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Patient and physician preferences for multiple sclerosis treatments in Germany: A discrete-choice experiment study

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Abstract

Objective: To assess heterogeneity in patient and physician preferences for multiple sclerosis treatment features and outcomes via a discrete-choice experiment.

Method: Patients with self-reported multiple sclerosis and treating physicians participated in an online discrete-choice experiment. Patients, each considering a better or worse reference condition, and physicians, each considering two patient profiles, chose between hypothetical treatment profiles defined by seven attributes with varying levels: years until disability progression, number of relapses in the decade, mode of administration, dosing frequency, and risks of mild, moderate, and severe side effects. Latent class analysis was used to measure respondent preferences and identify potential subgroups with distinct preferences.

Results: Distinct treatment preferences emerged among subgroups of patients ($n = 301$) and physicians ($n = 308$). Patients in class 1 (43% of sample) were most concerned about side effects; chief concerns of class 2 patients (57%) were delaying disability progression and avoiding severe side-effect risks. The most important attributes for physicians (by class) were delaying disability (class 1, 45%), avoiding severe side-effect risks and (class 2, 33%), and avoiding all side-effect risks (class 3, 22%).

Conclusion: Patients and physicians have diverse preferences for multiple sclerosis treatments, reflecting heterogeneity in the disease course and available therapies and the need for shared decision making.

Keywords: Multiple sclerosis, discrete choice, patient, physician, preferences, heterogeneity

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Introduction

Multiple sclerosis (MS) is a complex disease with a highly variable disease course.[1] Patients with MS exhibit considerable heterogeneity in terms of clinical features, pathogenesis, and response to treatment.[1] As a result of this disease heterogeneity, clinical guidelines for MS do not recommend a single treatment pathway; instead, individualized treatment decisions should consider an individual patient's clinical profile, the benefits and risks of the available therapies, and patient preference.[2,3] The MS treatment landscape is broad, and treatment decisions involve tradeoffs among efficacy, safety, mode of administration (i.e., oral, subcutaneous (SC) or intramuscular injection (IM), and intravenous (IV) infusion), and frequency of administration of the many available treatments.

Previous studies have identified efficacy (including delaying disease progression and preventing MS symptoms), adverse events, and dosing features as key drivers of patient preferences for MS treatments.[4–15] Some of these studies have explored MS treatment preferences among subgroups of patients defined by demographic or clinical characteristics, finding heterogeneity between subgroups in the relative importance of the attributes evaluated.[7–11] Further, physician preferences for MS treatments

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have not been extensively evaluated and may be a primary driver of treatment choices in MS management, given the lack of a prescriptive treatment pathway. Patient and physician perspectives on MS treatment strategies may not always align, however.[16] Understanding patient and physician preferences for MS treatments and exploring how preferences differ may inform shared decision making in MS.

The objective of this study was to assess the features and outcomes of treatments for MS that drive patient and physician decision-making via a discrete-choice experiment (DCE) conducted in Germany. Specific aims of the study were to measure patient and physician preferences for treatment features and outcomes, to explore heterogeneity between patients and physicians by comparing preferences between these populations, and to explore heterogeneity within each population by determining whether there are subgroups of patients and physicians with distinct preferences through a latent class analysis (LCA).

Materials and methods

This study used an online DCE survey to elicit patient and physician preferences for particular attributes of MS therapies. In DCEs, respondents choose between pairs of hypothetical treatment profiles, defined by attributes with varying levels, in a series of DCE questions. The hypothetical profiles are combinations of attribute levels but do not necessarily characterize existing treatments. Profiles and profile pairs are determined by an experimental design. Respondents' choices depend on the relative importance of attribute levels, and the implicit importance weights consistent with observed patterns of choices can be estimated through statistical analysis (see Figure 1).

Survey development

The survey instruments were developed following good research practices.[17] Each choice question (Figure 2) asked the respondent to choose between a pair of hypothetical treatments for MS, where each treatment was characterized by seven attributes with varying levels (Table 1). Attribute selection and descriptions were informed by observed disability

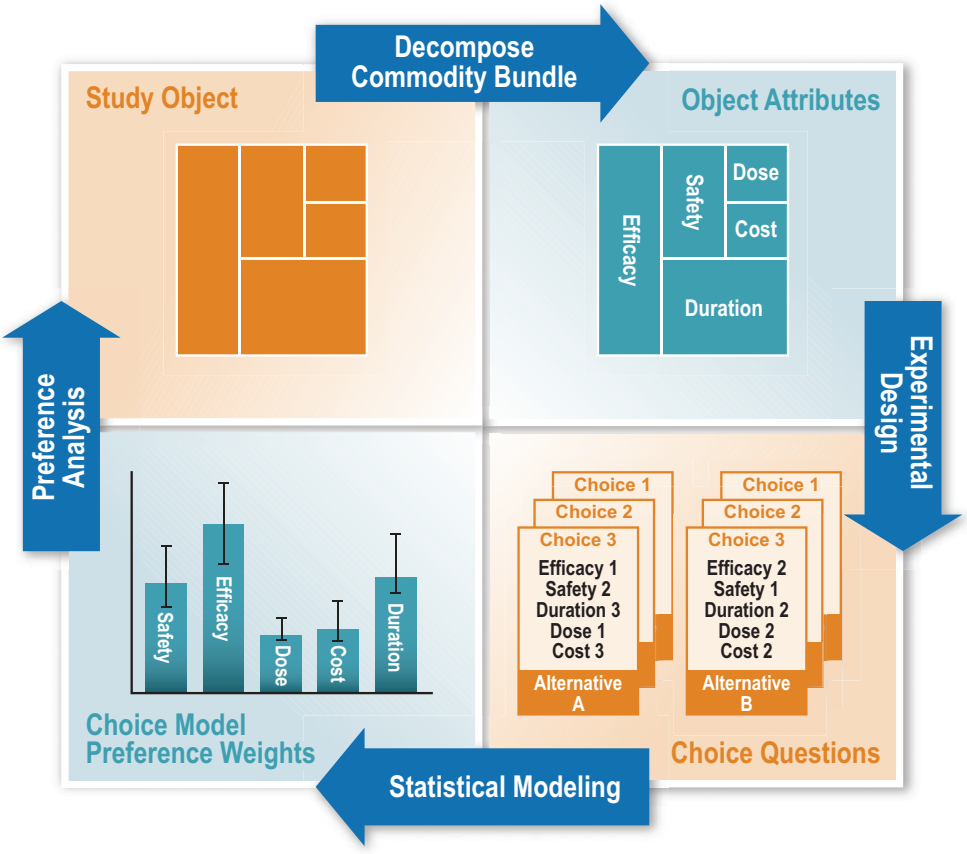

Figure 1. Discrete-choice experiment steps.

