ORIGINAL RESEARCH ARTICLE

Informing Medication Discontinuation Decisions among Older Adults with Relapsing-Onset Multiple Sclerosis

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Abstract

Background For older adults with relapsing-onset multiple sclerosis (MS), limited information is available to inform if, or when, disease-modifying drugs (DMDs) may be safely discontinued.

Objective The aim of this study was to project the outcomes of DMD discontinuation among older adults with relapsing-onset MS.

Methods We projected the 10-year outcomes of discontinuation of a DMD (interferon-β, fingolimod, or natalizumab) among older adults (aged 55 or 70 years) who were relapse-free for 5 or more years and had not reached an Expanded Disability Status Scale (EDSS) score of 6. Outcomes included the percentage of people who had at least one relapse or reached EDSS 6, and quality-adjusted life-years (QALYs), which incorporated both relapses and disability. We used a simulation modeling approach. With increased age, relapses decreased and the effectiveness of DMDs for disability outcomes also decreased.

Results We found lower projected benefits for DMD continuation at 70 years of age than at 55 years of age. Compared with discontinuation, the projected benefit of DMD continuation ranged from 0.007 to 0.017 QALYs at 55 years of age and dropped to 0.002–0.006 at 70 years of age. The annual projected benefits of DMD continuation (0.1–3.0 quality-adjusted life-days) were very low compared with typical patient preferences regarding treatment burden.

Conclusion The benefits of DMDs may not be substantial among older adults with relapsing-onset MS. Direct clinical evidence remains limited and the decision of whether to discontinue a DMD should also take into account patient preferences. It is important to gain a better understanding of how age-related changes in the trajectory of relapsing-onset MS affect treatment effectiveness among older adults.

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Key Points

We projected the results of discontinuation of disease-modifying drugs among older adults with multiple sclerosis using evidence-anchored simulations.

The projected benefits of drug continuation were relatively low, compared with typical patient preferences regarding the burden of taking medication.

1 Introduction

Multiple sclerosis (MS) is a chronic immune-mediated and neurodegenerative disease of the brain and spinal cord. In recent decades, the prevalence of MS and the mean age of people with MS have increased, representing

approximately 800,000 people living with MS in North America, with an average age of 55–64 years [1, 2]. The first disease-modifying drugs (DMDs) for MS became available in the 1990s and required regular injections (the β-interferons) [3]. In 2004, natalizumab, a monthly infusion, was approved in the US, and, in 2010, the first oral drug, fingolimod, became available [4, 5]. Today there are over ten different DMDs licensed for use in MS; the majority are specifically for treating the relapsing form of MS. Once a DMD is initiated, the optimal duration of time that a person should take the drug is unknown. Treatment guidelines have predominantly focused on when to initiate DMDs and how to optimize adherence, and there is a paucity of recommendations specifically for older adults [6].

DMDs, such as interferon-β, fingolimod, or natalizumab, can be burdensome for people with relapsing-onset MS and their families. Treatment burdens may include adverse events (e.g. flu-like symptoms, serious infections, cardiovascular problems, and visual disturbances), invasive drug delivery methods or laboratory monitoring, and high costs [3–5, 7]. DMDs are generally considered more effective in people who are younger, with a shorter time since disease onset, and who have higher disease activity, such as frequent relapses or greater lesion burden based on magnetic resonance imaging (MRI) [8, 9]. People over 55 years of age were typically excluded from the key clinical trials of DMDs [10]. Disease activity decreases with age, and a threshold level of disease activity may be necessary for the benefits of DMDs to outweigh the treatment burden for older people with relapsing-onset MS [11–15]. People who discontinue medication when they are older are less likely to relapse compared with younger people [16–18], but few studies of DMD discontinuation focused on older adults have been completed [14, 19].

Our objective was to project the outcomes of DMD discontinuation among older adults with relapsing-onset MS. Outcomes included relapses, disability, and quality-adjusted life-years (QALYs), which captured both relapse and disability outcomes. We incorporated an age-related decrease in relapses and underlying disease heterogeneity (subgroups with different rates of relapse and disability progression) to reflect the reduced relapse activity among older adults with relapsing-onset MS. We quantified the loss of clinical benefit from discontinuing a DMD (prior to consideration of the burden of taking the DMD) and compared these results with quantitative estimates of treatment burden derived from the literature.

