

# The Dilemma of When to Stop Disease-Modifying Therapy in Multiple Sclerosis

## A Narrative Review and Canadian Regional Reimbursement Policies

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**Background:** Disease-modifying therapy (DMT) has changed the landscape of multiple sclerosis (MS) care. However, there is lack of consensus on the duration of treatment and the selection of individuals most likely to benefit from continued treatment. Current evidence, practice guidelines, health policy, and ethical considerations presented together may further inform challenging clinical decision making and future directions. The objectives of this study were to conduct a narrative review of original research and practice guideline recommendations on discontinuation of DMTs in MS; to collect information regarding Canadian regional reimbursement policies for DMT coverage in MS; and to present ethical considerations applicable to such decision making.

**Methods:** A literature review was conducted of the MEDLINE/PubMed, OneFile (GALE), Scopus (Elsevier), and ProQuest Biological Science Collection databases. Data regarding Canadian regional reimbursement policies for DMT coverage in MS were collected from the ministry/government websites. Ethical considerations were reviewed in the context of the identified evidence, guidelines, and policies.

**Results:** The literature lacks evidence from prospective randomized controlled trials that directly address the issue of discontinuation of DMTs in MS. Current practice guidelines advocate the vital role of patient choice in decision making. There are regional variations in Expanded Disability Status Scale criteria scores for continuing MS DMT coverage among Canadian provinces/territories.

**Conclusions:** In the absence of strong evidence on discontinuation of DMTs, shared decision making and consideration of the ethical complexities could help in the decision-making process. *Int J MS Care*. 2020;22:75-84.

**D**isease-modifying therapies (DMTs) are known to reduce relapse frequency and the development of new magnetic resonance imaging (MRI) lesions in patients with relapsing-remitting multiple sclerosis (RRMS).<sup>1</sup> However, there are limited data on the efficacy of DMTs in patients with secondary

progressive multiple sclerosis (SPMS).<sup>2</sup> Inflammatory activity in multiple sclerosis (MS) and the frequency of relapses decline with increasing patient age.<sup>3</sup> In addition, as time from disease onset increases, relapses in patients with MS exert less effect on disease progression.<sup>4</sup> These clinical and natural history findings may create deci-

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sional dilemmas when deciding on when to discontinue DMTs. There is no clear consensus on the appropriate subset of patients with MS for DMT discontinuation, and differences in policy exist that influence treatment decisions. The aim of this narrative review was to summarize factors for consideration in the complex decision of DMT discontinuation to assist with informed decision making. The objectives of this study are to conduct a narrative review of individual studies and practice recommendations on discontinuation of DMTs in MS, collect information regarding Canadian regional reimbursement policies for MS DMT coverage, and present ethical considerations applicable to decision making for DMT discontinuation in MS.

## Methods

We conducted a narrative review of studies and practice guideline recommendations on discontinuation of DMTs in MS. This narrative review was performed using the SALSA framework (Search, Appraisal, Synthesis, and Analysis).<sup>5</sup> Data regarding Canadian regional reimbursement policies for DMT coverage in MS were also collected and compared. Ethical principles surrounding discontinuation of DMTs were then applied to the identified evidence, guidelines, and policies.

## Data Sources and Search Strategy

For the narrative review, a comprehensive literature search was conducted of the MEDLINE/PubMed, OneFile (GALE), Scopus (Elsevier), and ProQuest Biological Science Collection databases. A focused internet search was also performed on Google. The keywords used as search terms included *multiple sclerosis, disease-modifying therapies, (Avonex/interferon [IFN] beta-1a or Betaseron/interferon beta-1b or Extavia/interferon beta-1b or Rebif/interferon beta-1b or Copaxone/glatiramer acetate or Tecfidera/dimethyl fumarate or Aubagio/teriflunomide or Plegridy/PEGinterferon beta-1a or Tysabri/natalizumab or Gilenya/fingolimod hydrochloride or Lemtrada/alemtuzumab or Mavenclad/cladribine or Ocrevus/ocrelizumab), discontinuing disease-modifying therapies, guidelines/recommendations on disease-modifying therapies, and rebound disease activity/rebound inflammation*. Canadian regional reimbursement policies for DMT coverage in MS were collected from ministry/government websites and a focused internet search on Google using the following keywords: *multiple sclerosis coverage criteria, names of the individual Canadian province/territories, and names of individual DMTs*.