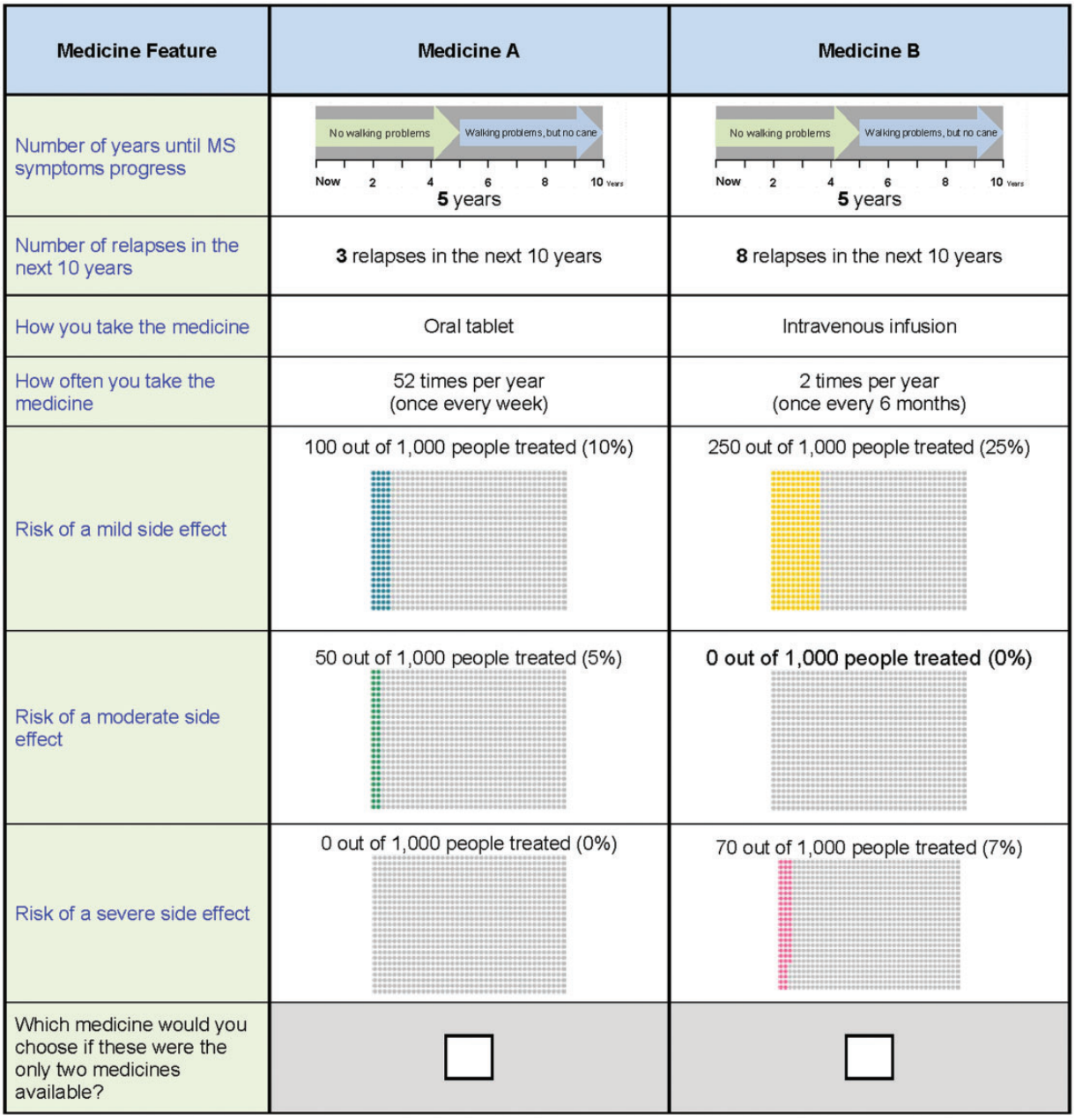

Figure 2. Sample choice question.
MS: multiple sclerosis.

progression, relapse, and side effect (SE) rates from clinical trials, expert clinical opinion, the medical literature, and the product labels of available treatments.[18–30] Attribute levels were selected to include the range of clinically relevant endpoints for comparability with the profiles of treatments available at the time of the survey. Patients were randomly assigned to consider an assigned reference condition and answer the choice questions as though the assigned reference condition described their current health state (see Table S-1 in Appendix A). All physicians considered each of the patient profiles when answering the choice questions, but the order in which the two profiles were considered was randomly assigned (see Table S-2 in Appendix A). The physician survey also included a question to explore physicians' concerns about immunosuppression caused by long-acting disease-modifying MS therapies.

The surveys were developed in English and translated and culturally adapted for Germany. They were

Table 1. Attributes and attribute levels for discrete-choice experiment.

Type of attribute	Attribute	Level	
Treatment benefit	Number of years until disability progression	2 years	
		5 years	
		8 years	
		10 years	
	Number of relapses in the next 10 years	Three relapses in the next 10 years	
		Five relapses in the next 10 years	
		Eight relapses in the next 10 years	
Treatment administration	Mode of administration	Oral tablet	
		Subcutaneous injection	
		Intramuscular injection	
		Intravenous infusion[a]	
	Dosing frequency	Two times per year (once every 6 months)	
		12 times per year (once every month)	
		52 times per year (once every week)	
		730 times per year (twice every day)	
Treatment risks	Risk of mild side effect	None	
		100 out of 1000 people treated (10%)	
		250 out of 1000 people treated (25%)	
		400 out of 1000 people treated (40%)	
	Risk of moderate side effect	None	
		50 out of 1000 people treated (5%)	
		200 out of 1000 people treated (20%)	
		300 out of 1000 people treated (30%)	
	Risk of severe side effect	Narrow-risk range	Wide-risk range
		None	None
		10 out of 1000 people treated (1%)	10 out of 1000 people treated (1%)
		70 out of 1000 people treated (7%)	70 out of 1000 people treated (7%)
		100 out of 1000 people treated (10%)	150 out of 1000 people treated (15%)

[a]The experimental design was restricted such that intravenous (IV) infusions could only be administered two or 12 times per year and would not be taken 52 or 730 times per year. This restriction was based on pretest interview findings that physicians believed the more frequent IV dosing is not feasible or realistic.

pretested with convenience samples of 15 patients and 15 physicians in Germany before they were administered online to the study population.

