treatment is in fact efficacious in delaying disability progression, weak RCT results may reflect various factors, such as slow disability progression, short study periods, limited study sample sizes, EDSS measurement limitations, and study population selection biases. If short study periods are the critical factor, significant results may emerge from long-term surveillance of RCT study participants.[24-29] Regardless, postmarketing studies are required to demonstrate the effectiveness of DMDs in the "real-world" setting of clinical practice.

Short-term DMD effectiveness was estimated using pretreatment and post-treatment observational data from a representative population-based sample of R-onset MS patients, stratified into relapsing–remitting (RRMS) and secondary progressive (SPMS) groups.[19]

Our study objective was to estimate the effectiveness of DMDs, as a class, in delaying MS disability progression in RRMS, SPMS, and R-onset patients under "real-world" conditions.

METHODS

Study population. The Dalhousie Multiple Sclerosis Research Unit (DMSRU) database has 25 years of clinical data, including up to 6 years of treatment data for all persons whose DMDs were paid for completely by Nova Scotia's public universal drug insurance coverage program, as an insurer of last resort. Included are 29 persons who enrolled, between July and October 1995, in a 24-month placebo RCT for interferon-1a 22 μg subcutaneously weekly in RRMS.[30,31] DMSRU clinical data were linked to Nova Scotia Department of Health vital statistics and health services utilization data using encrypted IDs. As part of this study, Health Utilities Index Mark III[8,32] and certain other measures of health-related quality of life were administered at DMRSU visits between March 2002 and March 2004.

All persons in our study population had at least one DMSRU clinic visit between 1980 and March 2004. The DMSRU provides Nova Scotia's only specialized referral service for MS and is the sole source of provincially funded DMDs. Demographic data including years since onset (yso) of symptoms were recorded at first clinic visit. Neurologists estimated age at onset of MS symptoms from patient histories, and EDSS was recorded at each clinic visit, by the same three neurologists, from 1980 to January 2002. All clinic records in the period 1980 through 2004 were reviewed for all active attending patients as of March 2004, and for former DMSRU patients as of their last visit date or date of death. Patients were classified as RRMS or SPMS based on this review.

In 1998, DMDs were included as an insured benefit of the Exception Drug Fund, Nova Scotia Department of Health. This fund provides access to necessary medications for Nova Scotians who have no other means of obtaining funding for approved drugs. The treatment eligibility criteria for DMDs include a definite diagnosis of MS (Poser criteria), R-onset course, and EDSS $\leq$ 6.5 at initial injection. The DMSRU delivers Nova Scotia's MS DMD program and is solely responsible for determining treatment eligibility, education, treatment prescriptions, monitoring, and treatment switches or termination. Prescriptions are dispensed by the Queen Elizabeth II Health Sciences Centre pharmacy. All DMD costs (except for a small dispensing fee) are borne by the Department of Health, which in turn bills private insurers to recover copayments for those few patients with partial private insurance coverage.

Before first injection, all patients must complete a DMSRU education program on expected treatment benefits and limitations, side effects and their management, long-term compliance commitments and responsibilities, and prospective monitoring of outcomes. Physicians and patients jointly choose any of the insured DMDs, based on clinical judgment regarding efficacy, route of administration, dosing frequency, adverse drug reaction profile, and patient preferences and past experience. Contraindications to therapy include concurrent illness likely to alter compliance or reduce life expectancy, pregnancy planned or occurring, nursing mothers, and active severe depression.

Analysis strategy. How does one go about estimating clinical effectiveness in delaying disability progression in a complex chronic progressive disease such as R-onset MS? Our strategy is guided by nautical advice that says, "If you don't know how to tie the right knot, tie plenty of them." Not knowing of a single "right" model, we estimated DMD effect size for various subgroups of treatment-eligible persons, using fixed effects models. Here we report models for R-onset patients who were treated with DMDs within 20 years since symptom onset (table 1).

DMD treatment effect size was estimated in absolute terms and also relative to MS natural history. Estimates of annual disability progression were made for pretreatment years, for treatment years, and for post-treatment years using 25 years of clinical data. This article estimates EDSS natural history paths and DMD treatment paths for an RRMS group, an SPMS group, and an R-onset group. These reference groups include persons with clinic visit data that met criteria chosen by the investigators. They are part of a larger population of DMD-treated and never-treated persons with R-onset definite MS who attended the DMSRU clinic in 1980 through 2004. Our retrospective analysis was stratified by "final" MS classification at March 31, 2004, or most recent visit. A comprehensive record review validated this "final" classification variable.[19] The RRMS group included all persons with R-onset MS who had not converted to SPMS by their last visit, who had EDSS $\leq$ 3.5 at clinic visits occurring up to 20 years since onset of MS, and who were treated with DMDs. The SPMS group included all persons who had converted to SPMS by their last visit, who had EDSS $\leq$ 6.5 at clinic visits occurring up to 20 years since onset of MS, and who were treated with DMDs. Only five patients with

Table 1 Descriptive statistics for three reference groups of DMD-treated persons with R-onset definite MS in the Nova Scotia study population, 1980 through 2004

