Factors Associated with Patient Preferences for Disease-Modifying Therapies in Multiple Sclerosis

Ana L. Hincapie, PhD, MS; Jonathan Penm, PhD, BPharm; and Craig F. Burns, PhD, MS

ABSTRACT

BACKGROUND: Treatment adherence in patients with multiple sclerosis (MS) is essential to reduce the rate of acute neurological attacks, severity of relapses, and hospitalizations and to slow its progression. Adherence rates in MS patients have been shown to be affected by multiple factors, including physical or cognitive difficulties, perceived lack of treatment efficacy, treatment-related adverse events, injection anxiety, and frequency of administration.

OBJECTIVE: To elicit the preferences of MS patients for noneconomic and economic attributes of current disease-modifying therapies (DMTs).

METHODS: We used conjoint analysis to estimate preferences from a convenience sample through a web-based online survey. Patients were invited to participate in the study using web portals and newsletters for MS patients. The conjoint survey included the following 6 attributes: (1) overall efficacy based on autoimmune disease progression stabilization; (2) acute increase in disease activity (flare-up); (3) rate of respiratory tract infections; (4) rate of serious respiratory tract infections (leading to hospitalization); (5) medication use; and (6) patient monthly out-of-pocket medication costs. Using a fractional factorial design, 24 product profiles were created. Each respondent reviewed a random selection of 8 profiles. With each profile, subjects were asked to indicate their likelihood to try the hypothetical products on a scale from 0 to 100. Random effects linear regression was used to elicit preferences.

RESULTS: After exclusion of respondents with incomplete information, data from 129 subjects were included in the analysis. The overall relative importance of each attribute for the ranges presented were (1) 38.4% for monthly out-of-pocket cost; (2) 21.5% for route and frequency of administration; (3) 15.9% for risk of hospitalization by infection; (4) 11.9% for risk of respiratory tract infection; (5) 7.4% for risk of flare-ups; and (6) 5.0% for disease progression stabilization. Preference weights indicated that subjects favored subcutaneous (beta coefficient [β] = -2.26, 95% CI = -4.22 to -0.22) and oral administration (β = 7.93, 95% CI = 5.95 to 10.2) over intramuscular (β = -5.67, 95% CI = -8.67 to -3.56), but no significant differences were found between subcutaneous over intramuscular administration. Monthly out-of-pocket cost was the most influential attribute, with an overall relative importance of 38%. The most preferred level was \$75 (β = 12.85, 95% CI = 10.64 to 15.06) followed by \$150 (β = 3.41, 95% CI = 0.98 to 5.84) when compared between \$75, \$150, \$300, and \$450 a month.

CONCLUSIONS: Conjoint analysis proved to be a convenient tool to quantify respondents' relative preferences for DMT characteristics. Respondents gave higher weight to DMT monthly out-of-pocket costs and mode of administration than to adverse effects or efficacy. These findings may assist in the development of DMT cost-sharing strategies and shared decision making at the point of care.

J Manag Care Spec Pharm. 2017;23(8):822-30

Copyright © 2017, Academy of Managed Care Pharmacy. All rights reserved.

What is already known about this subject

- Treatment adherence in patients with multiple sclerosis (MS) is essential to slow its progression.
- Disease-modifying therapies (DMT) with different mechanisms of action and modes of administration have become more available to patients.
- Previous studies using stated-preference methods have found variation in patient preferences for DMT characteristics, but none of them have explored variation in potential out-of-pocket costs.

What this study adds

- Study results showed that of the drug attributes explored, monthly out-of-pocket costs associated with these treatments appeared to be a significant factor affecting MS patients' decision making regarding their interest in trying an MS product.
- Study findings suggest that drug administration route and frequency are of great importance to patients when considering trying a new product.