Study population

Kantar Health invited panelists from their consumer and physician panels to be screened for eligibility for the patient survey or the physician survey, respectively. Eligible patients were residents of Germany, 18 years of age or older with a self-reported physician diagnosis of MS. Eligible physicians were licensed, residing and practicing in Germany, and treating people with MS weekly. To reflect practice patterns in Germany, neurologists, internists, and general practitioners were eligible for the study. All patients and physicians were able to read and understand German to provide informed consent and complete the survey instrument.

The study was approved by the RTI International institutional review board and complied with the Declaration of Helsinki. All respondents provided informed consent electronically.

Statistical analyses

The DCE data were analyzed using LC models[31] to quantify patients' and physicians' preferences for treatment features and outcomes. LC models are one way to examine heterogeneity in preferences. LC models probabilistically identify subgroups or classes of respondents (patients or physicians) with distinct preferences (see Appendix B) without having to rely on preidentified subgroups. Information criteria (i.e., Bayesian information criterion,[32] Akaike information criterion,[33] and modified Akaike information criterion)[34] were evaluated and then plotted to understand the optimal number of

Table 2. Treatment profiles used in preference share analysis.

	Profiles of injectable treatments				Profiles of oral treatments		Profiles of intravenous infusion treatments	
Attribute	SC profile A	SC profile B	IM profile A	IM profile B	Oral profile A	Oral profile B	IV profile A	IV profile B
Number of years until disability progression	5 years	2 years	5 years	2 years	8 years	2 years	10 years	5 years
Number of relapses in the next 10 years	Three	Four	Three	Four	Two	Four	Two	Two
Mode of administration	SC	SC	IM	IM	Oral	Oral	IV	IV
Dosing frequency (times per year)	52 times	156 times	52 times	156 times	365 times	730 times	Two times	13 times
Risk of mild side effect	12.5%	12.5%	12.5%	12.5%	0.0%	0.0%	0.0%	0.0%
Risk of moderate side effect	0.0%	0.0%	0.0%	0.0%	7.5%	7.5%	0.0%	0.0%
Risk of severe side effect	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.5%	2.5%

IM: intramuscular; IV: intravenous; SC: subcutaneous.
For each of the four modes of administration, profile A included the attribute levels expected to be most preferred, and profile B included the attribute levels expected to be least preferred (for attributes that could be ordered) conditional on the attribute level ranges likely to be observed in clinical practice (based on the information in product inserts for currently available products). For example, based on the annualized relapse rate reported in the product inserts, the number of relapses over 10 years ranges from three to four for injectable treatments, from two to four for oral treatments, and is fixed at two for IV treatments.

classes. In LCA, these information criteria are used as indices of the fit of models and how the fit changes as the number of classes changes.[35] For each LC, the model yielded a set of log-odds relative preference weights for each attribute level in Table 2. The weights indicate the strength of preference for the corresponding level. Logit regression analysis examined patient and physician characteristics associated with likely class membership (see Appendix B and Appendix E).

The study included an internal validity test of respondents' sensitivity to absolute differences in the additional risk of severe SE, known as a scope test.[36] To implement the scope test, respondents were randomly assigned to one of two ranges of risk of severe SE: narrow (0–10%) or wide (0–15%) (see Appendix C). Both the patient and the physician samples passed the scope test, suggesting that respondents, on average, were attentive to absolute risk levels and were not thinking about the risk levels in qualitative terms (e.g., low, medium, and high). Thus, data from both risk arms of each sample were pooled for the preference analysis.

Conditional relative importance—or the maximum change in utility achievable with any attribute level changes, conditional on the levels chosen for the attributes in the study—was calculated for each attribute as the difference between the preference weight for the level with the highest preference weight and the level of the same attribute with the lowest preference weight.

To explore how preference heterogeneity may affect treatment choice, the LC model parameters were used to compare patient and physician likely treatment choices across classes. The estimated LC model parameters were used to predict how likely treatment choices among a set of treatment profiles (or preference shares) vary across preference classes. Treatment profiles were developed based on the different classes of disease-modifying treatments. To capture variability in treatment outcomes, two treatment profiles were defined for each mode of administration (SC, IM, oral, and IV) (Table 2), with attribute levels used to characterize profiles based on the MS treatments available at the time of the study. For each mode, profile A included the attribute levels expected to be most preferred, and profile B included the attribute levels expected to be least preferred for attributes that could be ordered, including years of delay in disability progress, number of relapses, and treatment frequency.

All injectable treatments were assumed to have a risk of mild SEs but no risk of moderate or severe SEs; all oral treatments were assumed to have a risk of moderate SEs but no risk of mild or severe SEs; and all IV treatments were assumed to have a risk of severe SEs but no risk of mild or moderate SEs. The treatment profiles presented in Table 2 were organized into 16 sets of medicine profiles (choice sets). Each choice set included three treatment profiles: one injectable (SC or IM), one oral, and one IV, from a list of eight possible treatment profiles (Table 3). We used the LC model results to calculate the preference share, or average probability that a likely member of each preference class would select a treatment with specified characteristics from each choice sets.

Results

Survey respondents

Patients. Among the 301 patients who completed the survey, the average age was 46 years, 60% were female, and 76% had been diagnosed with MS less than 1 year ago. Overall, 52% of respondents had relapsing-remitting MS, 27% had secondary-progressive MS, 12% had primary-progressive MS, and 7% had progressive-relapsing MS. In total, 42% of respondents reported no limitations or mild symptoms (some activity limitations but no difficulty with gait) associated with their MS, whereas 58% reported more severe symptoms, ranging from difficulty with gait to using a wheelchair as their primary form of mobility. Among patient respondents, 154 were assigned to the better reference condition and 147 were assigned to the worse reference condition. Subgroup analyses indicated no statistically significant systematic differences between patients who considered the different reference conditions; thus, patient data from the two reference conditions were pooled for the analyses (see Appendix A).

Physicians. Among the 308 physicians who completed the survey, the average age was 53 years, and 77% were male. Consistent with recruitment quotas, 50% of respondents were neurologists, and 50% were internists or general practitioners. All physician respondents treated patients with MS each week, and 60% treated $\geq$6 patients with MS weekly. Among physician respondents, 171 physicians were assigned to answer choice questions considering the better hypothetical patient profile first and 137 physicians were assigned to answer choice questions considering the worse hypothetical patient profile first. Subgroup analyses indicated no statistically significant systematic ordering effects between physicians who considered the hypothetical profiles in a different order; thus, physician data from the two profiles were pooled for the analyses (see Appendix A).