2 Methods

2.1 Study Design

We used a simulation modeling approach to project the 10-year outcomes of discontinuation of a DMD (interferon-β, fingolimod, or natalizumab) among older adults (55 or 70 years of age) who were relapse-free for 5 or more years and had not reached an Expanded Disability Status Scale (EDSS) score of 6. The three drugs were selected for this study because they represent three different routes of administration (injections, oral medication, and intravenous infusion) and different levels of risk and benefit. Relative to other DMDs, typically interferon-β is considered to have lower risk and efficacy, while natalizumab and fingolimod have greater risk; natalizumab offers greater efficacy, while fingolimod is less burdensome in delivery, as an oral medication [3–5, 20]. Our outcomes were the percentage of people who experienced at least one relapse or reached EDSS 6 or above within the next 10 years, and QALYs, which captured each simulated person's relapses and disability over the time period. The EDSS is an ordinal scale ranging from 0 (no neurological abnormality) to 10 (MS-related death); EDSS 6 is equivalent to requiring a cane to walk [21]. The EDSS measure of disability is known to have limitations, but it remains widely used in clinical trials [22]. We anchored the simulation of DMD continuation versus discontinuation at two age-based milestones—55 and 70 years of age. These ages were selected because relapse rates are relatively low in these age groups and an ongoing randomized trial of DMD discontinuation enrolled participants aged 55 years and older [12, 13, 19]. Additionally, an observational study of DMD discontinuation reported only one relapse among adults aged 60 years and older (mean age 68 years) during up to 2 years of follow-up [14], and an autopsy study found that the inflammatory markers associated with pathologically active disease were similar among older people with MS (median age 76 years) and age-matched controls [23].

2.2 Markov Model

We developed a Markov state-transition model to simulate adults with relapsing-onset MS (Fig. 1). We characterized disability by four categories based on the EDSS. Each year, a simulated person could have a relapse(s) or not and progress in disability or not, based on a set of probabilities, including an age-specific background mortality risk (Table 1) [24]. Because advanced disability is associated with increased mortality risk [25–27], an additional risk of death was assumed for individuals with EDSS scores of 8.0–9.5 (Fig. 1). The simulation started from MS symptom onset at age 30 years, which is the approximate mean onset
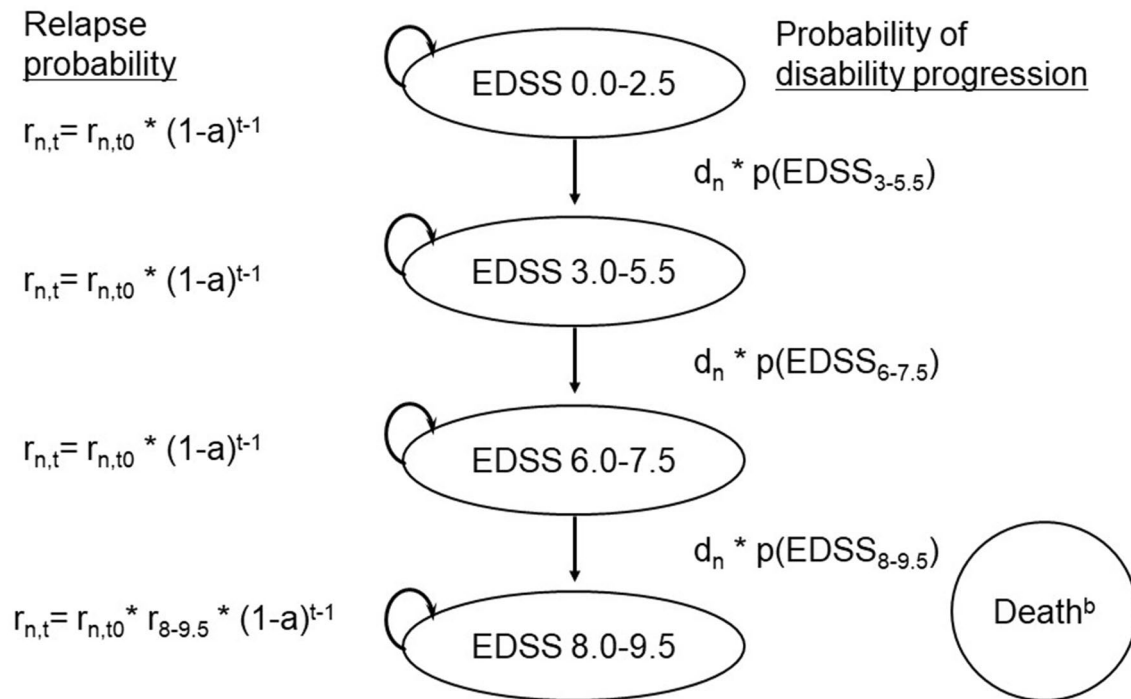
Fig. 1 Schematic representation of the Markov model simulating people with relapsing-onset multiple sclerosis. *ARR* annualized relapse rate, *MS* multiple sclerosis, $r_{n,t}$ ARR over time by subgroup n, a annual age-specific decrease in ARR, $r_{n,t0}$ ARR at onset (age 30 years in the Markov model) by subgroup n, t years post-onset, *EDSS* Expanded Disability Status Scale, d_n relative risk of disability progression by subgroup n, p(EDSS) average annual probability of progression (EDSS scores categorized as 0.0–2.5, 3.0–5.5, 6.0–7.5, 8.0–9.5); $r_{8-9.5}$ relapse probability for people with EDSS scores of 8–9.5 relative to 0–7.5. [b]Age-specific background mortality was applied to simulated individuals at all EDSS scores, with an additional risk of death from MS for individuals with EDSS scores of 8.0–9.5