## Eligibility Criteria

The study inclusion criteria for the narrative review included randomized trials, observational studies, practice guidelines, or expert opinion practice recommendations related to the treatment of DMTs; primary or secondary aims of individual studies needed to include the topic of discontinuing DMTs in MS; published in the past 15 years; and full text available online in the English language. The exclusion criteria included case reports or case series with fewer than ten cases;

studies conducted on pediatric patients with MS; and full text not available online in the English language. For Canadian regional reimbursement policies for DMT coverage in MS, only criteria available online in the English language were included. We included studies addressing discontinuation of Health Canada–approved DMT treatments and classified them according to the Health Canada indications as first line (injectable IFN $\beta$ -1a [Avonex (Biogen), Rebif (EMD Serono Inc)], pegylated IFN $\beta$ -1a, IFN $\beta$ -1b [Betaseron (Bayer Health-Care Pharmaceuticals), Extavia (Novartis Pharmaceuticals Corp)], glatiramer acetate, oral dimethyl fumarate, and teriflunomide) and second line (oral fingolimod hydrochloride, cladribine, infusion natalizumab, alemtuzumab, and ocrelizumab). Categorization of MS first- and second-line treatments across the globe may differ from this categorization.

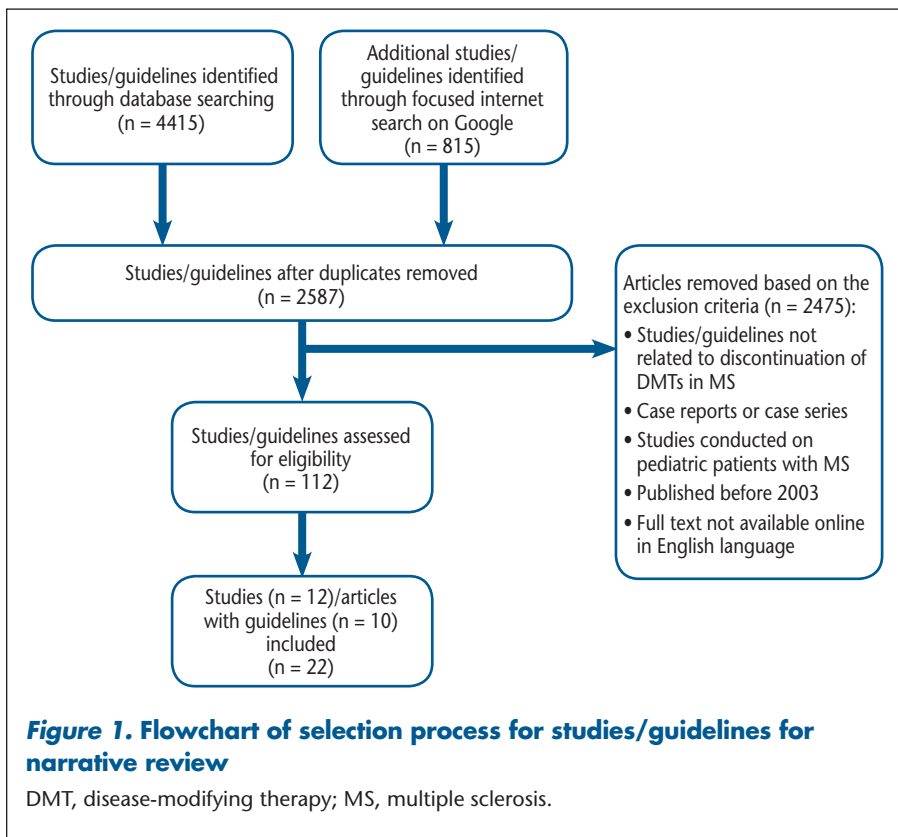
## Data Extraction and Synthesis

After the initial title and abstract screening, articles deemed relevant were considered for subsequent full-text review. Figure 1 illustrates a flowchart of the screening process used for narrative review of studies/guidelines on discontinuation of DMTs. Data extracted from discontinuation studies included study design, sample size, study groups, pretreatment characteristics, on-treatment characteristics, and the main finding(s) of posttreatment discontinuation. The extracted data from the selected discontinuation studies were presented in a chart framework. Discontinuation recommendations from practice recommendations were extracted and are presented in the Results section. For Canadian regional reimbursement policies, Expanded Disability Status Scale (EDSS) criteria scores used for reimbursement were extracted and summarized in a chart framework.

## Results

### Overview of Selected Articles for Narrative Review

Twenty-two articles were included in the review, including 12 studies on discontinuation of DMTs<sup>6-17</sup> in MS and ten articles with practice recommendations from published guidelines and national organizations.<sup>18-27</sup> Of the 12 discontinuation studies, seven were prospective cohort studies, three retrospective cohort studies, one a combined prospective/retrospective cohort study, and one a randomized clinical trial. Table S1 (published in the online version of this article at [ijmsc.org](http://ijmsc.org)) summarizes the pretreatment, on-treatment, and posttreatment discontinuation findings of individual studies. Published recommendations on DMT discontinuation were provided by the National Institute for Health and Care Excellence's (NICE's) technology appraisal guidance for individual DMTs (five articles pertaining to five DMTs), the American Academy of Neurology (AAN), the Association of British Neurologists (ABN), the Canadian Multiple Sclerosis Working Group (CMSWG), the European Commit-



tee for Research and Treatment of Multiple Sclerosis (ECTRIMS)/European Academy of Neurology (EAN), and the Canadian Agency for Drugs and Technologies in Health (CADTH).