Preference weights and conditional relative importance

Patient preferences. An LCA model with two classes of patients with distinct preferences was the best fit for the patient data: 43% of patient respondents were likely to be in patient class 1 (SE-risk-minimizing class), and 57% of patient respondents were likely to be in patient class 2 (delay-maximizing, severe-risk-minimizing class) (Table 4). Among patients, women, parents, and patients with not-yet-severe symptoms were more likely to be in the SE-risk-minimizing class (patient class 1) when making treatment choices. Appendix E presents the characteristics associated with likely membership in each class in further detail. Figure S-3 displays preference weights relative to the mean attribute effect for the patient sample (see Appendix D).

Figure 3 presents the conditional relative importance estimates for the MS-treatment features in the study for both patient classes. Given the ranges of the attribute levels included in the study, the most important attribute for the SE-risk-minimizing class was the risk of a severe SE, followed by the risk of a moderate SE and the risk of a mild SE. These results suggest that members of the SE-risk-minimizing class focused on avoiding SE risks. The estimates for the delay-maximizing, severe-risk-minimizing class, in comparison, show that delay in disability progression was the most important attribute, followed by the risk of a severe SE and the risk of a mild SE. These results suggest that members of this class had a focus on delaying disability progression and avoiding SE risks, particularly severe and mild SE risks.

Physician preferences. An LCA model with three classes of physicians with distinct preferences was the best fit for the physician data: 45% of physician respondents were in class 1 (delay-maximizing class), 33% of physician respondents were in class 2 (severe-risk-minimizing class), and 22% of physician respondents were in class 3 (SE-risk-minimizing class) (Table 4). Physicians who were in their 40s (rather than 30s or aged 50–79 years), who were

Table 3. Preference shares for treatment profiles.

		Patient classes, preference shares (95% CI)		Physician classes, preference shares (95% CI)		
Choice set	Treatment profiles[a]	Class 1 (risk-minimizing class)	Class 2 (disability delay-maximizing and serious-risk-minimizing class)	Class 1 (delay-maximizing class)	Class 2 (severe-risk-minimizing class)	Class 3 (all-risk-minimizing class)
1	Best oral	57.7% (24.5–90.9%)	36.4% (23.7–49.0%)	19.5% 5.0–33.9%)	62.1% (34.5–89.8%)	33.6% (22.0–45.2%)
	Best IV	18.9% (−5.7–43.4%)	45.6% (32.6–58.6%)	72.3% (56.5–88.0%)	37.0% (9.9–64.0%)	37.4% (25.0–49.9%)
	Best SC	23.4% (−3.8–50.6%)	18.0% (10.8–25.2%)	8.3% (3.3–13.2%)	0.9% (−1.4–3.1%)	29.0% (18.4–39.6%)
2	Best oral	70.3% (36.2–104.4%)	34.7% (21.5–47.9%)	20.7% (5.1–36.3%)	62.7% (35.2–90.2%)	35.6% (22.5–48.7%)
	Best IV	23.0% (−5.6–51.5%)	43.6% (31.1–56.0%)	76.9% (61.3–92.4%)	37.3% (9.8–64.8%)	39.8% (27.1–52.4%)
	Worst SC	6.8% (−5.9–19.4%)	21.7% (11.1–32.4%)	2.4% (0.2–4.6%)	0.0% (0.0–0.0%)	24.6% (12.9–36.3%)
3	Best oral	45.4% (9.3–81.4%)	38.0% (24.9–51.0%)	18.3% (5.0–31.7%)	62.5% (34.9–90.2%)	33.5% (22.2–44.9%)
	Best IV	14.8% (−5.5–35.1%)	47.6% (34.3–60.9%)	68.0% (50.8–85.2%)	37.2% (9.9–64.5%)	37.4% (24.8–50.0%)
	Best IM	39.8% (1.9–77.7%)	14.4% (8.6–20.2%)	13.6% (4.4–22.8%)	0.3% (−0.6–1.2%)	29.0% (18.7–39.3%)
4	Best oral	65.1% (27.2–103.1%)	36.6% (23.3–49.9%)	20.3% (5.1–35.6%)	62.7% (35.2–90.2%)	35.6% (22.9–48.4%)
	Best IV	21.3% (−4.6–47.1%)	45.9% (33.4–58.4%)	75.5% (59.8–91.2%)	37.3% (9.8–64.8%)	39.7% (27.2–52.2%)
	Worst IM	13.6% (−10.6–37.8%)	17.5% (9.7–25.4%)	4.2% (0.2–8.2%)	0.0% (0.0–0.0%)	24.6% (13.9–35.4%)
5	Best oral	42.8% (17.3–68.2%)	53.3% (40.9–65.7%)	63.8% (45.0–82.7%)	93.8% (81.6–106.0%)	36.6% (25.6–47.6%)
	Worst IV	39.9% (12.6–67.2%)	20.3% (12.1–28.5%)	9.1% (2.5–15.7%)	4.9% (−4.6–14.4%)	31.8% (21.6–41.9%)
	Best SC	17.3% (−5.2–39.9%)	26.4% (16.0–36.7%)	27.1% (10.1–44.0%)	1.3% (−2.1–4.8%)	31.6% (20.3–43.0%)
6	Best oral	49.3% (21.1–77.4%)	49.9% (35.6–64.1%)	79.4% (64.8–93.9%)	95.0% (85.2–104.8%)	39.1% (27.1–51.1%)
	Worst IV	46.0% (18.3–73.7%)	19.0% (10.5–27.5%)	11.3% (2.8–19.9%)	5.0% (−4.8–14.7%)	33.9% (22.5–45.3%)
	Worst SC	4.8% (−4.7–14.2%)	31.2% (15.8–46.5%)	9.3% (−0.7–19.3%)	0.0% (0.0–0.1%)	27.0% (13.4–40.5%)
7	Best oral	35.6% (9.0–62.1%)	56.8% (44.5–69.1%)	53.0% (32.2–73.8%)	94.7% (83.9–105.5%)	36.6% (25.8–47.4%)
	Worst IV	33.2% (7.4–59.0%)	21.6% (13.1–30.1%)	7.6% (1.6–13.5%)	4.9% (−4.7–14.6%)	31.7% (21.6–41.9%)
	Best IM	31.2% (−2.8–65.3%)	21.6% (13.0–30.1%)	39.4% (18.1–60.7%)	0.4% (−1.0–1.8%)	31.7% (20.8–42.6%)

(continued)