	RRMS, EDSS ≤ 3.5, yso ≤ 20		SPMS, EDSS ≤ 6.5,5 yso ≤ 20		R-onset = RRMS + SPMS, yso ≤ 20	
Nova Scotia MS DMD program		SD		SD		SD
Patient characteristics						
No. of persons	390		200		590	
No. of clinic visits	2,156	100%	1,451	100%	3,607	100%
No. of pre-DMD visits	783	36%	680	47%	1,463	41%
No. of post-DMD visits	1,373	64%	771	53%	2,144	59%
% Female		79%		77%		78%
Age at onset, y	29.9	8.1	31	8.5	30.4	8.3
EDSS at first injection	2.12	0.82	4.64	1.47	2.91	1.58
Fixed effects model						
EDSS, dependent variable mean, explanatory variable mean, %	2.12	0.85	4.43	1.63	3.05	1.67
Years since onset	8.0	5.1	10.2	5.2	8.91	5.24
Range, min–max	0.05–19.99		0.08–19.99		0.05–19.99	
DMD treatment years (all Rx)	2.96	1.71	3.65	1.66	3.14	1.73
Range, min–max	0.1–8.4		0.1–8.2		0.1–8.4	
DMD Rx switches ≥ 1	16%		25%		18.5%	
DMD stopped	2%		5%		3%	
Years since DMD stopped	0.03	0.02	0.06	0.41	0.04	0.29
DMD years × years stopped	0.23	1.53	0.58	2.64	0.32	1.89
DMD treatment years by Rx						
Avonex	23%		12%		20%	
Betaseron	18%		48%		27%	
Copaxone	25%		12%		21%	
Rebif6	24%		14%		21%	
Rebif12	11%		14%		12%	

Unit of observation = clinic visit; DMD = disease-modifying drug; R-onset = relapsing-onset; MS = multiple sclerosis; RRMS = relapsing-remitting MS; EDSS = Expanded Disability Status Scale; yso = years since onset; SPMS = secondary progressive MS.

RRMS and yso ≤ 20 had at least one visit where EDSS > 3.5 and EDSS ≤ 6.5. These five comprised only 1.3% of 395 treated persons with a final MS classification of RRMS and yso ≤ 20. There were too few to make a separate group, and they were sufficiently atypical that we decided to exclude them from the RRMS reference group. They may be secondary progressive cases not yet classified as such.

The study groups were selected for the following reasons. Nova Scotia's DMD insurance program covers only R-onset definite MS patients with EDSS scores ≤ 6.5 at onset of treatment. Clinic visit data up to 20 years was chosen because this time period is often used when modeling long-term treatment effectiveness and cost-effectiveness. We used the pretreatment data of our subjects as self controls rather than data from untreated subjects as controls because treated persons differ systematically from their never-treated contemporary counterparts, particularly with respect to disease severity.

We estimated the effectiveness of DMDs as a new class of drugs. Other studies have demonstrated efficacy. There are various reasons for analyzing DMDs as a class, rather than separately. A pragmatic reason is that by analyzing DMDs as a class, it is feasible to estimate DMD effectiveness for more subgroups and treatment scenarios. The analysis of DMDs as a class also facilitates the modeling of DMD switches, stops, and post-treatment progression paths, which is precluded when DMDs are analyzed separately.

Statistical models. A basic and an expanded fixed effects model were used to estimate DMD absolute treatment effect size, measured by annual EDSS increase avoided per treatment year, as well as relative treatment effect size, measured by absolute treatment effect size divided by the estimated annual EDSS increase in pretreatment years. Hausmann tests indicated that fixed effects models, rather than random effects models, were appropriate.[33,34]

Our basic fixed effects model (table 2) estimated 1) annual EDSS change in pretreatment years (βyso), 2) DMD absolute effect size per treatment year (βDMDy), and 3) annual EDSS change in treatment years (βyso + βDMDy). Only years since onset and treatment years variables are modeled. Quadratic and cubic years since onset variables are

Table 2 Estimated DMD treatment effects for three reference groups of persons with R-onset definite MS and yso ≤ 20; basic fixed effects model

Reference group	RRMS, EDSS ≤ 3.5, yso ≤ 20			SPMS, EDSS ≤ 6.5, yso ≤ 20			R-onset = RRMS + SPMS, yso ≤ 20		
Model variable	Coeff	SE	$p > \|t\|$	Coeff	SE	$p > \|t\|$	Coeff	SE	$p > \|t\|$
Intercept, Int	1.590	0.078	0.000	1.458	0.151	0.000	1.476	0.081	0.000
Years since onset, βyso	0.098	0.030	0.001	0.317	0.056	0.000	0.162	0.031	0.000
yso squared, βyso^2	−0.002	0.004	0.513	0.001	0.006	0.818	0.006	0.004	0.114
yso cubed, βyso^3	0.000	0.000	0.501	0.000	0.000	0.260	0.000	0.000	0.122
DMD treatment years, βDMDy	−0.098	0.015	0.000	−0.025	0.024	0.292	−0.145	0.014	0.000
Relative effect = $-\beta$DMDy/βyso	100%			8%			90%		
R^2									
Within person (group)	0.048			0.503			0.282		
Between persons (groups)	0.056			0.015			0.090		
Overall	0.045			0.136			0.118		
No. of visit observations	2,156			1,451			3,607		
No. of persons (groups)	390			200			590		
Min observations per group	1			1			1		
Max observations per group	17			26			26		

Models are populated with Nova Scotia Dalhousie Multiple Sclerosis Research Unit clinic visit data from 1980 through March 2004.
DMD = disease-modifying drug; R-onset = relapsing-onset; MS = multiple sclerosis; yso = years since onset; RRMS = relapsing–remitting MS; EDSS = Expanded Disability Status Scale; SPMS = secondary progressive MS; Coeff = coefficient.

included to test for nonlinear pretreatment EDSS paths. All EDSS observations are included in our models when estimating EDSS natural history path slopes and DMD treatment path slopes even though some observations may be transitorily high or low, because such fluctuations are characteristic of MS disability progression. (Nonlinear results are not presented graphically in this article.)