### Individual Studies Addressing Discontinuation of DMTs

#### Discontinuation of First-Line DMTs

Of the four studies reporting on first-line DMTs, two examined patients with RRMS,<sup>6,7</sup> one examined patients with SPMS,<sup>8</sup> and one examined patients with an unspecified MS phenotype.<sup>9</sup> A prospective cohort study was conducted in Poland with 43 patients with RRMS who discontinued IFN $\beta$ .<sup>6</sup> At the time of this study, the reimbursement plan in Poland was limited to 24 months of coverage. The study concluded that the annualized relapse rate (ARR) returned to the pre-treatment rate after discontinuation of IFN $\beta$  therapy in 65% of the study sample. Disability progression was greater in the 2 years after treatment discontinuation compared with the 2 years while on treatment (mean  $\pm$  SD RRMS EDSS score change, 0.74  $\pm$  0.42 vs 0.05  $\pm$  0.14,  $P = .0001$ ).<sup>6</sup> Another prospective cohort study conducted in Austria included 221 patients with RRMS and at least 2 years of follow-up.<sup>7</sup> On multivariate analysis, the combination of age older than 45 years and the

absence of relapses for 4 years on treatment was the strongest predictor of relapse outcome after treatment discontinuation (hazard ratio [HR], 0.06 [95% CI, 0.01-0.44],  $P < .001$ ). An HR less than 1 indicates a lower risk of relapses after treatment discontinuation. This combination also resulted in lower risk of disability progression after treatment discontinuation (HR, 0.65 [95% CI, 0.18-2.34]), yet this did not reach significance ( $P = .347$ ). The only statistically independent predictors of disability progression were longer duration of disease (HR, 1.21), EDSS score at discontinuation (HR, 1.47), and age at discontinuation (HR, 1.33).<sup>7</sup>

In SPMS, a retrospective cohort study was conducted in France with 100 consecutive clinic patients who had stopped treatment.<sup>8</sup> The ARR<sub>1</sub> and ARR<sub>3</sub> were similar, with 16 people experiencing relapses after treatment stop. Presence of gadolinium-positive MRI within the 3 years before treatment discontinuation was the strongest predictor of disease activity (relapse or MRI activity) (HR, 4.2 [95% CI, 1.9-9.1],  $P = .0004$ ). These data suggest a role for MRI in predicting outcomes after treatment discontinuation in patients with SPMS. Treatment discontinuation seemed to have no consequence on the percentage of people with disability progression when comparing EDSS score change before and after treatment discontinuation. Treatment discontinuation at an EDSS score of 6 or greater was associated with lower risk of relapse or MRI activity after discontinuation (HR, 0.4 [95% CI, 0.2-0.9],  $P = .03$ ).<sup>8</sup>

A propensity score-matched large prospective cohort study reported that DMT discontinuation (ie, DMT stoppers) was associated with a shorter time to disability progression compared with continued treatment (DMT stayers).<sup>9</sup> This study involved participants from the MSBase registry with MS phenotype unspecified. The inclusion criteria required no history of relapses for at least 5 years. The DMT stoppers had to be fol-

lowed up for at least 3 years after discontinuation and had not restarted treatment for at least 3 months after stopping. The DMT stoppers were successfully matched with DMT stayers for age, sex, disease duration, EDSS score, and time on treatment. However, they were not matched for on-treatment or pretreatment disease activity. The HR for earlier disability progression was 1.47 (95% CI, 1.18-1.84;  $P = .001$ ) in DMT stoppers, yet the time to first relapse and ARRs were similar between groups. Younger age and lower baseline disability were significant predictors of increased relapse risk in DMT stoppers.<sup>9</sup>

### **Discontinuation of Second-Line DMTs**

Of the six studies reporting on discontinuing second-line DMTs, three examined only patients with RRMS,<sup>10-12</sup> two included patients with RRMS and SPMS,<sup>13,14</sup> and the MS phenotype was not specified for one study.<sup>15</sup> All the studies pertained only to natalizumab discontinuation, addressing the issue of increased disease activity or a rebound effect. A rebound effect, in general terms, implies an increase in disease activity above the level observed before treatment was started.