Table 3. Continued

		Patient classes, preference shares (95% CI)		Physician classes, preference shares (95% CI)		
Choice set	Treatment profiles[a]	Class 1 (risk-minimizing class)	Class 2 (disability delay-maximizing and serious-risk-minimizing class)	Class 1 (delay-maximizing class)	Class 2 (severe-risk-minimizing class)	Class 3 (all-risk-minimizing class)
8	Best oral	46.7% (17.8–75.6%)	53.8% (40.6–66.9%)	74.2% (56.6–91.7%)	95.0% (85.3–104.8%)	39.1% (27.5–50.6%)
	Worst IV	43.6% (17.1–70.1%)	20.5% (11.9–29.0%)	10.6% (2.5–18.7%)	5.0% (−4.8–14.7%)	33.9% (22.7–45.1%)
	Worst IM	9.7% (−8.8–28.3%)	25.8% (13.6–37.9%)	15.3% (−0.3–30.8%)	0.0% (0.0–0.0%)	27.0% (14.5–39.5%)
9	Worst oral	20.6% (4.9–36.4%)	25.0% (16.4–33.5%)	0.9% (0.2–1.6%)	0.7% (−1.2–2.7%)	22.7% (14.6–30.8%)
	Best IV	35.4% (−2.3–73.1%)	53.8% (41.7–65.9%)	88.9% (82.1–95.8%)	96.9% (89.5–104.4%)	43.6% (30.4–56.8%)
	Best SC	43.9% (5.5–82.4%)	21.2% (13.2–29.3%)	10.2% (3.7–16.7%)	2.3% (−3.3–7.9%)	33.7% (22.4–45.1%)
10	Worst oral	31.0% (8.1–54.0%)	23.7% (16.0–31.3%)	1.0% (0.2–1.8%)	0.8% (−1.3–2.9%)	24.4% (16.3–32.5%)
	Best IV	53.2% (15.4–91.1%)	51.0% (37.4–64.5%)	96.0% (92.7–99.3%)	99.2% (97.0–101.4%)	46.7% (32.3–61.2%)
	Worst SC	15.7% (−5.0–36.4%)	25.4% (14.9–35.9%)	3.0% (0.3–5.8%)	0.0% (−0.1–0.1%)	28.9% (17.5–40.3%)
11	Worst oral	13.7% (2.2–25.1%)	26.3% (17.0–35.5%)	0.8% (0.2–1.5%)	0.8% (−1.3–2.8%)	22.7% (14.5–30.9%)
	Best IV	23.4% (−8.5–55.4%)	56.6% (45.0–68.2%)	82.6% (70.6–94.7%)	98.6% (94.4–102.7%)	43.5% (30.4–56.6%)
	Best IM	62.9% (26.3–99.6%)	17.1% (10.3–24.0%)	16.6% (4.8–28.3%)	0.7% (−1.6–2.9%)	33.8% (22.4–45.1%)
12	Worst oral	26.2% (9.5–42.9%)	25.1% (16.8–33.5%)	0.9% (0.2–1.7%)	0.8% (−1.3–2.9%)	24.3% (16.4–32.3%)
	Best IV	45.0% (4.2–85.8%)	54.2% (41.7–66.6%)	93.8% (88.3–99.4%)	99.2% (97.1–101.3%)	46.7% (32.7–60.7%)
	Worst IM	28.8% (−3.9–61.4%)	20.7% (12.9–28.5%)	5.2% (0.1–10.3%)	0.0% (0.0–0.0%)	29.0% (18.5–39.4%)
13	Worst oral	12.4% (−0.3–25.2%)	39.9% (28.7–51.2%)	6.2% (2.4–10.0%)	6.5% (−5.7–18.6%)	25.1% (16.2–34.0%)
	Worst IV	61.1% (24.3–97.8%)	26.1% (15.3–37.0%)	23.6% (7.7–39.5%)	73.4% (35.0–111.8%)	37.5% (25.1–49.9%)
	Best SC	26.5% (−4.3–57.3%)	34.0% (24.1–43.8%)	70.2% (53.3–87.1%)	20.1% (−7.4–47.5%)	37.3% (26.1–48.5%)
14	Worst oral	15.6% (−1.5–32.7%)	36.7% (27.4–45.9%)	12.6% (6.6–18.6%)	8.1% (−9.5–25.7%)	27.2% (19.1–35.3%)
	Worst IV	76.5% (47.0–106.0%)	24.0% (11.8–36.2%)	47.9% (21.8–74.0%)	91.7% (73.5–109.9%)	40.6% (25.4–55.7%)
	Worst SC	7.9% (−6.2–22.0%)	39.4% (26.1–52.6%)	39.5% (14.7–64.2%)	0.2% (−0.6–1.0%)	32.3% (19.4–45.1%)
15	Worst oral	9.5% (0.3–18.8%)	43.3% (30.8–55.9%)	4.1% (1.2–7.0%)	7.6% (−8.0–23.1%)	25.1% (16.1–34.1%)

(continued)

Table 3. Continued

Choice set	Treatment profiles[a]	Patient classes, preference shares (95% CI)		Physician classes, preference shares (95% CI)		
		Class 1 (risk-minimizing class)	Class 2 (disability delay-maximizing and serious-risk-minimizing class)	Class 1 (delay-maximizing class)	Class 2 (severe-risk-minimizing class)	Class 3 (all-risk-minimizing class)
16	Worst IV	46.7% (7.2–86.1%)	28.4% (17.4–39.3%)	15.4% (2.0–28.9%)	85.7% (57.7–113.6%)	37.5% (25.3–49.6%)
	Best IM	43.8% (6.1–81.6%)	28.3% (19.4–37.2%)	80.5% (65.5–95.5%)	6.8% (−7.6–21.2%)	37.4% (26.4–48.4%)
	Worst oral	14.3% (0.2–28.4%)	40.3% (30.5–50.2%)	9.7% (4.8–14.6%)	8.1% (−9.5–25.7%)	27.2% (19.2–35.1%)
	Worst IV	70.1% (33.4–106.7%)	26.4% (14.4–38.5%)	36.9% (9.5–64.3%)	91.8% (74.0–109.7%)	40.5% (25.8–55.2%)
	Worst IM	15.7% (−9.5–40.8%)	33.2% (22.7–43.7%)	53.3% (24.8–81.8%)	0.1% (−0.2–0.3%)	32.3% (20.6–44.1%)

CI: confidence interval; IM: intramuscular; IV: intravenous; SC: subcutaneous.
[a]For each mode of administration, one profile (referred to as "best") represented the best levels of all attributes (except mode, which was fixed), conditional on the attribute level ranges likely to be observed in clinical practice (based on the information in product inserts for currently available products). For example, based on the annualized relapse rate, the number of relapses over 10 years ranged from three to four for injectable treatments, from two to four for oral treatments, and was fixed at two for IV treatments. The "worst" profile for each mode represented the worst levels of all attributes (except mode, which was fixed), conditional on the attribute level ranges likely to be observed in clinical practice (based on the information in product inserts for currently available products). In total, four treatment profiles for injectable treatments (two profiles for SC treatments and two profiles for IM treatments), two for oral treatments, and two for intravenous treatments were used in the preference share calculations.