Treatment adherence in patients with multiple sclerosis (MS) is essential to reduce the rate of acute neurological attacks, severity of relapses, and hospitalizations and to slow its progression. However, like many chronic illnesses, nonadherence is commonly encountered in patients with MS. A study of 2,648 patients with relapsing-remitting MS reported that 25% of patients were nonadherent.¹ Discontinuation rates appear the highest within the first 6 months after treatment initiation, ranging from 9% to 20%.^{2,3} Identifying patient treatment preferences will allow clinicians to incorporate them into the decision-making process and increase the likelihood of patient adherence.

Medication adherence rates in patients with MS have been shown to be affected by multiple factors, including physical or cognitive difficulties, drug costs, patient preferences determined by the perceived lack of treatment efficacy, treatment-related adverse events, injection anxiety, and burden of administration frequency.⁴⁻⁷ Patient preferences have become increasingly important, since many alternatives to traditional injection therapies (interferons or glatiramers) have been developed to address adherence issues. Newer treatments include infusion therapies (natalizumab or alemtuzumab) or oral

therapies (dimethyl fumarate, teriflunomide, and fingolimod).⁸ Although infusion therapies have been shown to be the most effective treatment option for patients with relapsing-remitting MS, there have been concerns about their association with the development of progressive multifocal leukoencephalopathy, a potentially disabling and fatal complication.^{9,10} Faced with safer injection therapies or more convenient oral therapies, patients and physicians often need to identify which factors are the most important to them when initiating MS treatments.

Stated-preference methods, such as discrete-choice experiments and conjoint analysis, allow researchers to elicit and quantify patient preferences for attributes of different treatments options. Both approaches infer patient valuation of attributes that are presented in a series of hypothetical scenarios. Statistical analyses of patient selection (either as a discrete choice in discrete-choice experiments or as rating or ranking selections in conjoint analysis) across scenarios show the relative importance of individual attributes and the trade-offs between them (e.g., the reduction in treatment efficacy that patients would accept for an improvement in dosing frequency).¹¹

In past studies, stated-preference methods have been used to identify attributes that patients prefer for MS treatments.¹²⁻¹⁹ Some studies have focused on specific treatment attributes, such as efficacy compared with safety,¹² administration attributes,¹⁵ and device usability.¹⁴ Although these studies focused on specific treatment attributes, they have provided insight into the use of stated-preference methods to measure patient preference for MS therapies. More recently, other studies have investigated multiple treatment attributes and their relative preferences in patients with MS.^{13,16-18} Although these studies focused on a variety of attributes, none of them have investigated patient preference based on the cost of therapy.

Cost of therapy has been shown to be a strong factor that affects patient adherence to MS treatments and should be considered when initiating therapy. A review of administrative claims from 1996 to 2000 of MS patients on disease-modifying treatments (DMTs) showed that their mean annual copayment rate for their medications was 6.47% (+7.50%). This equates to about \$242 per year out of pocket.²⁰ Furthermore, multivariate modeling suggested that for every 1% increase in a patient's copayment share, there was a 14% decrease in the use of these expensive therapeutic agents (hazard ratio = 0.865, $P < 0.001$).²⁰ With an increasing amount of therapeutic options available for patients with MS, many patients are required to make a trade-off among efficacy, safety, administration, and costs. To help clinicians and other stakeholders identify these trade-offs, the main objective of this study was to estimate the relative patient preferences (i.e., strengths) for clinical and economical attributes of pharmacological therapies used in MS.

Methods

Study Design and Subject Selection

An online, cross-sectional conjoint analysis survey was conducted. Conjoint analysis is a stated-preference elicitation technique grounded in utility theory, which quantifies consumer preferences for a set of predetermined characteristics (named attributes) of a product or service. Conjoint analysis assesses the joint effect of a product's level of 2 or more attributes on consumer choices.²¹ In conjoint analysis, an overall evaluation of a product is decomposed into component scores ascribed to each product's attribute level or combination of levels. In this process, subjects are asked to evaluate a hypothetical product or service profile and provide an overall preference score (as a rating option). This step is repeated for multiple product profiles, which have varied levels of attributes. This approach has the advantage of reducing response burden because product profiles are presented independently. In addition, conjoint analysis also allows the researcher to measure how sensitive a respondent would be to changes in 1 level of attributes relative to another. This is a valuable tool for elucidating the thought processes that MS patients use in assessing treatment options and identifying which product attributes are the most influential in the decision-making process.^{21,22}