A single-blind, phase 4, randomized controlled trial compared a tapered natalizumab discontinuation protocol (additional infusions at weeks 6 and 8) with immediate discontinuation in 50 patients with RRMS.<sup>10</sup> Participants had to have been on natalizumab therapy for at least 24 months and contemplating discontinuation. The immediate discontinuation group was significantly younger (45.7 vs 52.6 years,  $P = .005$ ). The immediate discontinuation group developed significantly more new T2 lesions (predominantly in the first 6 months), and a greater proportion experienced relapses (59.3% vs 30.5%,  $P = .040$ ). No differences in gadolinium lesion formation or disability progression were observed during the 1-year follow-up between the tapered and immediate discontinuation groups.<sup>10</sup> A retrospective cohort study conducted in Italy with 54 patients with RRMS reported that disease activity after natalizumab discontinuation (ARR, 0.94; EDSS score, 2.75) did not increase above that reported before natalizumab treatment (ARR, 1.74; EDSS score, 3.0).<sup>11</sup> Relapse activity was still lower on treatment (ARR, 0.21) compared with the off-treatment periods. These results support a low risk of rebound disease activity in this cohort. No predictors of return of disease activity or rebound were identified in this study.<sup>11</sup>

A retrospective cohort study recruited 132 patients with RRMS from two Italian MS centers.<sup>12</sup> Ninety-five participants were switched to another treatment after a median natalizumab washout period of 5 months, including 57 participants who switched to fingolimod. Disease reactivation (MRI and/or relapse) occurred in 54.5% of the sample after natalizumab discontinuation, and 21.2% met the study criteria for rebound. A multivariate analysis adjusted for the number of infusions, washout period before a switch, therapeutic strategies after natalizumab discontinuation (no treatment, first-line treatment, fingolimod or natalizumab restart), and relapses in the 2 years before natalizumab treatment. Relapses in the 2 years before natalizumab treatment was the strongest predictor of relapse activity after treatment (HR, 1.43 [95% CI, 0.7-2.9],  $P = .31$ ). A switch to fingolimod or restarting natalizumab versus no treatment decreased the risk of relapses (HRs, 0.45 and 0.29, respectively). Of the 57 participants who switched to fingolimod, 23 had return of disease activity (relapse or MRI).<sup>12</sup> A single-center Italian prospective cohort study recruited 110 patients with MS having had at least 12 natalizumab infusions before they were switched within 1 month to either IFN $\beta$  ( $n = 18$ ) or glatiramer acetate ( $n = 72$ ), or within 3 to 6 months to fingolimod ( $n = 10$ ) or to no treatment ( $n = 10$ ).<sup>15</sup> By 1 year, 75% of the sample experienced return of disease activity (MRI/relapse) after natalizumab discontinuation, and 10% of the study sample met the study criteria for rebound. The high-risk period for disease activity or rebound occurred between months 2 and 8. Patients with a higher ARR (2.08) in the year before starting natalizumab compared with a lower ARR (1.54) were at greater risk for relapses after treatment discontinuation ( $P < .005$ ). Patients with a higher mean number of pretreatment enhancing lesions (2.60 vs 1.08,  $P < .04$ ) were also at greater risk for relapses. Year 1 after natalizumab discontinuation, median EDSS scores worsened from 2.0 to 3.0 ( $P < .001$ ).<sup>15</sup>

A single-center prospective cohort study recruited 32 patients with MS on treatment for at least 1 year. Participants could have RRMS or SPMS but had to demonstrate no relapses on natalizumab after the first 3 months of treatment and be followed up for at least 1 year after treatment discontinuation.<sup>13</sup> The cumulative probability of relapse alone after treatment discontinuation was 52.9% and for rebound was 39%. Rebound criteria in this study, similar to the studies previously herein, required a relapse and at least five gadolinium

lesions in addition to exceeding the pretreatment gadolinium lesion count. In the multivariate analysis, the only predictors of rebound were a pretreatment lower EDSS score (HR, 0.63 [95% CI, 0.003-1.89],  $P = .0015$ ) and a higher ARR (HR, 2.25 [95% CI, 1.17-4.67],  $P = .014$ ).

A single-center prospective cohort study in the United States recruited 84 natalizumab-treated patients with MS (mixed sample of RRMS and SPMS) who received 12 or more infusions.<sup>14</sup> Eighty-one percent of the study sample (68 of 84) had dosage interruption and 28% of these participants (19 of 68) experienced a clinical relapse within 6 months of suspension. None of the participants with ongoing treatment experienced any relapses during the 12 to 18 months of treatment ( $P = .017$ ). Beyond treatment interruption, no significant predictors of relapse were identified. Number of relapses at baseline in the year before treatment was already slightly higher in the treatment interruption group (mean, 1.85) compared with the treatment continuation group (mean, 1.29;  $P = .082$ ).<sup>14</sup>