age [28]. We used five subgroups to represent heterogeneity in the MS population. The course of MS varies across individuals, with some people experiencing more relapses than others [15], and wide variation in long-term disability outcomes [29, 30]. Simulated individuals had different risk levels for relapses and disability progression, instead of assuming that all simulated persons face the same risks. We used TreeAge Pro 2018, R2.0 software (Tree Age Software Inc., Williamstown, MA, USA).

2.3 Clinical Cohort

The British Columbia Multiple Sclerosis (BCMS) database in Canada represents one of the largest sources of clinical information collected on people with MS prior to the widespread availability of DMDs [28]. The BC provincial government's coverage of the first MS DMD (β-interferon-1b) began in 1996. Data were prospectively collected at each visit to one of the four MS clinics in BC, with a clinical history (including early relapses) taken at the first MS clinic visit by the attending neurologist. These data are considered population-based and included an estimated 80% of people who were living with MS in BC during the study period [31]. The overall cohort (n =2203) included adults

(age ≥ 18 years at their initial visit) with MS confirmed by an MS specialist neurologist based on the prevailing criteria at the time of diagnosis, a relapsing-onset disease course, and at least two available disability assessments. In order to reduce potential biases due to excluding people who died or moved away, no minimum follow-up time was required. We defined subgroups of people in the BCMS cohort by the number of relapses during the 5 years following the onset of MS symptoms (0–1, 2, 3, 4, and ≥ 5), excluding the onset relapse. When creating these subgroups, we focused on the period prior to widespread availability of DMDs by limiting the subgroup sample (n =934) to patients with an initial clinic visit prior to January 1996. We also required a clinic visit at least 5 years after onset, and hence disease onset prior to January 1991. The full study period was from 1980 to 2009 to enable assessment of disability outcomes. DMD use remained low for several years after 1996 [12], and limited DMD exposure was a strength of our clinical cohort. However, our estimates of heterogeneity in disability progression may be conservative (i.e. heterogeneity could be greater in people without DMD exposure).

Table 1 Summary parameters for the Markov model simulating a cohort of adults with relapsing-onset multiple sclerosis