Our expanded fixed effects model (table 3) includes additional standardizing variables for years after drug switches and for post-treatment years. This expanded model estimates mean annual EDSS change in 1) pretreatment years (βyso), 2) treatment years using the first prescribed drug (βyso + βDMDy), 3) treatment years after switches to one or more other drugs (βyso + βDMDy + βDMDsw), and 4) post-treatment years (βyso + βDMDy + βDMDsw + βpDMDy + βDMDy × βpDMDy).

The models weight persons equally, regardless of their number of clinic visits, when estimating beta coefficients. Each β coefficient estimate represents the marginal, or extra, effect of one independent variable on annual EDSS change, after standardizing for all other variables. To get estimated total (net) annual EDSS change for ever-treated persons after treatment starts, switches, or stops, the appropriate β coefficients are added.

The models compute within-person, between-persons, and overall variance (R^2) of EDSS for the RRMS group, the SPMS group, and the R-onset group. Fixed effects models include only time-dependent variables explicitly. However, relevant time-invariant variables for each person are numerous and include such factors as date of birth, genetic endowment, age at onset, initial visit EDSS score and EDSS subscale scores, time from onset of symptoms to first injection, and age at first injection. These served as unmeasured standardizing variables in fixed effects model analysis of within-person annual EDSS change. Such time-invariant variables, which vary across persons, although they do not enter the model explicitly, account in part for systematic differences in results for within-person, between-persons, and overall explained variance (R^2) of EDSS scores.

A retrospective perspective is appropriate when interpreting DMD effectiveness estimates for the RRMS and SPMS groups, stratified by "final" classification as of March 2004. In contrast, an intention-to-treat perspective is appropriate when interpreting effectiveness estimates for the R-onset group, because their "final" classification was unknown when treatment was started.

RESULTS Table 1 contains descriptive statistics for the three reference groups of DMD-treated subjects. The RRMS group included 390 persons (2,156 visits), the SPMS group included 200 persons (1,451 visits), and the R-onset group included these 590 persons (3,607 visits). Pre–DMD treatment visits represented 36%, 47%, and 41% of all visits. Treatment duration ranged from a minimum of 0.1 year (37 days) to a maximum of 8.4 years (3,068 days). Almost all patients started treatment after August 1998 and had up to 5.6 years treatment duration as of March 2004. Twenty-nine patients who had participated in a clinical trial of interferon-1a 22 μg subcutaneously weekly had up to 8.4 treatment years. Years since onset, which includes treatment years, had a mean of 8.9 years (SD 5.2) for the R-onset group.

Table 3 Estimated DMD treatment effects for three reference groups of persons with R-onset definite MS and yso ≤ 20; expanded fixed effects model

Reference group	RRMS, EDSS ≤ 3.5, yso ≤ 20			SPMS, EDSS ≤ 6.5, yso ≤ 20			R-onset = RRMS + SPMS, yso ≤ 20		
Model variable	Coeff	SE	$p > \|t\|$	Coeff	SE	$p > \|t\|$	Coeff	SE	$p > \|t\|$
Intercept, Int	1.604	0.030	0.000	1.456	0.151	0.000	1.494	0.081	0.000
Years since onset, βyso	0.092	0.004	0.002	0.304	0.056	0.000	0.154	0.031	0.000
yso squared, βyso^2	−0.002	0.000	0.609	0.003	0.006	0.059	0.007	0.004	0.065
yso cubed, βyso^3	0.000	0.016	0.568	0.000	0.002	0.149	0.000	0.000	0.071
DMD treatment years, βDMDy	−0.103	0.069	0.000	−0.065	0.256	0.011	−0.162	0.015	0.000
DMD switches ≥ 1, βDMDsw	0.067	0.112	0.333	0.473	0.126	0.000	0.174	0.071	0.015
Post-DMD years, βpDMDy	0.214	0.026	0.066	0.079	0.096	0.408	0.039	0.075	0.046
DMDy × pDMDy, β(DMDy × pDMDy)	−0.007	0.078	0.790	0.046	0.031	0.133	0.042	0.021	0.062
Relative effect = −βDMDy/βyso	112%			22%			105%		
R^2									
Within person (group)	0.050			0.511			0.287		
Between persons (groups)	0.056			0.015			0.093		
Overall	0.045			0.138			0.122		
No. of visit observations	2,156			1,451			3,607		
No. of groups (persons)	390			200			590		
Min observations per group	1			1			1		
Max observations per group	17			26			26		

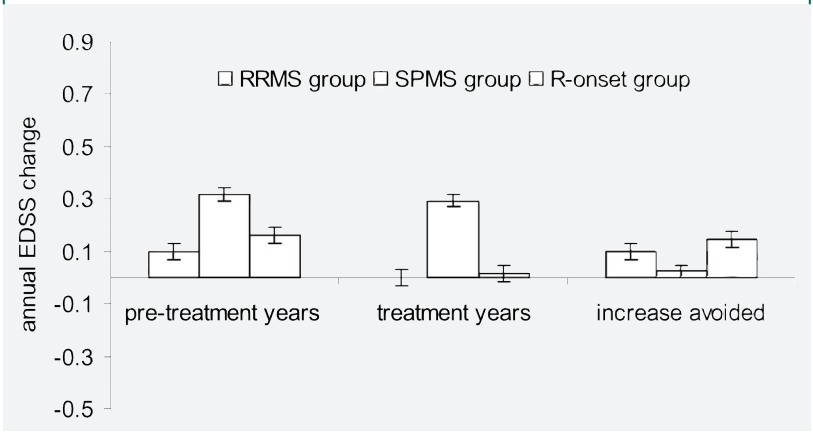
Models are populated with Nova Scotia Dalhousie Multiple Sclerosis Research Unit clinic visit data from 1980 through March 2004.
DMD = disease-modifying drug; R-onset = relapsing-onset; MS = multiple sclerosis; yso = years since onset; RRMS = relapsing–remitting MS; EDSS = Expanded Disability Status Scale; SPMS = secondary progressive MS; Coeff = coefficient.