#### **Discontinuation in Mixed Sample of First- and Second-Line DMTs**

A combined prospective and retrospective cohort study was conducted in Sweden with a mixed sample of patients with RRMS and SPMS.<sup>16</sup> One group of patients with MS ( $n = 15$ ) was recruited who received treatment with natalizumab for longer than 5 years without any evidence of disease activity on treatment. They were then followed up for 19 months, with scheduled clinical/MRI evaluations 3, 6, and 10 months after their last natalizumab infusion. This group of patients was compared with a retrospectively analyzed cohort ( $n = 55$ ) of patients with MS who were treated with first-line DMTs and discontinued treatment after an analogous stable course. Mean pretreatment ARR in the natalizumab group was higher: 2.3 versus 1.7 ( $P = .016$ ). During follow-up, 67% of the natalizumab group relapsed at a median of 5 months versus 35% in the first-line group at a median of 23 months. Rebound occurred in 33% of patients ( $n = 5$ ) in the natalizumab group, where rebound was defined in this study as a relapse with a larger increase in EDSS score or an increased number of gadolinium lesions compared with before treatment.<sup>16</sup>

#### **Discontinuation Without DMT Specifications**

A prospective cohort study conducted in the United States consisted of 77 patients with SPMS who were advised to stop DMTs and a smaller group of 17

patients with RRMS who stopped DMTs on their own.<sup>17</sup> The patients with SPMS required no evidence of new central nervous system inflammation on MRI and no relapses for at least 2 years before they were advised to stop DMTs. Nine of the patients with SPMS (11%) had return of disease activity after DMT discontinuation compared with 58.8% of the patients with RRMS. In the SPMS group, the median age was 61 (range, 47-76) years, and younger age was associated with return of disease activity. Older patients ( $\geq 7$  decades) with no evidence of inflammatory disease for at least 2 years had almost a 90% probability of remaining relapse-free after DMT stop. The median EDSS score for the SPMS group was 6, and DMT treatment duration ranged from 2 to 20 years. Neither of these later variables were statistically significantly different between stable and active patients after DMT discontinuation.<sup>17</sup>

### **Practice Recommendations**

#### **AAN Guidelines**

According to the AAN guidelines, clinicians should counsel stable patients with RRMS (who want to discontinue DMTs) regarding the need for ongoing follow-up and periodic reevaluation of their decision to discontinue DMTs. The AAN recommended that "Clinicians should advocate that people with MS who are stable (that is, no relapses, no disability progression, stable imaging) on DMT should continue their current DMT unless the patient and physician decide a trial off-therapy is warranted."<sup>18(p8)</sup> In patients with SPMS, clinicians should assess the likelihood of future relapse by evaluating patient age, duration of disease, relapse history, and activity detected on MRI. Clinicians may advise discontinuation of DMTs in patients with SPMS without ongoing relapses (or gadolinium-enhanced lesions on MRI activity) and who are nonambulatory (EDSS score  $\geq 7$ ) for at least 2 years. In patients with clinically isolated syndrome (not diagnosed as having MS and taking DMTs), the associated risks of continuing DMTs versus those associated with stopping DMTs should be reviewed by clinicians.<sup>18</sup>

#### **ABN Guidelines**

The ABN emphasizes the central importance of patient choice in the decision to stop treatment. The MS neurologist should fully inform patients of the known facts and associated uncertainties before making discontinuation decisions. According to ABN, it is not possible to have mandatory stopping criteria that apply to all patients. However, clinicians should consider dis-

continuing DMTs in patients with major adverse effects, development of nonrelapsing SPMS, and pregnancy.<sup>19</sup>

#### **CMSWG Guidelines**

According to CMSWG guidelines, “It may be prudent to discuss stopping treatment with a patient with significant disease progression (EDSS>6) who has not experienced a relapse in the preceding 2 years. However, it should be noted that no clinical criteria have been developed to identify candidates for treatment cessation and the decision to stop therapy must be made on a case-by-case basis and in accordance with the preferences of the patient.”<sup>20(p318)</sup> To aid in this decision, a 3- to 6-month drug holiday may be followed by a clinical and radiologic reevaluation of the patient.<sup>20</sup>

#### **ECTRIMS/EAN Guidelines**

Together, ECTRIMS and the EAN released guidelines on the use of DMTs in patients with MS. According to these guidelines, a DMT should be continued if a patient with RRMS is clinically and radiologically stable without any safety or tolerability issues. All women of reproductive age should be advised that DMTs are not licensed during pregnancy, except for glatiramer acetate.<sup>21</sup>

#### **NICE Guidelines**

For individual DMTs (IFN $\beta$ , glatiramer acetate, dimethyl fumarate, fingolimod, natalizumab, and teriflunomide), NICE has given technology appraisal guidance. According to NICE guidelines, people with MS who are currently on any of the previously mentioned DMTs should have the option to continue therapy until a joint decision is made between the patient and the clinician to stop treatment.<sup>22-26</sup>