Model parameter	Estimate (or formula)
Age-specific decrease in ARR (*'a'* in Fig. 1) per 5 years [32]	0.28
Relapse probability for people with EDSS scores of 8–9.5 relative to 0–7.5 ($_{r8-9.5}$ in Fig. 1) [32]	0.44
ARR at onset[a] ($r_{n,t0}$ in Fig. 1) by subgroup (subgroups as a percentage of the cohort at onset[a])	
Subgroup 1 (21% of the cohort; lowest risk)	0.11
Subgroup 2 (37% of the cohort)	0.22
Subgroup 3 (17% of the cohort)	0.45
Subgroup 4 (13% of the cohort)	0.68
Subgroup 5 (12% of the cohort; highest risk)	1.07
Percentage of simulated cohort by EDSS score category during the first Markov model cycle (at age 30 years) [32]	
EDSS 0–2.5	95%
EDSS 3.0–5.5	5%
Median time to sustained EDSS 6	30.8 years
Average annual probability of disability progression [32]	
EDSS 0–2.5 to 3.0–5.5	0.0418
EDSS 3.0–5.5 to 6.0–7.5	0.0843
EDSS 6.0–7.5 to 8.0–9.5	0.0456
Risk multipliers for annual probability of disability progression by subgroup	
Subgroup 1 (lowest risk)	0.93
Subgroup 2	0.93
Subgroup 3	0.98
Subgroup 4	1.11
Subgroup 5 (highest risk)	1.43
Annual probability of MS-specific mortality at EDSS scores of 8.0–9.5, beyond age-specific background mortality[b]	0.0675
DMD efficacy: relative risk of relapse over 24 months [20]	
Fingolimod	0.72
Interferon-β	0.89
Natalizumab	0.56
DMD efficacy: $1 - (1 - \mathrm{RR_{DMD}}) \times (r_{n,t}/r_{n,t0})$	
Fingolimod	$1 - (1 - 0.86) \times (r_{n,t}/r_{n,t0})$
Interferon-β	$1 - (1 - 0.83) \times (r_{n,t}/r_{n,t0})$
Natalizumab	$1 - (1 - 0.64) \times (r_{n,t}/r_{n,t0})$
Utility weights [33, 40]	
EDSS 0–2.5	0.824
EDSS 3.0–5.5	0.679
EDSS 6.0–7.5	0.533
EDSS 8.0–9.5	0.491
Relapse disutility [33, 34]	0.0235

a age-specific decrease in ARR per year, *ARR* annualized relapse rate, *BCMS* British Columbia Multiple Sclerosis, *EDSS* Expanded Disability Status Scale, *DMD* disease-modifying drug, *MS* multiple sclerosis, $r_{n,t0}$ ARR at symptom onset (age 30 years in the Markov model) by subgroup *n*, $r_{n,t}$ ARR over time by subgroup *n*, RR_{DMD} reduction in the risk of disability worsening while taking a DMD based on a network meta-anlaysis [20], *t* years post-onset

[a]Multiple sclerosis symptom onset was represented by age 30 years in the Markov simulation model

[b]Based on model calibration using a previously published finding that BCMS database patients had a 6-year decrease in life expectancy compared with the general population [61]

2.4 Relapses and Disability

We allowed for an annual age-related decrease in the annualized relapse rate (ARR) (Table 1) [32]. The variation in relapse rates across subgroups 1–5 in the simulation model was based on the results of the BCMS cohort analysis. We selected the overall ARR (0.40 at symptom onset) by reviewing observational studies reporting relapses among older adults with MS [12, 13, 32] and the limited number

of observational studies of DMD discontinuation among older adults [14, 16].

We assumed the risk of disability progression was based on the current EDSS level (Fig. 1, Table 1). Within subgroups, progression was independent of relapses. This assumption highlights the role of aging in progression [29, 30] and was similar to previous studies that projected long-term outcomes for people with relapsing-onset MS [33, 34]. To estimate the relative risk of disability progression among subgroups, we analyzed the BCMS cohort using Kaplan–Meier survival analyses, overall and by subgroup, with a primary endpoint of median time to EDSS 6 (sustained, with no subsequent EDSS scores below 6.0). We used these results to develop adjustments (multipliers) that accounted for the variation across subgroups in the overall rate of disability progression (Table 1). Across subgroups, we assumed that relapses and disability progression co-varied (e.g. those with a lower initial ARR progress slower in disability) based on the clinical view that residual disability may accrue following relapses, as shown by short-term data from clinical trials [35–37].