Visits were less frequent and at more irregular intervals in pre-DMD years 1980 through 1998, when most visits were initiated by patients and their referring physicians when a consultation was needed. Since 1998, all patients receiving DMDs were required to return for an annual assessment as a condition for continuing treatment. Patients were seen more frequently for assessment and management of relapses, often with a visit 3 to 6 months after relapse in addition to mandatory yearly visits. Patients were also seen for symptom management. Irrespective of the type of visit, a neurologic examination was conducted and an EDSS was recorded.

A strength of our clinic data are that all patients except the 29 RCT participants were "DMD therapy naive" before August 1998. Only 4 of 590 patients treated with DMDs were treated concurrently with mitoxantrone. None of our study population patients were ever treated with cyclophosphamide, azathioprine, methotrexate, or any other immunosuppressive therapies. We used pulse steroids for acute relapses, with the usual protocol of 1 g methylprednisolone IV daily for 3 days, sometimes followed by a rapid taper with oral prednisone (over 1 to 2 weeks) but this is done for all patients, irrespective of DMD treatment. We did not use pulse steroids (oral or IV) monthly or otherwise, in absence of relapses.

Basic fixed effects model estimates of annual EDSS disability progression in pretreatment and post-treatment years (table 2) are shown in figures 1 and 2. The estimated pretreatment EDSS increase per year (βyso) was 0.098 EDSS points for the RRMS group, 0.317 EDSS points for the SPMS group, and 0.162 EDSS points for the R-onset group. Estimates of the absolute treatment effect (βDMDy) were consistently negative and reflected decreased accumulation of disability per treatment year. For the RRMS group, treatment with DMDs resulted in a statistically significant absolute treatment effect estimate of −0.098 EDSS points change per year ($p = 0.000$), for a relative treatment effect size of 100%. Estimates for the SPMS group were much smaller (−0.025 EDSS points, relative treatment effect 8%) and not significant ($p = 0.292$). Estimates for the combined R-onset group were large (−0.145 EDSS points, relative treatment effect 90%) and significant ($p = 0.000$).

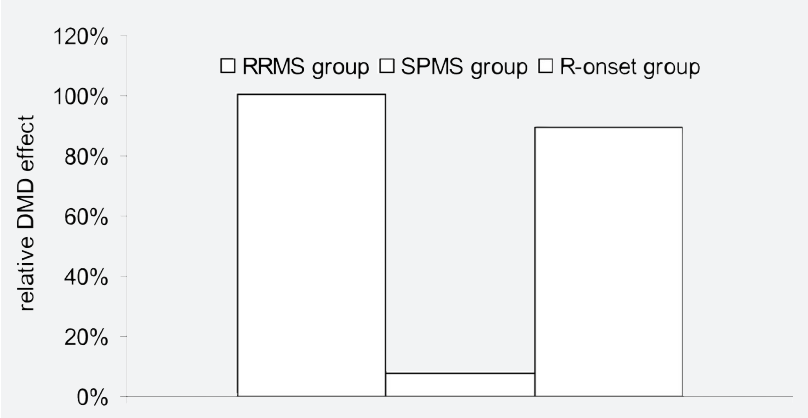
Figure 1 Annual EDSS change before and after DMD treatment: Basic model



Estimates of Expanded Disability Status Scale (EDSS) pretreatment path slopes, treatment path slopes, and EDSS increases avoided, with standard errors, for relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), and relapsing-onset (R-onset) reference groups of disease-modifying drug-treated persons; basic fixed effects model.

Results from our expanded fixed effects model (table 3), which standardized for years since onset of MS, treatment years, drug switches, treatment termination, and years since termination, are illustrated in figures 3 through 5. Figure 5 shows, for the RRMS, SPMS, and R-onset groups, estimates of annual EDSS change in 1) pretreatment years, 2) DMD treatment years in which the first prescribed drug was used, 3) treatment years after switches to another drug occurred at least once, and 4) post-treatment years after treatment termination. (The x-axis in figure 5 is arbitrarily divided into four equal time intervals.) Expanded model estimates of annual EDSS change during pretreatment years were similar to, but slightly smaller than, the basic model estimates. Expanded model estimates of DMD effectiveness for persons treated with only one drug were significant for the RRMS group (−0.103 EDSS increase avoided per treatment year, $p = 0.000$), the SPMS group (−0.065 EDSS increase avoided, $p = 0.011$), and the R-onset group (−0.162 EDSS increase avoided, $p = 0.000$), whereas estimated relative treatment effect size were 112%, 21%, and 105%.