Table 4. Patient and physician classes.

Sample	Class	Class label and ordering of chief concerns	%
Patients ($N = 301$)	Class 1	SE-risk-minimizing class • Risk of a severe SE • Risk of a moderate SE • Risk of a mild SE	43.0
	Class 2	Delay-maximizing, severe-risk-minimizing class • Delay in disability progression w • Risk of a severe SE • Risk of a mild SE	57.0
Physicians ($N = 308$)	Class 1	Delay-maximizing class • Delaying disability progression • Risks of severe, moderate, and mild SEs	44.6
	Class 2	Severe-risk-minimizing class • Risk of a severe SE • Delay in disability progression	33.2
	Class 3	SE-risk-minimizing class • Risk of a severe SE • Risk of a moderate SE • Risk of a mild SE • Number of relapses	22.2

SE: side effect.

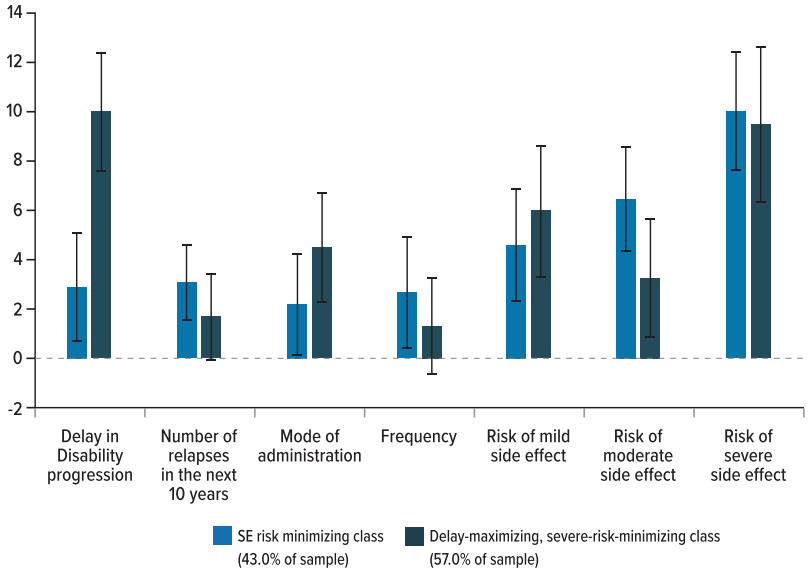

Figure 3. Patient conditional relative importance of attributes.

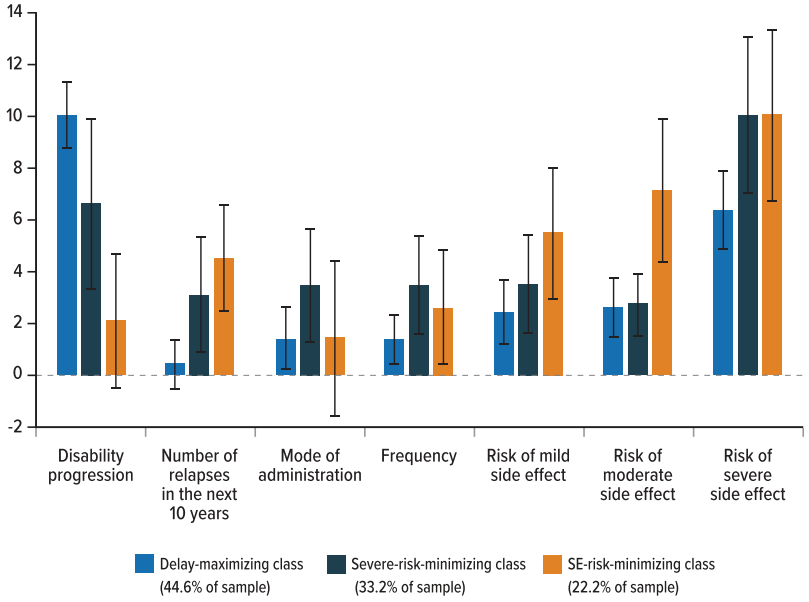

Figure 4. Physician conditional relative importance of attributes.

less concerned about the immunosuppressive effects of long-acting disease-modifying therapies, and who had considered the worse hypothetical patient profile first, were likely to be in the delay-maximizing class. Those who considered the better hypothetical patient profile first and those who believed that progression would impact more than ambulation were likely to be in the severe-risk-minimizing class. Finally, physicians who treated more than 10 patients with MS per week were more concerned about the immunosuppressive effects of long-acting disease-modifying therapies, were in their 70s (rather than younger), believed the hypothetical treatments in the survey would impact MS symptoms other than ambulation, and were likely to be members of SE-risk-minimizing class. Appendix E presents the characteristics associated with likely membership in each class in detail. Figure S-4 displays preference weights relative to the mean attribute effect for the physician sample (see Appendix D).

The conditional relative importance estimates for the physician classes are shown in Figure 4. Given the ranges of the attribute levels included in the study,

delaying disability progression was the most important attribute for the delay-maximizing class, followed by the risks of severe, moderate, and mild SEs. The number of relapses in the next 10 years was the least important attribute for this class. These results suggest that members of this class had a focus on delaying disability progression and, to a lesser extent, avoiding severe SE risks. For members of the severe-risk-minimizing class, the risk of a severe SE was the most important treatment attribute, followed by delay in disability progression. The risk of a moderate SE was the least important attribute for this class. These results suggest that members of this class had a focus on avoiding severe SE risks and, to a lesser extent, delaying disability progression. The most important attribute for the SE-risk-minimizing class was the risk of a severe SE, followed by the risk of a moderate SE, the risk of a mild SE, and the number of relapses. For this class, delaying disability progression and mode of administration were the least important attributes. These results suggest that members of this class had a focus on avoiding SE risks and, to a lesser extent, minimizing relapses.

Preference share analysis

Preference shares for patients. The preference share results for each choice set are shown in Table 3 for patients. Members of the SE-risk-minimizing class were most likely to choose oral profile A (more-preferred levels) if it was in a choice set. When oral profile A was not available, IV profile B (less-preferred levels) was most likely to be preferred. This class was more likely to prefer IV profile B over IV profile A, all else being equal. This counterintuitive result is a result of the disordering in preference weights for disability progression (statistically significant) and dosing frequency (not statistically significant). Members of this class were more likely to select IM profile A than the SC profile A because of a statistically significant preference for IM over SC injections in this class.