This study used a convenience sample of approximately 100 study participants recruited via postings on the websites of a variety of regional and national MS patient advocacy groups. In the absence of a method to determine sample size in conjoint analysis, a minimum of 100 respondents has been recommended to ensure stable estimates of regression coefficients and standard errors.^{11,22} Depending on the policies of the advocacy groups whose websites were being used, invitation to participate in the study and a link to the questionnaire were posted directly on the websites or included in e-newsletters that were sent to members of the organizations.

Of the patients who accessed the online survey, entry was provided for patients who met all of the following inclusion/exclusion criteria: (a) provided informed consent to participate in the study; (b) were 18 years or older; (c) confirmed that they were patients and not friends, family members, or other caregivers; and (d) indicated that they regularly took medications for MS. Patients responding to the survey were offered the opportunity to win 1 of 5 gift cards worth \$25.

Conjoint Analysis Design

The first step in this conjoint analysis was to develop a list of attributes and levels that defined the different therapeutic products available to MS patients. Attribute identification of the efficacy, side effects, cost, and administration route of MS disease-modifying drugs were informed by package inserts approved by the U.S. Food and Drug Administration and previously published studies in the literature.^{14,23,24} Attribute selection took into account patient perspective and the ability

FIGURE 1 Example of a Conjoint Analysis Product Profile

Product A

- About **85 out of 100 patients** taking this drug had their disease stabilized (that is, their MS did not get any worse) over a 2-year period, and 1 out of every 5 patients experienced no MS flare-ups during this period.
- However, about **14 out of 100 patients** taking this drug experienced an infection, usually in the nose, throat, or chest, but none of the patients experienced an infection so serious that they needed to stay in the hospital.
- You (or your caregiver) will have to **inject this drug 1 time each week** into a muscle (for example, when you get a vaccine shot).
- This drug will cost you **\$75** out of your own pocket each month, for a total of \$1,800 each year.

How Likely Are You to Try This Product to Treat Your MS?

MS = multiple sclerosis.

to expand a research question to include other autoimmune conditions, such as rheumatoid arthritis and lupus, for a future study. Six attributes were selected for this study's survey: (1) overall efficacy based on autoimmune disease progression stabilization; (2) acute increase in disease activity (flare-up); (3) rates of respiratory tract infections (as a common minor side effect)²⁵; (4) rate of serious respiratory tract infections (leading to hospitalization); (5) medication use; and (6) patient monthly out-of-pocket medication expenses. Attributes and their different levels were described in lay terminology to increase understanding and response rate (Appendix, available in online article).

The next step in this analysis was the construction of profiles to be presented to respondents. Given the 6 product attributes, with 2-4 levels per attribute, a full factorial design yielded 7,076 possible product attribute scenarios. Statistical precision is improved by asking a large number of difficult trade-off questions; however, measurement errors can occur if respondents use simplifying decision heuristics, become fatigued by too many tasks, become confused or overwhelmed by too many tasks, or become inattentive during the study.²² Thus, asking respondents to review 7,076 different attribute scenarios was not feasible.

In addition to optimizing response efficiency, conjoint analysis studies seek to optimize statistical efficiency, which allows for better precision around parameter estimates. Efficient conjoint analysis designs aim at being orthogonal—which indicates that each pair of levels from different attributes appears equally often across all pairs of attributes—and balanced, which means that each level of an attribute appears with equal frequency.²² To improve response efficiency and maintain statistical precision, this study used a near-balanced, near-orthogonal plan generated by the Orthogonal Design Feature (ORTHOPLAN) of SPSS version 19.0 (IBM Corp., Armonk, NY), which uses

algorithms that construct designs to optimize the D-score (a measure of conjoint analysis design efficiency) for the smallest possible design that identifies all the necessary parameters. This design identified a subset of the full factorial design (i.e., the fractional factorial) of all possible combinations of attribute level combinations placed into groups of alternatives.²² After removing implausible or illogical combinations of product attributes, the best plan for this study yielded 24 profile plans.