Figure 2 Relative DMD treatment effect size: Basic model



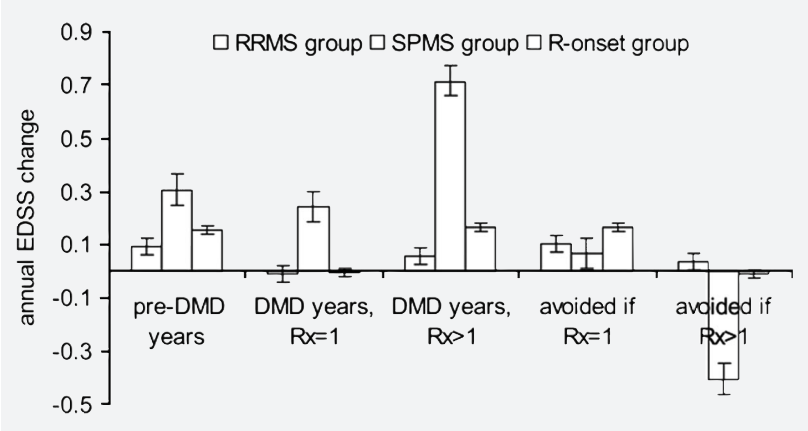
Estimates of disease-modifying drug (DMD) treatment effect size relative to pretreatment annual Expanded Disability Status Scale changes, for relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), and relapsing-onset (R-onset) reference groups of DMD-treated persons; basic fixed effects model.

The effect of drugs switches on accumulation of disability was consistently positive, with all groups showing an increase in the rate of disability progression after the first switch. While the estimated positive incremental annual EDSS change in years after drug switches was not significant for the RRMS group (0.067 EDSS points, $p = 0.333$), it was significant for the SPMS group (0.473 EDSS points, $p = 0.000$) and the R-onset group (0.174 EDSS points, $p = 0.015$). Estimated additional positive incremental annual EDSS change in years after DMD treatment termination were not significant for the RRMS and SPMS groups, but were significant for the combined R-onset group.

Three goodness-of-fit R^2 statistics are reported for fixed effects models: a within-person R^2, a between-persons R^2, and an overall R^2. Similar patterns emerged from the basic and expanded models, with slightly larger R^2 for the expanded model. For the RRMS group, all three R^2 statistics were small (≤0.056). For the SPMS group, the within-person R^2 was very large (0.511), the between-persons R^2 was very small (0.015), and the overall R^2 was 0.138. For the R-onset group, the within-person R^2 was 0.282, the between-persons R^2 was 0.090, and the overall R^2 was 0.118.

DISCUSSION Our "real-world" estimates indicate that DMDs, as a class, were effective in delaying disability progression in R-onset MS. Absolute treatment effect size, measured by EDSS increase avoided per treatment year, was small. But absolute effect size relative to EDSS natural history increase was large, estimated at 90% for R-onset patients treated in Nova Scotia from July 1998 through March 2004. Estimated benefits were much greater for patients who were classified as RRMS at the start of treatment and still classified as RRMS in March 2004, compared with patients who were classified as either RRMS or SPMS at the start of treatment but were classified as SPMS in March 2004. Although the benefit of DMDs was clearly less in patients classified as SPMS at the start of treatment or who converted to SPMS after treatment started, there was an

Figure 3 Annual EDSS change before and after DMD treatment: Expanded model

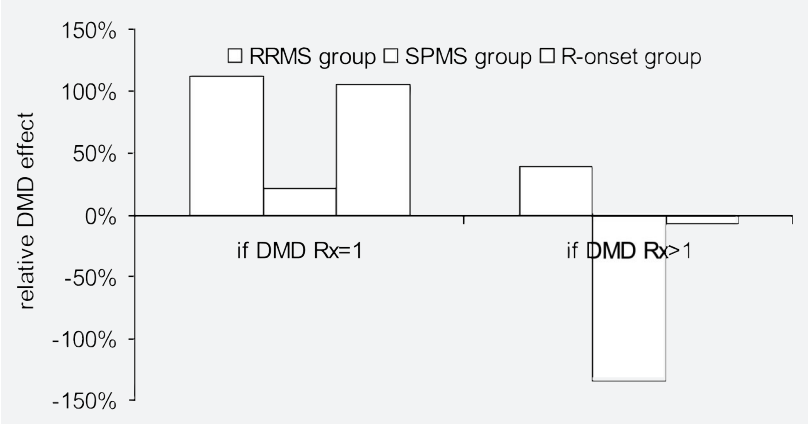


Estimates of Expanded Disability Status Scale (EDSS) pretreatment path slopes, treatment path slopes if no Rx switches occurred, treatment path slopes if Rx switches occurred, EDSS increases avoided if no Rx switches occurred, and EDSS increases avoided if Rx switches occurred, with standard errors, for relapsing–remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), and relapsing-onset (R-onset) reference groups of disease-modifying drug (DMD)–treated persons.

overall benefit for R-onset patients on DMDs. There are no RCT results directly comparable to these observational results for R-onset MS.