In comparison, members of the delay-maximizing and severe-risk-minimizing class would be most likely to choose the IV followed by the oral treatment in all choice sets with IV profile A (with the levels of delay, relapse, and treatment frequency expected to be most preferred). For most of the choice sets with IV profile B (with the levels of delay, relapse, and treatment frequency expected to be least preferred), members of the severe-risk-minimizing class were most likely to choose the oral treatment, followed by the injectable treatment. They were least likely to choose IV profile B.

Preference shares for physicians. The preference share results for each choice set are shown in Table 3 for physicians. Members of the delay-maximizing class preferred IV profile A in choice sets that included that treatment profile. In choice sets that did not include IV profile A, this class preferred oral profile A and if that was not available, injectable profile A. Members of the severe-risk-minimizing class preferred oral profile A in choice sets that included that treatment profile. In choice sets that did not include oral profile A, this class preferred IV profile A. The results indicate that members of this class were not likely to select injectable treatments. Finally, members of the SE-risk-minimizing class were approximately as likely to choose an oral, IV, or injectable profile. However, they were slightly more likely to choose the IV profile A in choice sets that included that treatment profile. In choice sets that did not include IV profile A, this class preferred oral profile A. In all choice sets, the injectable profile was not the profile that was most likely to be preferred.

Discussion

This DCE study of patient and physician preferences for MS treatments demonstrated heterogeneity in preferences within physician and patient subgroups, as well as variable preferences between patient and physician samples. The LCA revealed that, among patients, one class focused on avoiding severe, moderate, and mild SEs, whereas the other focused on delaying disability and avoiding severe SEs. Among physicians, one class focused on delaying disability progression and, to a lesser extent, avoiding severe SE risks, whereas a second class focused on avoiding severe SE risks and, to a lesser extent, delaying disability progression. The third class, in contrast, focused on avoiding SE risks and, to a lesser extent, reducing the number of relapses in the next 10 years. Although these results may not be representative, they indicate that not only are patient and physician preference heterogeneous within groups, but they are also heterogeneous between the patient and physician samples in that patient classes do not overlap with the physician classes and vice versa. There were no patient classes and physician classes with the same preference pattern.

Moreover, the preference share calculations suggest that, given the same set of MS treatment options, patients and physicians may choose different

treatments, even if their pattern of attribute importance was similar. In these analyses, no class had a simple ranking of the treatment profiles because of the variability within classes. Further, patient and physician classes with similar or overlapping priorities did not have the same preference shares, further emphasizing heterogeneity in stakeholders' preferences.

Previous preference research has identified heterogeneity in patients' preferences for MS treatments.[7–9] LCA is increasingly used to explore heterogeneity in health preferences generally[37] and is a parsimonious way to identify variations in preferences in a sample without the need for predefined subgroups.[38] LCA has been used to evaluate heterogeneity in patients' MS treatment preferences in one previous study: a best-worst scaling study conducted in Canada.[39] This study identified distinct preferences for five LCs, three of which were most concerned about avoiding serious adverse events and two of which were most concerned about symptom improvement.[39] To our knowledge, however, no previous studies have used LC methods to analyze DCE data or evaluated physician preferences with a DCE. Further, the preference share results from our study provide insights into stakeholders' benefit-risk assessments and likely behavior when evaluating treatment options. Taken together, these studies demonstrate heterogeneity within and between patient and physician treatment preferences. These findings are critical in understanding drivers of treatment choices and can promote shared decision making in MS, in turn improving adherence to and persistence with treatment, as well as treatment outcomes.[16]

Some strengths and limitations of the study must be noted. Development of the survey instrument, the experimental design, and the random-parameters logit methods followed best practices.[17,38,40] Nevertheless, respondents evaluated hypothetical treatments and profiles, and their choices do not have the same significance as choices involving actual treatment decisions. In particular, patients who were assigned to a hypothetical reference condition that differed from their own disease status in ways that were meaningful to respondents (e.g., more or less progressed) may have had different preferences than patients assigned to a reference condition that was relatively more similar to their own health state. In addition, this study used a web panel to recruit people with MS and physicians who treat MS, and a large proportion of the sample had received an MS diagnosis somewhat recently; thus, study respondents and their preferences may not be representative of the overall population of people with MS and physicians who treat MS in Germany. Further, although the attributes and levels evaluated in the survey were carefully selected to be clinically relevant, they represent a subset of the features of the available treatments. The hypothetical treatment profiles presented in the survey are not fully representative of the characteristics of the available therapies. Finally, MS diagnoses and all patient and physician characteristics were self-reported, and administration of the survey instrument online may have resulted in information and selection bias.

Conclusion

Results from this study indicate that patients with MS have heterogeneous treatment preferences, as do physicians who treat MS. Whereas some patients and physicians in this study prioritized avoidance of SE risks, even moderate or mild SEs, others prioritized delaying disability. The predicted treatment choice probabilities varied across patient and physician classes, even those with similar preference patterns, suggesting that even patients and physicians who have similar concerns would likely make different treatment choices. Understanding patient preferences is a key aspect of the shared decision-making model, and these results underscore the importance of a shared-decision framework in which physician and patients share information about the attributes of MS treatments that patients and physicians value most.

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Conflicts of Interest

Mehul Jhaveri, Elizabeth Kinter, and Craig Wakeford are salaried employees and shareholders of Biogen. Brennan Mange and Christine Poulos are salaried employees of RTI Health Solutions. Thomas Schenk is employed at the Ludwig-Maximilians-Universität München, Germany and received consulting fees from Biogen.

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Supplemental Material

Supplemental material for this article is available online.