2.5 Disease-Modifying Drug (DMD) Treatment

Parameters and ranges for the relative risk of relapse or disability worsening while exposed to a DMD (interferon-β, fingolimod, and natalizumab) were obtained from a network meta-analysis that examined relapses and disability worsening over 24 months [20]. For disability worsening, we assumed that treatment effectiveness was proportional to a person's relapse activity as represented by the ARR, which decreased with age (as shown by *'a'* in Fig. 1 and Table 1). This assumption was based on evidence that DMDs are most effective in people who are younger and who have more frequent relapses, with limited efficacy, if any, for people with secondary progressive MS [8, 9, 38]. Although some studies have found no DMD benefit among adults ≥ 40 years of age [39], these results represent group averages. Because DMDs might offer benefits for older adults who continue to have disease activity, we linked effectiveness to disease activity as a conservative assumption (rather than assuming that all benefits stop at age 40 years, for example). We modeled the reduction in the risk of disability worsening while taking a DMD (RR_{DMD}) as a function of the ARR at a given age (r_t) compared with the ARR at the age of MS symptom onset (r_{t0}): $1 - (1 - RR_{DMD})*(r_t/r_{t0})$. For example, if the ARR had decreased by half since symptom onset, then the reduction in the risk for disability worsening with a DMD would also decrease by half. The treatment effectiveness for relapse was assumed to be constant (and thus DMD benefits for relapses decreased with age only, by decreased ARR).

2.6 Utilities

Utilities are a preference-based measure for health-related quality of life. QALYs weight years of life by utilities. Utilities for disability status and relapse events were derived from published assessments of people in the US with relapsing-onset MS [33, 40]. The disutility (i.e. utility decrement) for a relapse was assumed to last 3 months. We compared the annual DMD benefits (prior to consideration of treatment burden) with DMD disutilities derived from published literature based on patient preferences regarding treatment delivery [33, 41, 42]. To do this, we translated our 10-year results into annual threshold values that represent the magnitude of perceived treatment burden equal to the projected DMD benefit. For example, if an individual was willing to 'trade' 30 quality-adjusted days per year in order to be free of DMD burdens, then the benefit of a DMD outweighs the burden of treatment only if the projected benefit is > 30 quality-adjusted days annually.

2.7 Analysis

We used a 10-year time horizon (the duration of continuation or discontinuation) in order to allow sufficient time to capture disability outcomes, and because a longer time duration of assumed DMD continuation or discontinuation may be less relevant to older adults making treatment decisions. Analyses required two sets of simulations (age 30–55 years and 55–64 years, for age 55 years analysis) because people in subgroups with a lower ARR were more likely to be relapse-free, thus the prevalence of subgroups changed over time among cohort members who were in a relapse-free interval (electronic supplementary Table 1). Model simulations were based on the average results of 30,000 simulated individuals.

2.8 Sensitivity Analyses

We examined a range of utility weights for the quality-of-life adjustments for disability status [33]. We also evaluated QALYs assuming all relapses were severe (0.0755) or mild (0.01575), which increased or decreased the weight of relapses relative to disability status in QALY outcomes, respectively. This sensitivity analysis represents scenarios where an individual perceives relapses as more/less severe or places more/less value on relapse prevention. Relapse is an important outcome, but, implicitly, relapses are weighted less than disability status in QALYs because relapses are infrequent events.

We examined heterogeneity by ARR only (subgroups with no differences by disability status) to evaluate the impact of our assumption that relapses and disability co-varied. We investigated the impact of a lower or higher ARR (averaged across subgroups) at age 55 years, with a

focus on relapse outcomes. Lastly, we assessed the impact of a longer time horizon on quality-of-life outcomes over the full remaining lifetime. This analysis evaluated lifetime QALYs for DMD continuation or discontinuation from 55 or 70 years of age, up to 100 years of age.

3 Results

3.1 Quality-Adjusted Life-Years

Among simulated adults with an EDSS score below 6 and a 5-year relapse-free interval, DMD treatment continuation yielded more QALYs than discontinuation in both age cohorts, prior to consideration of treatment-related disutility (Table 2). However, the QALY gains of continuation over discontinuation decreased with patient age. At age 55 years, the projected benefit of DMDs ranged from 0.007 QALYs for fingolimod to 0.017 QALYs for natalizumab, while at age 70 years, these QALY gains were only 0.002 and 0.006 QALYs for fingolimod and natalizumab, respectively. Continuation with interferon-β yielded QALY gains similar to those of fingolimod (0.008 QALYs at age 55 years; 0.002 QALYs at age 70 years) due to having similar effectiveness. Natalizumab had the largest benefit regardless of age, due to its greater effectiveness in preventing relapses and disability compared with interferon-β and fingolimod (Table 1) [20].