Our effectiveness results for R-onset patients classified as RRMS or SPMS are roughly similar to comparable RCT efficacy results that examined mean change in EDSS scores within their study periods for treatment and placebo groups. Both Phase III studies and this Phase IV study estimate small absolute effect size per treatment year, measured by EDSS increase avoided, and both estimate very large relative treatment effect size in RRMS groups compared with SPMS groups. For example, our DMD relative effect size estimates in RRMS range from 100% (basic model) to 112% (expanded model) for persons treated with a single DMD, whereas comparable RCT efficacy estimates range from 50%[5] to 132%.[11] Our relative effect size estimates in SPMS range from 8% (basic model) to 21% (expanded model) for persons treated with a single DMD, whereas comparable RCT efficacy estimates range from 16%[10,21] to 32%.[6]

Figure 4 Relative DMD treatment effect size: Expanded model



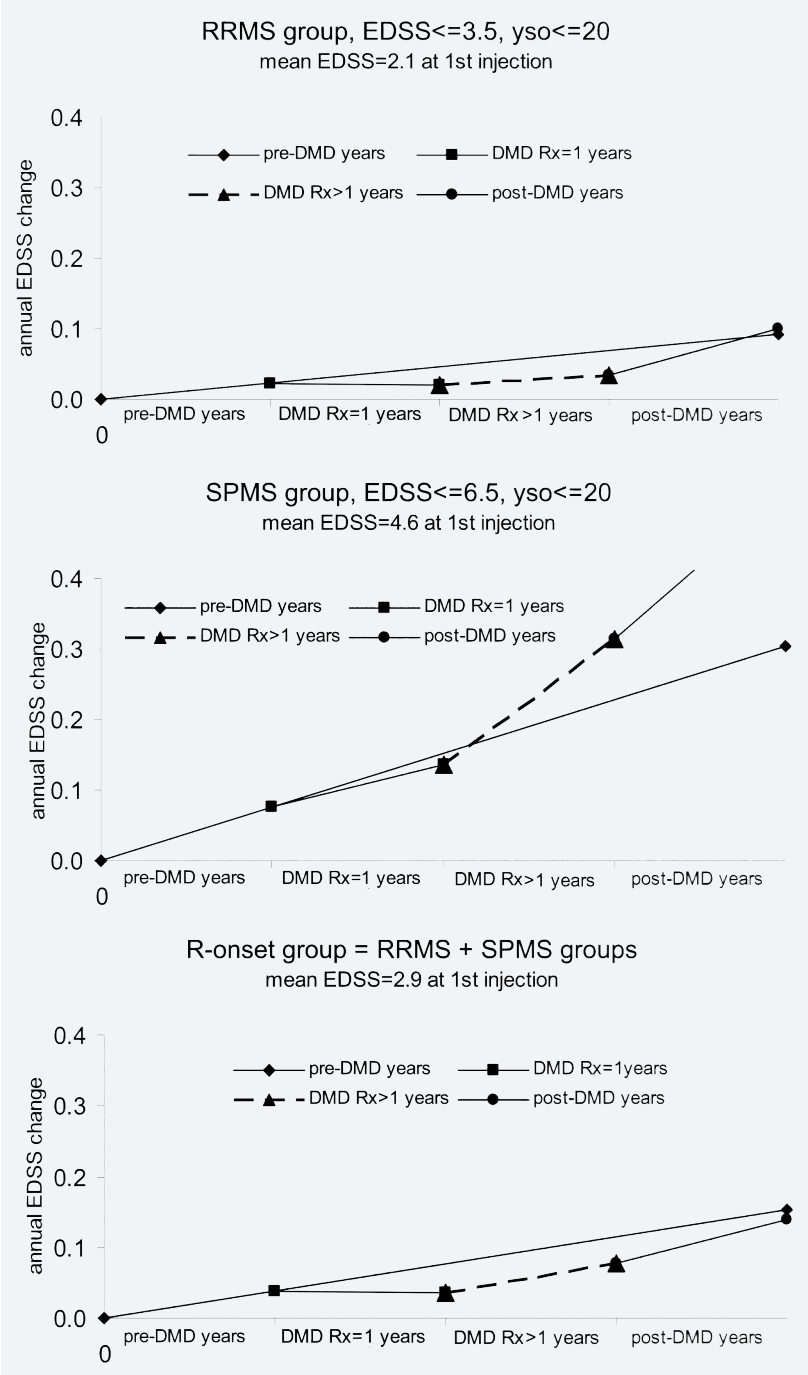
Estimates of disease-modifying drug (DMD) treatment effect size relative to pretreatment annual Expanded Disability Status Scale changes for relapsing–remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), and relapsing-onset (R-onset) reference groups of DMD-treated persons if no Rx switches occurred and if Rx switches occurred.

Whereas RCT efficacy studies have demonstrated only trends toward significance, our estimates are highly significant and robust. Although this greater significance may reflect larger study groups and longer treatment duration, other factors may also contribute. RCTs used matched placebo control groups, whereas we used DMD-treated persons as their own self-controls. RCTs compared treatment and control groups prospectively from the time of recruitment without standardizing for previous natural history progression, whereas our fixed effects models were populated with 1980 through 2004 EDSS data to estimate annual EDSS change for each person and their study group in pretreatment, treatment, and post-treatment years. Forty-one percent of R-onset group EDSS visit observations occurred in pretreatment years. RCTs estimated efficacy for particular DMDs, whereas we estimated effectiveness for DMDs as a class, using data from all treated persons irrespective of which DMDs were used and in what sequence. We classified persons in RRMS and SPMS groups retrospectively at the study end date, whereas persons in RCT studies were classified prospectively at recruitment.

Our expanded model estimated DMD effect size while standardizing for treatment years on the first prescribed drug (comparable with RCTs), treatment years on a second or third drug, and years since DMD treatment was stopped. Our study estimated that annual EDSS change was more rapid in years after drug switches and termination of treatment, whereas RCTs were unable to address this issue. Our results suggest that DMD switches and stops, in the context of clinical practice, may be markers for unmeasured biologic or other confounding factors, such as adverse drug reactions, antibody development, or comorbidities that increase MS disability progression.