Reviewing 24 full product profiles does raise the question of whether 24 profiles represents a significant burden to the study subjects; however, some practitioners advocate that respondents can complete up to 32 review tasks.¹¹ In order to reduce the burden on respondents and improve survey response rates, the 24 profiles were distributed as 3 blocks of 8 profiles, where each subject reviewed 1 block of 8 product profiles only. In this way, demographic items could be added as well. This approach not only reduced the burden on respondents but also helped preserved as many attributes and levels as possible and better characterized respondents, given the exploratory nature of this study.

In conjoint analysis studies, the evaluative score, or total evaluation of a profile, can be categorical, ordinal (ranking or rating), or ordinal-scaled. In this study, response choices indicated the likelihood of trying a specific MS product profile. The dependent variable for this study was the intention of respondents to use the hypothetical product based on their reviews of the full product profiles and responses to the question "Based upon this product's attributes, how likely are you to try this product to treat your MS?" Responses were measured using a scale of 0%-100%, where 0% indicated "very unlikely"; 50% indicated "undecided"; and 100% indicated "very likely" (Figure 1). Product profiles were pretested with 2 pharmacy students and a pharmacy resident to detect ambiguities in the product profiles or choice question.

TABLE 1 Sociodemographic and Clinical Characteristics of Respondents

Characteristics (N = 129)	n (%)	
Sociodemographic		
Age, mean (SD)	45.9	(12.1)
Sex		
Male	15	(11.6)
Female	114	(88.4)
Education		
≤High school	36	(28.1)
Completed college	61	(47.7)
Completed graduate school	31	(24.2)
Race/ethnicity		
White	105	(81.4)
Hispanic or Latino	8	(6.2)
Other/declined	16	(12.4)
Employment		
Not employed	69	(53.5)
Employed part time	13	(10.1)
Employed full time	47	(36.4)
Income		
\$0-\$49,999	59	(47.2)
\$50,000-\$74,999	22	(17.6)
\$75,000 or more	44	(32.2)
Insurance		
Private insurance	80	(62.0)
Medicare	31	(24.0)
Medicaid or SCHIP	7	(5.4)
Other	11	(8.5)
Clinical		
Health literacy		
Adequate	113	(87.6)
Inadequate	16	(12.4)
MS type		
Relapsing-remitting	109	(84.5)
Secondary-progressive	6	(4.7)
Progressive-relapsing	2	(1.6)
Primary-progressive	7	(5.4)
Not sure	5	(3.9)
Number of years since diagnosis		
≤3 years	42	(32.6)
4-7 years	41	(31.8)
≥8 years	46	(35.7)
Overall health		
Excellent	10	(7.8)
Very good	32	(24.8)
Good	55	(42.6)
Fair	26	(20.2)
Poor	6	(4.7)
MS drugs ^a		
Copaxone (glatiramer)	30	(23.2)
Novantrone (mitoxantrone)	25	(19.3)
Tecfidera (dimethyl fumarate)	21	(16.3)
Gilenya (fingolimod)	16	(12.4)
Tysabri (natalizumab)	15	(11.6)
Rebif (interferon beta-1a)	12	(9.3)
Others (Aubagio, Extavia)	15	(11.6)

^aRespondents had the option to select more than 1 alternative.

SCHIP = State Children's Health Insurance Program; SD = standard deviation.