#### **CADTH Fingolimod Recommendation**

Except concerning fingolimod, CADTH has not specifically given any practice guideline recommendations for stopping DMT in MS. A CADTH committee recommends that treatment with fingolimod be stopped in patients with RRMS who either do not achieve at least a 50% reduction from baseline in the mean ARR after 2 years of treatment or attain an EDSS score greater than 5.0. According to CADTH, continued use of an expensive agent (fingolimod) is considered unwarranted in the absence of any substantial sustained clinical benefit.<sup>27</sup>

#### **Canadian MS DMT Reimbursement Processes**

Access to reimbursement may influence treatment decisions when drug costs are high, as is the case for MS DMTs. Drug reimbursement, broadly speaking, is defined as the process of having partial or complete

drug costs paid for by an external source.<sup>28</sup> In MS care, examples of external sources may include insurance companies, compassionate coverage from industry, or government funding. In Canada, the 13 provincial/territorial government insurance plans provide MS drug coverage for patients who fulfill the eligibility criteria for reimbursement. The exceptions to this include registered First Nations and recognized Inuit, members of the Canadian Armed Forces, refugees, and inmates in federal prisons. These groups are covered federally under a specialized program(s).<sup>29</sup>

Canadians have access to universal health care structured through 13 provincial and territorial governments responsible for the management, organization, and delivery of health services. The Canadian health care structure accounts for some differences in provincial and territorial coverage plans for MS DMT.<sup>30</sup> A detailed comparison of the government insurance plans and policies across Canada relevant to MS DMTs are beyond the scope of this review. Table 1 highlights the eligibility criteria for DMT funding from the government insurance plans that are most relevant to drug discontinuation, namely, the upper limit for the EDSS score and the MS disease course. Depending on the provincial and territorial ministry of health policies and on family income, patients may have to pay some of the cost themselves, either as a proportion of the total drug cost (co-payments) with every prescription of drug filled or up to a fixed maximum amount per year (deductibles).<sup>28</sup> Alberta has the highest EDSS criteria cutoff score ( $\leq 6.5$ ) for natalizumab and alemtuzumab, and Quebec has the highest EDSS criteria cutoff score ( $< 7$ ) for fingolimod hydrochloride. For first-line DMTs, Quebec has the highest EDSS criteria cutoff score ( $< 7$ ), and Nova Scotia and Saskatchewan have the lowest EDSS criteria cutoff score ( $\leq 5.5$ ). The coverage criteria details for MS drugs for Nunavut and the Northwest Territories are not available online.

Once an MS DMT is approved by Health Canada, each provincial and territorial government may consider multiple sources of information to establish eligibility criteria for funding. Established in 2003, CADTH conducts a common drug review of drug products for provinces and territories to consider in their decision making, except for Quebec, which conducts its own review. The common drug review is a pan-Canadian process that aims to conduct objective reviews of the clinical, economic, and patient evidence for drugs.<sup>45</sup> A limitation of

**Table 1. Regional variations in reimbursement policies for provincial/territorial coverage of MS DMTs in Canada**

DMT <sup>a</sup>	EDSS criteria scores for reimbursement in Canadian provinces/territories <sup>b</sup>												
	AB	BC	MB	NB	NL	NS	ON	PE	QC	SK	NT	NU	YT
First line													
IFNβ-1a (Avonex, Rebif)	≤6.5	≤6.5	≤6.5	≤6.5	≤6.5	≤5.5	≤6	≤6.5	<7	≤5.5	NA	NA	≤6.5
IFNβ-1b (Betaseron)	≤6.5	≤6.5	≤6.5	≤6.5	≤6.5	≤5.5	≤6	≤6.5	<7	≤5.5	NA	NA	≤6.5
IFNβ-1b (Extavia)	≤6.5	≤6.5	NI	≤6.5	≤6.5	≤5.5	≤6	≤6.5	<7	≤5.5	NA	NA	NI
Glatiramer acetate	≤6.5	≤6.5	≤6.5	≤6.5	≤6.5	≤5.5	≤5	≤6.5	<7	≤5.5	NA	NA	≤6.5
Dimethyl fumarate	NA	≤6.5	NR	≤6.5	≤6.5	≤5.5	≤5	≤6.5	<7	≤5.5	NA	NA	≤6.5
Teriflunomide	≤6.5	≤6.5	≤6.5	≤6.5	≤5.5	≤5.5	≤5	≤6.5	<7	≤5.5	NA	NA	≤6.5
Pegylated IFNβ-1a	NA	NC	≤6.5	≤6.5	≤6.5	≤5.5	≤6	≤6.5	NI	≤5.5	NA	NA	≤6.5
Second line													
Natalizumab <sup>c</sup>	≤6.5	NR	≤5	≤5	NI	≤5	≤5	NI	≤5	≤5	NA	NA	≤5
Fingolimod hydrochloride	≤6.5	≤5.5	≤5.5	≤5.5	≤5.5	≤5.5	≤5.5	≤5.5	<7	≤5.5	NA	NA	≤5.5
Alemtuzumab	≤6.5	≤5	≤5	≤5	NI	≤5	≤5	≤5	≤5	≤5	NA	NA	≤5

Abbreviations (see also below): DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IFN, interferon; MS, multiple sclerosis; NA, not available online; NC, not covered; NI, no information in provincial drug formulary; NR, not required for coverage.