Our Phase IV effectiveness estimates for DMDs as a class complement Phase III RCT efficacy results for particular DMDs. RCT study samples are not representative of MS populations, whereas DMSRU clinical data are represen-

Figure 5 Annual EDSS change before and after DMD treatment: Expanded model



Estimated annual Expanded Disability Status Scale (EDSS) change in pretreatment years, disease-modifying drug (DMD) Rx = 1 years, DMD Rx > 1 years (after switches), and DMD Rx = 0 years (after stopped), for relapsing–remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), and relapsing-onset (R-onset) groups of DMD-treated persons.

tative of Nova Scotia's MS population, particularly since 1998, when DMD insurance coverage began. EDSS progression rates in Nova Scotia more closely resemble the relatively slow rates recently reported from British Columbia[35] rather than the faster rates reported in earlier studies from Ontario[28] and Sweden.[36] RCT studies have high internal validity but low external validity, whereas Phase IV observational studies have lower internal validity but higher external validity.

The interpretation of dose–response statistical relationships in prospective placebo-controlled RCTs with high internal validity is clearer than is the interpretation of statistical associations described by retrospective observational studies with relatively low internal validity. For example, whereas it is plausible to interpret descriptive statistical associations between treatment years on a single DMD and slower EDSS progression as a causal dose–response relationship, it is implausible to interpret descriptive statistical associations between drug switches or treatment termination and faster EDSS progression as dose–response relationships. In both cases, there are confounding factors present, including placebo effects, whose role may be clarified by further research. More frequent visits in the post DMD era may well have been a factor (in terms of better management of symptoms and involvement of allied health professionals) in slowing disability progression.

The development of neutralizing antibodies (Nab_+) after interferon beta treatment has been shown to reduce treatment effect size and to increase EDSS annual progression rate.[22] Because our models do not standardize for NAb_+, we likely underestimate effect size for NAb-negative subgroups and overestimate effect size for NAb_+ subgroups.

DMD effectiveness was examined by comparing individuals' estimated annual changes in EDSS scores in the years before and after treatment. Because the EDSS is an ordinal scale, and not an interval measure, it can be argued whether mean annual EDSS change is a meaningful outcome. However, we have previously shown that, despite its limitations, the EDSS has high concordance with the Health Utility Index, a measure of health-related quality of life that does have interval measurement properties, and that concordance is highest in EDSS range 0 to 6.5.[37]

DMDs are not expected to be equally effective for all R-onset patients and in all stages of disability progression. Our varying estimates for persons with R-onset definite MS, RRMS, or SPMS illustrate the complexity of MS disability progression and the challenges of estimating the extent to which DMDs delay progression. Because a single "right" model for estimating MS natural history and DMD effectiveness remains elusive, we adopted a research strategy that applies the same

model when estimating DMD effectiveness for various patient subgroups. A general picture then emerges of how DMD effectiveness varies across subgroups. This is one way of dealing with MS complexity when analyzing large databases.

This article reports effect size estimates for an RRMS reference group with mild disability, an SPMS reference group with mild or moderate disability, and a combined R-onset reference group with up to 20 years since onset. Further research could retrospectively estimate DMD effectiveness in other subgroups, such as those that include ever-treated and never-treated controls and groups that differ by disability severity, years since onset, and treatment duration. Comparison of groups who switched drugs with those who did not switch could also be undertaken. DMD effectiveness could also be estimated with patient health status measured by a generic health utilities index instead of the MS-specific EDSS.

The current study did not estimate, directly, whether DMDs extend the time spent within "mild" and "moderate" disability severity categories or whether DMDs increase the time spent with an RRMS classification before being reclassified as SPMS. However, because our estimates show that DMDs slow EDSS progression in groups with "mild" disability (no ambulatory aids needed) and "moderate" disability (ambulatory aids needed eventually), it is likely that the time from onset to "severe" disability (wheelchair dependence) and "extreme" disability (confined to bed) also increases.

"Real-world" effectiveness evidence such as that presented here contributes to ongoing debates regarding which patients are good candidates for DMDs and, if so, when treatment should start, switch, or cease. Although DMD treatment years data in this study is longer than that in all but one pivotal RCT, it still represents relatively "short-term" treatment. The credibility of Phase IV study estimates will increase as treatment duration data accumulates. Short-term effectiveness evidence is required when modeling long-term effectiveness and cost-effectiveness. It is also useful in simulation studies of the effectiveness and cost-effectiveness of emerging DMDs, of DMD combination therapies, and of genetic markers that may predict disease course in R-onset MS and response to DMD treatment. Because Nova Scotia estimates of DMD relative treatment effect size for RRMS subgroups are very large (100% to 110%) for the initial DMD, treatment may temporarily arrest disability progression or even reduce disability slightly. Given this evidence, incremental health outcomes (beyond that attributable to current DMDs) from treatment with newer DMDs and with DMD combination therapy may be small for those RRMS patients who are able to continue treatment on their initial DMD. If so, incremental cost-effectiveness ratios for newer DMDs and combination therapies will likely be larger than those for current DMDs, depending on pricing. The development of genetic markers capable of predicting disability progression and "final" MS classification for persons with R-onset MS would greatly facilitate clinical decisions regarding which patients to treat, which drugs to prescribe, and for how long. If such genetic markers also identify persons destined to have very little disability progression over their lifetime, unnecessary long-term DMD treatment may be avoided.