Instrument Design and Data Collection

The self-administered, anonymous online survey instrument was developed and deployed using QUALTRICS software (Qualtrics, Provo, UT). QUALTRICS randomly chose 1 of the preloaded 3 blocks of 8 disease-specific conjoint analysis profiles to present to a respondent. Thus, even though 24 profiles were reviewed, any given respondent reviewed no more than 8 product profiles. To account for the potential confounding of respondent preference variation, 23 items measured common demographic, economic, and insurance-related information and health literacy and patient autonomy levels on all subjects. Respondents were also asked to provide a global assessment of their current, overall health status. Since the level of health literacy may influence a respondent's ability to fully understand the product profiles appearing in the survey, a 1-item screening question was included that has been shown to identify those patients with inadequate health literacy.^{26,27} In addition, 5 items were included to obtain information regarding MS disease form (i.e., relapsing-remitting, secondary progressive, progressive relapsing, or primary progressive), time since diagnosis, and MS medication currently taken. Data were collected between January and December 2014. Ethics approval to conduct this study was granted by the Institutional Review Board at California Northstate University.

Data Analysis

The analytical sample was described for all patients. For all continuous variables, means and standard deviations (SDs) were reported, as were proportions for all categorical variables. The date and time of survey submission were automatically recorded by QUALTRICS. To investigate possible nonresponse bias, demographic characteristics of the first quartile of responders (i.e., early responders) were compared with those of the last quartile (i.e., late responders) using Student's t-test for continuous variables and chi-square test for independence.

By recording the dependent variable as a continuous rating variable, a linear compensatory model is assumed for the preference model. That is, it is assumed that patients will prefer higher drug efficacy to less efficacy, and fewer side effects are preferred to more side effects.²² Random effects linear regression of subject ratings on product profiles assessed the preference (preference weights) for each attribute level, while adjusting for the potential correlation between the 8 profiles nested within each respondent. Using effects coding, the regression model's beta coefficients indicated differences from the mean overall levels for each attribute. The relative importance of the overall attributes was calculated by determining the range of the beta coefficients for each attribute, dividing the range by the sum of all ranges, and multiplying by 100.²⁸ All data analyses were conducted with Stata software version 14 (StataCorp, College Station, TX).

TABLE 2 Relative Importance of Attributes Based on Regression Analysis

Attribute	Level	Beta Coefficients (Preference Weights)	95% CI	P Value ^a
Disease progression stabilization	65% ^b	-0.94	-2.70 to 0.83	0.299
	75%	2.03	0.20 to 3.87	0.029
	85%	-1.10	-3.23 to 1.04	0.314
Risk of flare-ups	20% ^b	-0.05	-1.82 to 1.71	0.953
	33%	2.36	0.46 to 4.26	0.015
	40%	-2.30	-4.44 to -0.16	0.035
Risk of respiratory tract infection	72% ^b	-2.84	-5.46 to -0.23	0.033
	30%	-1.83	-3.79 to 0.14	0.068
	14%	4.67	2.73 to 6.61	<0.001
Risk of hospitalization from infection	5% ^b	-5.02	-6.39 to -3.65	<0.001
	0%	5.02	3.65 to 6.39	<0.001
Route/frequency	1 IM×week ^b	-5.67	-8.67 to -3.56	<0.001
	SC 2×week	-2.26	-4.22 to -0.22	0.050
	Oral daily	7.93	5.95 to 10.2	<0.001
Monthly out-of-pocket medication costs	\$450 per month ^b	-11.42	-13.81 to -9.03	<0.001
	\$300 per month	-4.84	-7.22 to -2.47	<0.001
	\$150 per month	3.41	0.98 to 5.84	<0.001
	\$75 per month	12.85	10.64 to 15.06	<0.001

Note: Model log-likelihood = -4449.4, AIC = 8928.749, BIC = 9001.986, ICC = 0.42.

^aCompared against the grand mean.

^bThe coefficients for the reference level using the effects coding were calculated as the negative of the sum of the coefficients for the other levels.