<sup>a</sup>The DMTs are approved for treating relapsing-remitting MS (RRMS) patients 18 years or older in all Canadian provinces and territories. In addition, the following exceptions apply: Quebec—IFNβ-1a (Avonex, Rebif) and IFNβ-1b (Betaseron, Extavia) are approved for secondary progressive MS (SPMS) patients with EDSS scores less than 7; Alberta—IFNβ-1b (Betaseron, Extavia) is approved for SPMS patients with relapses having EDSS scores of 5.5 or less; British Columbia—IFNβ-1b (Betaseron, Extavia) is approved for SPMS patients with EDSS scores of 6 or less; New Brunswick—IFNβ-1a (Avonex, Rebif), IFNβ-1b (Betaseron, Extavia), and glatiramer acetate are approved for SPMS patients with EDSS scores of 6.5 or less; Ontario—glatiramer acetate, IFNβ-1a (Avonex, Rebif), IFNβ-1b (Betaseron, Extavia), and pegylated IFNβ-1a are approved for clinically isolated syndrome. See Eligibility Criteria subsection for manufacturer information for DMT trade names.

<sup>b</sup>Canadian provinces (reference no.): AB, Alberta<sup>31</sup>; BC, British Columbia<sup>32</sup>; MB, Manitoba<sup>33,34</sup>; NB, New Brunswick<sup>35</sup>; NL, Newfoundland and Labrador<sup>36</sup>; NS, Nova Scotia<sup>37</sup>; ON, Ontario<sup>38</sup>; PE, Prince Edward Island<sup>39</sup>; QC, Quebec<sup>40</sup>; SK, Saskatchewan.<sup>41</sup> Canadian territories (reference no.): NT, Northwest Territories<sup>42</sup>; NU, Nunavut<sup>43</sup>; YT, Yukon.<sup>44</sup>

<sup>c</sup>Natalizumab is approved only for RRMS patients aged 18–65 years in Ontario.

the CADTH common drug review process is that clinical and/or economic evidence related to discontinuing DMTs is not specifically addressed.

### Ethical Considerations

An ethical framework may further inform clinical decision making, clinical research, and policy. The conventional bioethical principles of autonomy, justice, nonmaleficence, and beneficence are based on liberal individualism, giving the highest priority to individual autonomy.<sup>46</sup> Limitations of these principles include that they may be less applicable to current-day interdisciplinary practice<sup>47</sup> and to public health priorities.<sup>48</sup> In brief, public health ethics is a relatively new area of research with emerging ethical frameworks, placing greater emphasis on the “common good.”<sup>49</sup> One public health ethical framework proposes a relational approach toward autonomy that could “direct us to attend to the many and varied ways in which competing policy options affect the opportunities available to members of different social groups” and “to make visible the ways in which the autonomy of some may come at the expense of the justice demands of others.”<sup>50(p202)</sup> Public health ethics

frameworks may help reduce health inequities in MS treatment. In the absence of newer ethical frameworks that more fully incorporate the values relevant to the costly treatment of chronic progressive disease, the conventional ethical framework still provides a starting basis to inform decision making.

Autonomy describes the ability of individuals to retain control over their bodies and to make their own decisions.<sup>46,51</sup> It is the duty of a physician to provide patients with MS with meaningful objective information on which to base their decisions. Beneficence speaks to the obligation of a health care provider to bring about good through their actions.<sup>46,52</sup> Physicians must try to provide positive benefits to patients with MS by seeking a greater balance of good over harm in patient care. Physicians may take patients’ individual circumstances and related evidence into consideration when deciding whether DMT discontinuation will bring about good for their patient.

Nonmaleficence literally means “to do no harm.” Decisions (or lack of a decision) that could potentially harm patients, other people, or society must be

avoided.<sup>46,53</sup> Clinicians aim to consider both beneficence and nonmaleficence in decision making. The point for the decision to stop DMT treatment may be a moving and individualized target. Justice refers to the obligation of a health care provider to treat all patients equally, fairly, and impartially; to ensure fair distribution of scarce resources and new treatments; and to uphold respective laws and regulations when making choices.<sup>46,54</sup> Physicians may try to make judicious use of DMTs by prescribing these medications based on the individualized assessment of benefit versus harm and by prescribing within guidelines or policies. However, policy criteria may not seem to align consistently with a recommendation for an individual patient. In this context, evolving ethical practices that appreciate more fully “the importance of negotiating power relations and the larger socio-political context” are applicable to DMT discontinuation.<sup>48(p324)</sup> One recommendation includes the vital role of public consultation for enhancing the ethical analysis of dilemmas related to public policies and interests.<sup>55</sup>