ACKNOWLEDGMENT

The authors thank Gordon Flowerdew, PhD, for consultation regarding statistical analyses.

Received January 21, 2007. Accepted in final form April 30, 2007.

REFERENCES

1. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis: I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. Neurology 1993;43:655–661.
2. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol 1996;39:285–294.
3. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology 1995;45:1268–1276.
4. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Neurology 1995;45:1277–1285.
5. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon Beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet 1998;352:1498–1504.
6. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on Interferon Beta-1b in Secondary Progressive MS. Lancet 1998;352:1491–1497.
7. Goodin DS, Frohman EM, Garmany GP Jr, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcom-

mittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology 2002;58:169–178.
8. Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-Beta-1a in MS (SPECTRIMS) Study Group. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: clinical results. Neurology 2001;56:1496–1504.
9. National Institute for Clinical Medicine. Multiple sclerosis: management of multiple sclerosis in primary and secondary care. NICE Technical Appraisal Guidance no. 8. 2003.
10. Panitch H, Miller A, Paty D, Weinshenker B, North American Study Group on Interferon beta-1b in Secondary Progressive MS. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. Neurology 2004;63:1788–1795.
11. Johnson KP, Brooks BR, Cohen JA, et al. Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability. Copolymer 1 Multiple Sclerosis Study Group. Neurology 1998;50:701–708.
12. Johnson KP, Brooks BR, Ford CC, et al. Sustained clinical benefits of glatiramer acetate in relapsing multiple sclerosis patients observed for 6 years. Copolymer 1 Multiple Sclerosis Study Group. Mult Scler 2000;6:255–266.
13. Long-term efficacy of interferon-beta-1a in relapsing MS. PRISMS Study Group and the University of British Columbia MS/MRI Analysis Group. PRISMS-4. Neurology 2001;56:1628–1636.
14. Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging–measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. Ann Neurol 2001;49:290–297.
15. Kappos L, Polman C, Pozzilli C, et al. Final analysis of the European multicenter trial on IFNbeta-1b in secondary-progressive MS. Neurology 2001;57:1969–1975.
16. Kappos L, Weinshenker B, Pozzilli C, et al. Interferon beta-1b in secondary progressive MS: a combined analysis of the two trials. Neurology 2004;63:1779–1787.
17. Filippini G, Munari L, Incorvaia B, et al. Interferons in relapsing remitting multiple sclerosis: a systematic review. Lancet 2003;361:545–552.
18. Cohen JA, Antel JP. Does interferon beta help in secondary progressive MS? Neurology 2004;63:1768–1769.
19. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology 1996;46:907–911.
20. Johnson KP, Panitch HS, Ford CC, et al. Long-term slowing of disability progression in patients receiving continuous glatiramer acetate compared with those withdrawing from therapy: 10 year results from an ongoing trial. Neurology 2004;62:A180.
21. The North American Study Group on Interferon Beta-1b in Secondary Progressive MS. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. Neurology 2004;63:1788–1795.
22. Namaka M, Pollitt-Smith M, Gupta A, et al. The clinical importance of neutralizing antibodies in relapsing-remitting multiple sclerosis. Curr Med Res Opin 2006;22:223–239.
23. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444–1452.
24. Kinkel RP, Kollman C, O'Connor P, et al. IM interferon beta-1a delays definite multiple sclerosis 5 years after a first demyelinating event. Neurology 2006;66:678–684.
25. Ebers GC, Rice G, Wolf C, et al. 16 year long-term follow-up of interferon beta 1b treatment in patients with multiple sclerosis. Mult Scler 2005;11 (suppl 1):S156.
26. Rudick RA, Cutter GR, Baier M, et al. Estimating long-term effects of disease-modifying drug therapy in multiple sclerosis patients. Mult Scler 2005;11:626–634.
27. Kappos L, Traboulsee A, Constantinescu C, et al. Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS. Neurology 2006;67:944–953.
28. Weinshenker BG, Sibley WA. Natural history and treatment of multiple sclerosis. Curr Opin Neurol Neurosurg 1992;5:203–211.
29. Paty DW, Ebers GC. Multiple sclerosis. Philadelphia: FA Davis Co, 1998.
30. Evidence of interferon beta-1a dose response in relapsing-remitting MS: the OWIMS Study. The Once Weekly Interferon for MS Study Group. Neurology 1999;53:679–686.
31. Freedman MS, Francis GS, Sanders EA, et al. Randomized study of once-weekly interferon beta-1a therapy in relapsing multiple sclerosis: three-year data from the OWIMS study. Mult Scler 2005;11:41–45.
32. Torrance GW, Furlong W, Feeny D, Boyle M. Multi-attribute preference functions: Health Utilities Index. Pharmacoeconomics 1995;7:503–520.
33. Greene WH. Econometric analysis. Upper Saddle River, NJ: Prentice Hall, 2000.
34. Stata statistical software [computer program]. Version release 8.0. College Station, TX.
35. Tremlett H, Paty D, Devonshire V. Disability progression in multiple sclerosis is slower than previously reported. Neurology 2006;66:172–177.
36. Runmarker B, Andersen O. Prognostic factors in a multiple sclerosis incidence cohort with twenty-five years of follow-up. Brain 1993;116 (pt 1):117–134.
37. Fisk JD, Brown MG, Sketris IS, Metz LM, Murray TJ, Stadnyk KJ. A comparison of health utility measures for the evaluation of multiple sclerosis treatments. J Neurol Neurosurg Psychiatry 2005;76:58–63.