AIC = Akaike information criterion; BIC = Bayesian information criterion; CI = confidence interval; ICC = intraclass correlation coefficient; IM = intramuscular; SC = subcutaneous.

Results

Clinical and Sociodemographic Characteristics

A total of 141 respondents completed the survey, but only 129 completed responses for all 8 profiles. Thus, 12 MS individuals were excluded from further analyses. The median time for completing the survey was 12 minutes. Table 1 summarizes sociodemographic characteristics for the respondents. The majority of respondents were white females, with a mean age of 45.9 years (SD = 12.7), which is consistent with MS population demographics. Most of the respondents (84%, n = 109) self-reported in a relapsing-remitting stage, and over two thirds of respondents had been diagnosed with MS for more than 4 years. Glatiramer (Copaxone) and mitoxantrone (Novatrone) were the most used therapies by participants in the sample. The analysis of early responders versus late responders found these groups to be similar in all sociodemographic characteristics except for MS duration, where a larger proportion (54%) of late responders self-reported being diagnosed with MS for more than 8 years, compared with early responders (20%; $P < 0.01$), suggesting that nonresponders were potentially MS patients diagnosed with the disease for a longer time.

Conjoint Analysis

The relative preference weights of the respondents for each of the 6 levels of attributes for the decision to try a product are presented in Table 2 as the effect-coded beta coefficients of the

fixed and random mixed-effect regression model. Using effects coding, the reference level coefficients in each attribute were calculated as the negative sum of the coefficients on the non-omitted levels of that attribute. Findings indicated that subjects preferred lower levels of monthly out-of-pocket expenses (higher preference weights) and lower levels of safety-related attributes (risk of hospitalization due to infections and respiratory tract infections). All levels for these 2 attributes were statistically significant ($P < 0.05$). In addition, respondents preferred oral daily products to twice-weekly subcutaneous and once weekly intramuscular injections for route and administration frequency ($P < 0.05$).

Figure 2 shows an unexpected rank ordering for the mean preference weights estimates in the disease progression and flare-up risk attributes. Intermediate risk levels for these 2 attributes were most preferred (higher preference weights) than lower risk levels; however, these differences were not statistically significant, since their 95% confidence intervals overlapped. The differences between adjacent preference weights within each attribute can also be observed in Figure 2. For example, respondents put a greater importance on moving from subcutaneous twice weekly administration to oral daily administration (difference in preference weight of 10.2 points) than on moving from intramuscular injection once weekly to subcutaneous administration twice weekly (3.4 preference weight points change).

FIGURE 2 Respondent Preference Weights of Different Clinical and Economic Attributes of MS Drugs

Notes: Attribute levels with higher weights are preferred over attribute levels with lower weights. Vertical lines represent the 95% CIs of the preference weight mean point estimate.

CI=confidence interval; MS=multiple sclerosis; OOP=out of pocket; PO=oral administration.

Similarly, a 50% decrease in monthly out-of-pocket costs was attached to a greater importance change in preference weights when moving from \$150 to \$75 (9.4 points) than an equivalent 50% reduction when the amounts moved from \$300 to \$150 (8.2 points). The overall relative importance of the attributes for the ranges of the levels presented in the questions is displayed in Figure 3. Out-of-pocket monthly cost was the most important (38.4%), and route and frequency of administration was next in importance (21.5%), followed by risk of hospitalization (15.9%).

A sensitivity analysis was performed to compare differences in the magnitude and significance of preferences weights in the model excluding observations of 8 individuals (6% of sample size) who completed the survey in less than 7 minutes, which corresponded to the mean time of survey completion for the fastest

quartile of respondents. Similar results were observed between the entire sample and the subgroup analyses, so the results presented corresponded to the entire sample of 129 subjects.