References

1. Disanto G, Berlanga AJ, Handel AE, et al. Heterogeneity in multiple sclerosis: Scratching the surface of a complex disease. *Autoimmune Dis* 2010; 2011: 932351.
2. Montalban X, Gold R, Thompson AJ, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Mult Scler* 2018; 24(2): 96–120.
3. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurol* 2018; 90(17): 777–788.
4. Johnson F, Van Houtven G, Ozdemir S, et al. Multiple sclerosis patients' benefit-risk preferences: Serious adverse event risks versus treatment efficacy. *J Neurol* 2009; 256: 554–562.
5. Shingler S, Swinburn P, Ali S, et al. A discrete choice experiment to determine patient preferences for injection devices in multiple sclerosis. *J Med Econ* 2013; 16: 1036–1042.
6. Wicks P, Brandes D, Park J, et al. Preferred features of oral treatments and predictors of non-adherence: Two web-based choice experiments in multiple sclerosis patients. *Interact J Med Res* 2015; 4: e6.
7. Utz KS, Berg S, Lämmer A, et al. Patient preferences for disease-modifying drugs in multiple sclerosis therapy: A choice-based conjoint analysis. *Ther Adv Neurol Disord* 2014; 7: 263–275.
8. Wilson LS, Loucks A, Gipson G, et al. Patient preferences for attributes of multiple sclerosis disease-modifying therapies: Development and results of a ratings-based conjoint analysis. *Int J MS Care* 2015; 17: 74–82.
9. Mansfield C, Thomas N, Gebben D, et al. Preferences for multiple sclerosis treatments: Using a discrete-choice experiment to examine differences across subgroups of US patients. *Int J MS Care* 2017; 19(4): 172–183.
10. Poulos C, Kinter E, Yang JC, et al. Patient preferences for injectable treatments for multiple sclerosis in the United States: A discrete-choice experiment. *Patient* 2016; 9: 171–180.
11. Poulos C, Kinter E, Yang JC, et al. A discrete-choice experiment to determine patient preferences for injectable, multiple-sclerosis treatments in Germany. *Ther Adv Neurol Disord* 2016; 9: 95–104.
12. Poulos C, Kinter E, van Beek J, et al. Preferences of patients with multiple sclerosis for attributes of injectable multiple sclerosis treatments in the United Kingdom and France. *Int J Technol Assess Health Care* 2018; 34(4): 425–433.
13. Garcia-Dominguez JM, Muñoz D, Comellas M, et al. Patient preferences for treatment of multiple sclerosis with disease-modifying therapies: A discrete choice experiment. *Patient Prefer Adherence* 2016; 10: 1945–1956.
14. Frost N, Freeman J, Brixner D, et al. Patients' preferences and willingness-to-pay for disease-modifying therapies. *Mult Scler Relat Disord* 2019; 35: 55–60.
15. Bottomley C, Lloyd A, Bennett G, et al. A discrete choice experiment to determine UK patient preference for attributes of disease modifying treatments in multiple sclerosis. *J Med Econ* 2017; 20: 863–870.
16. Schlegel V and Leray E. From medical prescription to patient compliance: A qualitative insight into the neurologist-patient relationship in multiple sclerosis. *Int J MS Care* 2018; 20(6): 279–286.
17. Bridges JFP, Hauber AB, Marshall D, et al. Conjoint analysis applications in health—a checklist: A report of the ISPOR good research practices for conjoint analysis task force. *Value Health* 2011; 14: 403–413.
18. Copaxone (glatiramer acetate) prescribing information. Available at: https://www.copaxone.com/interactivepi (2019, accessed 6 September 2019).
19. Avonex (interferon beta-1a) prescribing information. Available at: www.avonex.com/content/dam/commercial/multiple-sclerosis/avonex/pat/en_us/pdf/Avonex%20US%20%20Prescribing%20Information.pdf (2019, accessed 6 September 2019).
20. Rebif (interferon beta-1a) prescribing information. Available at: http://www.emdserono.com/ms.country.us/en/images/Rebif_PI_tcm115_140051.pdf (2019, accessed 6 September 2019).
21. Betaseron (interferon beta-1b) prescribing information. Available at: https://labeling.bayerhealthcare.com/html/products/pi/Betaseron_PI.pdf (2019, accessed 6 September 2019).
22. Extavia (interferon beta-1b) prescribing information. Available at: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/extavia.pdf (2019, accessed 6 September 2019).
23. Plegridy (peginterferon beta-1a) prescribing information. Available at: https://www.plegridy.com/content/dam/commercial/multiple-sclerosis/plegridy/pat/en_us/pdf/plegridy-prescribing-information.pdf (2019, accessed 6 September 2019).
24. Glatopa (glatiramer acetate) prescribing information. Available at: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=5f01e40a-b6f6-40fb-b37c-3d06f1428e86&type=display (2019, accessed 6 September 2019).

25. Gilenya (fingolimod) prescribing information. Available at: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/gilenya.pdf (2019, accessed 6 September 2019).
26. Tecfidera (dimethyl fumarate) prescribing information. Available at: https://www.tecfidera.com/content/dam/commercial/multiple-sclerosis/tecfidera/pat/en_us/pdf/full-prescribing-info.pdf (2019, accessed 6 September 2019).
27. Aubagio (teriflunomide) prescribing information. Available at: http://products.sanofi.us/aubagio/aubagio.pdf (2019, accessed 6 September 2019).
28. Zinbryta (daclizumab HYP) prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761029s000lbl.pdf (2016, accessed 6 September 2019).
29. Tysabri (natalizumab) prescribing information. Available at: https://www.tysabri.com/content/dam/commercial/multiple-sclerosis/tysabri/pat/en_us/pdfs/tysabri_prescribing_information.pdf (2019, accessed 6 September 2019).
30. Lemtrada (alemtuzumab) prescribing information. Available at: http://products.sanofi.us/Lemtrada/Lemtrada.pdf (2019, accessed 6 September 2019).
31. Greene WH and Hensher DA. A latent class model for discrete choice analysis: Contrasts with mixed logit. *Transp Res Part B Methodological* 2003; 37(8): 681–698.
32. Hurvich CM and Tsai CL. Regression and time series model selection in small samples. *Biometrika* 1989; 76(2): 297–307.
33. McLachlan G and Peel D. *Finite mixture models*. New York: John Wiley & Sons, 2000.
34. Wedel M and Kamakura W. *Market segmentation: conceptual and methodological foundations*. 2nd ed. Boston: Kluwer Academic Publishers, 2000.
35. Deal K, Keshavjee K, Troyan S, et al. Physician and patient willingness to pay for electronic cardiovascular disease management. *Int J Med Inform* 2014; 83(7): 517–528.
36. Özdemir S, Johnson FR and Hauber AB. Hypothetical bias, cheap talk, and stated willingness to pay for health care. *J Health Econ* 2009; 28: 894–901.
37. Zhou M, Thayer WM and Bridges JFP. Using latent class analysis to model preference heterogeneity in health: A systematic review. *Pharmacoeconomics* 2018; 36(2): 175–187.
38. Hauber AB, Gonzalez JM, Groothuis-Oudshoorn CGM, et al. Statistical methods for the analysis of discrete choice experiments: A report of the ISPOR conjoint analysis good research practices task force. *Value Health* 2016; 19(4): 300–315.
39. Lynd LD, Traboulsee A, Marra CA, et al. Quantitative analysis of multiple sclerosis patients' preferences for drug treatment: A best-worst scaling study. *Ther Adv Neurol Disord* 2016; 9(4): 287–296.
40. Johnson FR, Lancsar E, Marshall D, et al. Constructing experimental designs for discrete-choice experiments: Report of the ISPOR Conjoint Analysis Discrete-Choice Experiment Experimental Design Good Research Practices Task Force. *Value Health* 2013; 16(1): 3–13.