3.2 Relapses and Disability

Among those who discontinued DMDs, relapses were lower at age 70 years than age 55 years, and, accordingly, we found a larger benefit for DMD continuation at age 55 years compared with age 70 years for relapse outcomes (Table 2). For

those who continued a DMD, we found a 3.3–5.8 percentage point reduction in the percentage of people with a relapse within 10 years for natalizumab, 2.3–3.5 for fingolimod, and 1.0–1.1 for interferon-β. DMD continuation resulted in a modest reduction in the percentage of people who reached EDSS 6 within 10 years (0.4–1.6 points at age 55 years and 0.0–0.5 at age 70 years) (Table 2).

3.3 Decision Threshold

3.3.1 DMD Benefit versus Burden

For older adults who perceive reduced health-related quality of life when taking a DMD, the quality-of-life losses from the drug burden may outweigh the benefits derived from the DMD effectiveness. We found that if a person was willing to give up less than one quality-adjusted life-day per year (0.3–0.6 at age 55 years and 0.1–0.2 at 70 years) to avoid the DMD burden and expense, then discontinuation of the DMD would be recommended (Table 3). These annual threshold values are smaller than the estimated disutility for DMDs (47–74 quality-adjusted life-days).

Estimates for the disutility of interferon-β incorporated minor adverse events such as soreness or infection around the injection site; disutilities for fingolimod and natalizumab were based on treatment administration only and did not include additional burdens related to adverse events such as serious infections [33, 41, 42].

3.4 Sensitivity Analyses

Examining higher or lower values for the relapse disutility produced few to no differences from the main analysis,

Table 2 Projected outcomes among simulated cohorts of adults with relapsing-onset multiple sclerosis

	Outcomes from age 55 years (10-year time horizon)			Outcomes from age 70 years (10-year time horizon)		
	QALYs	Percentage with a relapse	Percentage reaching EDSS 6	QALYs	Percentage with a relapse	Percentage reaching EDSS 6
Discontinue DMD	6.792	32.6	27.5	6.317	14.6	27.3
DMD continuation[a] (compared with discontinuation)						
	Difference in QALYs	Difference in percentage with a relapse	Difference in percentage reaching EDSS 6	Difference in QALYs	Difference in percentage with a relapse	Difference in percentage reaching EDSS 6
Fingolimod	0.007	− 3.5	− 0.4	0.002	− 2.3	− 0.0
Interferon-β	0.008	− 1.1	− 0.7	0.002	− 1.0	− 0.0
Natalizumab	0.017	− 5.8	− 1.6	0.006	− 3.3	− 0.5

People who were in a 5-year relapse-free interval and had not reached EDSS 6

DMD disease-modifying drug, *EDSS* Expanded Disability Status Scale, *QALYs* quality-adjusted life-years

[a]Results prior to consideration of a disutility for DMDs; the projected benefit for an individual may be less than the QALYs shown in this table, depending on their preferences regarding DMDs

Table 3 Decision threshold: annual projected benefit versus burden of disease-modifying drugs in quality-adjusted life-days

	DMD projected benefit[a,b]		DMD burden[c]
	Age 55 years	Age 70 years	
Fingolimod	0.3	0.1	47
Interferon-β	0.3	0.1	74
Natalizumab	0.6	0.2	51

DMD disease-modifying drug, *EDSS* Expanded Disability Status Scale, *QALY* quality-adjusted life-years

[a]DMD benefits were projected among simulated cohorts of adults with relapsing-onset multiple sclerosis who were in a 5-year relapse-free interval and had not reached EDSS 6

[b]Results prior to the consideration of a disutility for DMDs; the projected benefit for an individual may be less than zero, depending on their preferences regarding DMDs

[c]DMD disutilities were derived from published literature [33, 41, 42] based on average patient preferences regarding treatment delivery. Because we found no published studies of patient preferences for fingolimod or natalizumab, we derived disutilities by comparing results from a study of migraine treatments that evaluated patient preferences for treatment delivery [42] with average community-based disutilities estimated for interferon-β-1b (0.204, a loss of 74 quality-adjusted life-days per year) (Table 3) [33, 41]. Compared with 31–39 injections per 3 months (similar to the delivery of interferon-β-1b), the QALY gain was 0.074 (27 quality-adjusted life-days) for oral medication (once or twice daily), and 0.063 (23 quality-adjusted life-days) for only one injection per month. We used monthly injections as a conservative approximation of the disutility for natalizumab, which requires an intravenous infusion lasting at least 1 h every 4 weeks. Estimates for interferon-β included minor adverse events such as soreness or infection around the injection site; estimates for fingolimod and natalizumab were based on treatment administration only and did not include additional burdens related to adverse events such as serious infections