Discussion

This study sought to assess the preferences of MS patients for various DMT characteristics, as well as to evaluate their relative importance. Of the 6 drug attributes explored, monthly out-of-pocket costs associated with DMT treatments appeared to be the most significant factor affecting the decision making of MS patients with regard to their interest in trying an MS product. Drug administration route and frequency was found to be the second most important among all attributes, followed by drug safety outcomes, then general and specific efficacy outcomes. Hence, patients need to be aware of the increased convenience

FIGURE 3 Relative Importance of Attributes

OOP = out of pocket.

or safety of a therapy before they perceive that the additional costs are worthwhile.

Our findings regarding patients' preferred route of administration are consistent with those available in the literature. Utz et al. (2014) focused on exploring patient preference for administration mode and dosing features of MS therapies and showed that oral pills were preferred.¹⁵ This study also showed that injections were preferred when pills had more frequent mild side effects or more frequent dosing. Likewise, in Wilson et al. (2015) and Lynd et al. (2016), oral administration was preferred over yearly and monthly intravenous symptoms and over daily and thrice weekly subcutaneous injections.^{18,19} Poulos et al. (2016) focused only on injectable MS treatments and showed that a lower injection frequency and delayed disability progression were the 2 key drivers for patient preference.¹³ The results of these studies have important implications, since recent evidence has shown that medication adherence is not necessarily improved with oral MS treatments.^{29,30}

The literature also indicates that for patients currently receiving therapy, preferences shift toward preventing adverse events rather than increasing treatment efficacy, as was found in our investigation. This shift can be explained partially by having a sample of respondents not naive to treatment who might better understand the course of the disease and, thus,

focus on issues that affect quality of life. Wicks et al. (2015) focused on oral MS treatments and identified liver toxicity as the most important attribute of patient preference (25.8%, relative importance out of 100%), followed by severe side effects (15.3%), and delay to disability progression (10.7%).¹⁶ Wilson et al. investigated patient preference for injectable and oral MS treatments and showed that severe side-effect risks had the biggest effect on patient preference, with a 1% risk decreasing patient preference 5-fold compared with no risk (odds ratio = 0.22, $P < 0.001$).¹⁸ This finding can be explained by potential heterogeneity in responses from treatment-naïve and treatment-experienced patients.

One important factor associated with MS treatment non-adherence is cost of therapy. Our study included monthly out-of-pocket costs as 1 of the 6 attributes assessed. Monthly out-of-pocket costs had the highest preference weights among all attributes. Although cost of DMTs may place a high burden on patients, none of the previous studies on MS patient-stated preferences had explored monthly out-of-pocket costs. This is a significant characteristic to consider, since evidence shows that patients in high cost-sharing plans are less likely to receive DMT treatment than those in low cost-sharing plans. Similarly, patients in low cost-sharing plans are more likely to be adherent, with lower treatment abandonment rates.^{31,32} Not surprisingly, a recent study by Wang et al. (2016) found that in a sample of 6,662 patients nearly 25% reported using a type of financial assistance program.³³ Because of the rising costs of DMT treatment during the past years, DMT drug plan benefits may include different combinations of coinsurance and copayments, or step therapy therapy programs, which might be an impediment to some patients.

Limitations

Results from this study should be evaluated within the context of several limitations. First, findings are limited to the range of attribute levels included and may not perfectly capture the complete scope of influence for a particular attribute. Hence, there might be other meaningful attributes that were not included in the scope of this study. However, attributes and corresponding levels selected are consistent with those of similar studies. Second, although respondents were not able to see profiles that represented the entire possible attribute combinations (full factorial design), statistical efficiency of the fractional factorial design was assessed to minimize the risk of obtaining less reliable statistical estimates.

Third, the investigators were unable to confirm respondents' diagnoses and other self-reported demographic characteristics. Nevertheless, distribution of characteristics in this study reflects those of observational studies used as benchmarks for similar MS web-based studies.^{16,34} In addition, advertisement of the study was conducted only with specific MS patient association websites.

Fourth, this study is bounded to stated preferences by respondents that might not represent actual choices. However, to minimize this limitation, the attributes described in this study resembled real-world trade-offs.