## Discussion

This review assimilated evidence, practice guidelines, Canadian policies, and ethical considerations in the context of discontinuation of DMTs. Although this review is comprehensive, it is not exhaustive because we excluded case series reporting fewer than ten cases and limited the search to studies published in English. Practice guidelines and reimbursement policies do not highlight age or pretreatment disease activity in clinical decision making for stopping treatment; rather, the policies emphasize EDSS cutoff criteria. However, younger age and high pretreatment disease activity are associated with increased risk of return of disease activity. There are limitations in the present studies for identifying risk of nonmaleficence when stopping DMTs. In eight of the 12 studies, sample sizes were 100 participants or less, decreasing the power to detect valid predictors of outcomes. The MRI activity was variably reported in the studies, with some studies reporting percentages of patients with MS with MRI activity and others reporting MRI data only for patients who had relapse activity. Disability progression rates, important to people with MS, were inconsistently reported or compared between the periods of before, on, and after treatment.

Most currently available practice guidelines on discontinuation of DMTs advocate the central importance of patient choice in the decision-making process,

supporting the ethical principle of respect for patient autonomy. The AAN guideline demonstrates an effort to balance the principle of beneficence with nonmaleficence by considering the evidence supporting that those with active disease on treatment may be more likely to benefit from continued treatment and may be at increased risk for harm by earlier treatment discontinuation (ie, increased disease activity compared with when on treatment). Clinicians, however, may perceive risks and benefits differently than patients.<sup>56</sup>

Shared decision making plays a vital role when deciding on discontinuation of DMTs in MS, especially in the face of limited evidence. Shared decision making is the process by which collaborative decisions are made after providing trustworthy information in accessible formats and facilitating shifts in the power and control of interactions between patients and physicians.<sup>57,58</sup> Clinicians and patients could engage in collaborative decision making on discontinuing DMT treatment after considering potential risks and benefits. Most patients with MS prefer to be highly involved in decision making.<sup>59</sup> Although current guidelines recommend considering patient choice, they do not address the potential for conflict between the principles of respect for patients' autonomy, beneficence, nonmaleficence, and justice. For example, a variety of patients who meet the current AAN recommended criteria for considering stopping may be well-informed on the evidence pertaining to stopping but still choose to continue treatment. In a public health care system, the cost of continued treatment based on patient choice as the priority could result in an unfair distribution of limited resources.

Standardizing the criteria for discontinuation is challenging owing to the lack of significant evidence toward standardization. However, standardization may help satisfy the ethical principle of justice by treating similar

## PRACTICE POINTS

- In the absence of strong evidence about when to discontinue disease-modifying therapy (DMT) in MS, shared decision making and an appreciation of the ethical complexities could assist in the decision-making process.
- The vital significance of patient choice has been advocated for by most practice guideline recommendations concerning DMT discontinuation decision making in MS.



patients equally and distributing resources to those most likely to benefit. Individual risk profiling for beneficence or maleficence will require further epidemiologic research on the most critical predictors of return of disease activity after treatment stop. Precision medicine in MS DMT treatment may help meet the principles of both justice and beneficence. Precision medicine offers a model of care where treatment is tailored to the individual patient based on a calculated individual risk assessment for harm or benefit.<sup>60,61</sup> With an improved understanding of risk factors for disease progression off treatment (ie, the variables pretreatment and on treatment, as well as other confounding variables, such as genetic and lifestyle factors), reimbursement policies and future guidelines may consider precision medicine. Precision medicine could be combined with shared decision-making models of care whereby precision medicine identifies the critical thresholds for beneficence or maleficence with treatment discontinuation.

There is a need for prospective research in patients with SPMS and stable RRMS in particular to analyze the risk versus benefit of treatment discontinuation. The Discontinuation of DMTs in MS (DISCOMS) randomized trial in the United States will evaluate discontinuing DMTs in people with MS on treatment who are 55 years or older, relapse free for at least 5 years, and without new MRI activity for 3 years.<sup>62</sup> Global collaboration is needed and underway to understand the impact of drug discontinuation in other subgroups and on longer-term disability progression.<sup>63</sup>

In conclusion, the results from prospective randomized controlled trials that directly address the issue of discontinuation in nonactive progressive MS are still missing in the literature. Although inconsistencies exist in practice guideline recommendations on discontinuation of DMTs in MS, the vital significance of patient choice is advocated by most guidelines. In Canada, there are considerable regional variations in the EDSS criteria scores for reimbursement across provinces and territories. In the absence of strong evidence on when to discontinue DMTs, shared decision making and consideration of the ethical complexities may assist in the decision-making process and guide future research directions. □

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