particularly at age 70 years (electronic supplementary Table 2). Similarly, a range of different utility weights for disability status yielded small differences compared with the main analysis (electronic supplementary Table 3). Results were similar to the main analysis when examining heterogeneity by ARR only (subgroups with no differences by disability status) and a lower or higher ARR (electronic supplementary Table 4). Assuming a lower or higher ARR, the reduction in the percentage of people with a relapse (0.2–3.3 and 0.7–7.3 percentage points, respectively) was marginally lower or higher than the main analysis. Extending the duration of DMD continuation or discontinuation from 10 years to the full lifetime (45 years at age 55 years, and 30 years at age 70 years) produced annual QALY gains that were similar to the main analysis and very low compared with typical treatment burdens (0.3–0.7 quality-adjusted life-day per year at age 55 years, and 0.1–0.2 at age 70 years).

4 Discussion

In this simulation study of three different DMDs commonly used to treat people with MS, we found that the benefit of continuing DMDs among older adults was 0.007–0.017 QALYs at age 55 years, and 0.002–0.006 QALYs at age 70 years (Table 2). Despite the low gain in QALYs for DMD continuation, our results generally showed a reduction in the percentage of individuals with a relapse or reaching EDSS 6 ('requires a cane to walk') over 10 years. Whether these potential benefits are worth the burden of continuing to take a DMD will depend on an individual's preferences, clinical history, and previous MS disease activity, including relapses and disability progression. The treatment disutilities (depending on personal preferences) that would result in no benefit associated with DMD continuation were small compared with average patient preferences reported in the literature (Table 3) [33, 41, 42]. Our work highlights the importance of gaining a better understanding of aging with relapsing-onset MS.

For people with relapsing-onset MS, along with their clinicians, weighing the perceived treatment burden with uncertain benefits may require a challenging conversation or series of conversations. People may be unaware of age-related factors in the risks versus benefits of DMDs and some may have a strong preference for or against taking a specific DMD. Individuals have different preferences and perceptions of treatment burdens [33, 41, 42]. For example, for interferon-β, the 25th–75th percentile of estimated disutilities ranged from 0.230 (84 quality-adjusted life-days per year) to 0.001–0.003 (0.4–1.1 quality-adjusted life-days per year). Patient preferences are generally affected by convenience of drug delivery, perceptions of potential benefits, and risks of adverse events [42–44], as well as health insurance coverage and out-of-pocket cost. Even for people who are currently able to afford their treatment, uncertainty about changes in coverage, cost, and income may add to the burden of taking expensive drugs such as DMDs. In the US, drug costs are typically higher than in other countries, and DMDs can cost upwards of $US60,000 per person per year [7].

Broadly, our study contributes to the growing literature suggesting a lack of DMD benefits for older adults with MS. For example, the results of a regression model extending findings from a meta-analysis indicated no DMD benefit for the average person with MS over 53 years of age [45]. However, few people aged in their 50 s or older were included in the clinical studies that were included in the meta-analysis, and, clinically, DMDs are generally believed to offer some benefits for MS patients who continue to have disease activity such as relapses. We assumed DMD benefits persisted with increasing age in proportion to ARR decreases with age and still found very low benefits for continuing DMDs at

55 or 70 years of age. Previous studies in MS using Markov models to project long-term outcomes did not incorporate a decrease in relapses with age or examine stopping a DMD among older adults [33, 34, 46–48]. Thus, these previous models may have overestimated the benefits of DMDs for older adults by not accounting for the change in relapses with age. Observational studies have shown that people who discontinue DMDs when they are older are less likely to relapse compared with those who discontinue at a younger age [14, 16–18, 49]; however, these studies have been limited by sample size and duration of follow-up.

Our study has limitations, in part because it is inherently challenging to model aging with MS; the literature is sparse and we had to make several key assumptions. We could have overestimated the benefits of the DMDs if relapses eventually stop or 'burn out' [23, 50] rather than being a continuous linear decline as assumed in our model. Based on available data, we used relapses and disability status to calculate QALYs. It would be of value for future studies to include other outcomes that are important to people with MS, such as cognitive function or employment status. These outcomes are also lacking in, for example, phase III clinical trials.

Our study has several limitations in estimating treatment effectiveness. Age-related changes in the disease pathology of relapsing-onset MS or accrual of comorbidities may affect an older adult's response to a DMD or the risks associated with DMDs. We linked DMD effectiveness for disability worsening to disease activity based on the ARR. In addition, our model does not include comorbidities, JC viral status, or MRI, which is a biomarker of disease activity. Disability may accrue with or without the presence of a clinical relapse, possibly via distinct pathological processes, which may occur simultaneously [51]. Current evidence did not allow us to separately quantify treatment effectiveness based on inflammatory versus degenerative pathology or other biomarkers.

We used estimates for DMD efficacy based on the results of a network meta-analysis that ranked DMDs [20], however such meta-analyses in MS have produced varying results and rankings [52, 53]. Thus, small differences in study outcomes may not be clinically meaningful. We modeled three different DMDs, which represent a subset of those currently available. The use of these DMDs will also differ across jurisdictions. Essentially, our study encompasses scenarios of first- and second-generation DMDs with varying degrees of effectiveness, different modes of treatment administration, and both biologic and small molecule agents. Future work could incorporate estimates, such as relapse rates or treatment effectiveness, based on newly completed studies of older adults with relapsing-onset MS. This would allow the projection of long-term outcomes with updated or refined disease- and treatment-related assumptions, or comparison of a different set of DMDs.

Compared with first-generation DMDs (e.g. interferon-β and glatiramer acetate), the newer, second-generation drugs (e.g. fingolimod and natalizumab) have a higher risk of severe adverse events [3–5, 54]. For example, natalizumab increases the risk of progressive multifocal leukoencephalopathy (PML), and cases of this potentially fatal viral disease have also been reported with the use of fingolimod [55, 56]. Among people with MS who were taking natalizumab and who contracted PML, approximately one in four died [55]. Screening for anti-JC virus antibodies reduces the risk of PML [4], however the risk of fatal infections may be perceived as a significant treatment burden.

Allowing for switching between DMDs was beyond the scope of our model, as was examining the treatment history (e.g. early treatment strategies) prior to the decision point at age 55 or 70 years. We assumed a person with MS who continued a DMD remained on the drug for 10 years, which may not always be applicable. For a treatment period of < 10 years, benefits may be proportionally reduced. Although switching between DMDs could be approximated by weighting the proportion of time on each drug, a detailed analysis of switching would need to account for possible patient burdens and harms related to medication changes.

Data were limited for quantifying the potential adverse events of DMD continuation or discontinuation and we did not examine the potential for 'rebound' disease activity after discontinuation (i.e. where the person can experience an increase in relapse rates and MRI lesions immediately after stopping a drug), which has been reported for natalizumab and fingolimod [57, 58]. Our study focused on the choice faced by clinically stable older adults with relapsing-onset MS who could potentially choose to either continue or discontinue DMDs. We did not specifically address reasons for discontinuation such as perceived lack of effectiveness, drug intolerance, or a change in JC virus status. The complexity of discontinuation decisions implies that an understanding of how the trajectory of relapsing-onset MS changes with age is important for people of all ages with this disease, so that they can make informed decisions.

Additional support for people with MS to enable their personal preferences to guide DMD discontinuation decisions would be valuable. These could include clinical decision aids as well as allowing for patient preferences in clinical guidelines and drug reimbursement policies. Policies and tools that assist older adults in weighing the treatment burden and risks they experience against the benefits of DMD continuation may improve the quality of life for people with relapsing-onset MS.

5 Conclusion

The MS literature has emphasized the importance of early initiation of DMDs among younger adults and treatment adherence, but less attention has been given to examining how age-related changes in DMD efficacy and effectiveness pertain to the treatment of older adults [6]. Although further direct clinical evidence is needed [20, 54], our study illustrates that the benefits of DMDs for older adults with relapsing-onset MS may be limited and outweighed by the burden of taking DMDs. Deprescribing medication can be a controversial topic [54, 59, 60]. Our work emphasizes that the decision regarding whether to discontinue a DMD should factor in patient preferences. Further research with a specific focus on older adults with MS will be invaluable for optimizing MS care across the lifespan.

Compliance with Ethical Standards

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