Fifth, the sample size prohibited the exploration of the effect of subject characteristics on preference weights. The study by Lynd et al. found heterogeneity in patient groups using best-worst scaling and latent class models.¹⁹ Two general groups were identified, one with subjects most concerned about experiencing improvements in symptoms and another most concerned about preventing serious adverse drug events. The potential presence of heterogeneity highlights the need for further research that explores, for example, the effect of MS stage (e.g., relapsing-relapsing vs. secondary progressive), disease duration (from diagnosis), or sex on preference weights.

Finally, given the sampling approach used and the difference found between early responders and late responders, there is potential for nonresponse bias limiting the generalizability of the results to responders that have been recently diagnosed with MS.

Conclusions

Conjoint analysis proved to be a convenient tool to quantify respondents' relative preferences for DMT characteristics. This study provides evidence that DMT direct monthly out-of-pocket costs to patients, followed by mode and frequency of administration, have a relatively higher weight for patients than safety and efficacy. Patients need to be aware of the increased convenience or safety of a therapy before they perceive that the additional costs are worthwhile. Providers should discuss these issues with patients at the point of care. Plan benefit design managers and other stakeholders need to continue taking action to ensure that DMT treatments are affordable to guarantee adherence and therefore positive clinical outcomes.

Authors

ANA L. HINCAPIE, PhD, MS, and JONATHAN PENM, PhD, BPharm, James L. Winkle College of Pharmacy, University of Cincinnati, Cincinnati, Ohio. CRAIG F. BURNS, PhD, MS, College of Pharmacy, University of Oklahoma, Tulsa.

AUTHOR CORRESPONDENCE: Ana L. Hincapie, PhD, MS, Assistant Professor, James L. Winkle College of Pharmacy, University of Cincinnati, 3225 Eden Ave., Kowalewski Hall 369, Cincinnati, OH 45267-0004. Tel.: 513.558.7808; E-mail: Ana.Hincapie@uc.edu.

DISCLOSURES

No outside funding supported this study. The authors declare no potential conflicts of interest.

Study concept and design were contributed by Hincapie and Burns. Data were collected by Hincapie and Burns, and interpreted by all the authors. The manuscript was written by Hincapie, Penm, and Burns and revised by Penm, Hincapie, and Burns. At the time of data collection, Burns was a PhD candidate at The University of Oklahoma, College of Pharmacy.

REFERENCES

- Devonshire V, Lapierre Y, Macdonell R, et al. The Global Adherence Project (GAP): a multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis. *Eur J Neurol*. 2011;18(1):69-77.
- Tremlett HL, Oger J. Interrupted therapy: stopping and switching of the beta-interferons prescribed for MS. *Neurology*. 2003;61(4):551-54.
- Mohr D, Goodkin D, Likosk W, et al. Therapeutic expectations of patients with multiple sclerosis upon initiating interferon beta-1b: relationship to adherence to treatment. *Mult Scler*. 1996;2(5):222-26.
- Lugaresi A. Addressing the need for increased adherence to multiple sclerosis therapy: can delivery technology enhance patient motivation? *Expert Opin Drug Deliv*. 2009;6(9):995-1002.
- Patti F. Optimizing the benefit of multiple sclerosis therapy: the importance of treatment adherence. *Patient Prefer Adherence*. 2010;4:1-9.
- Menzin J, Caon C, Nichols C, White LA, Friedman M, Pill MW. Narrative review of the literature on adherence to disease-modifying therapies among patients with multiple sclerosis. *J Manag Care Pharm*. 2013;19(1 Suppl):S24-S40. Available at: <http://www.jmcp.org/doi/10.18553/jmcp.2013.19.s1.S24>.
- Higuera L, Carlin CS, Anderson S. Adherence to disease-modifying therapies for multiple sclerosis. *J Manag Care Spec Pharm*. 2016;22(12):1394-401. Available at: <http://www.jmcp.org/doi/full/10.18553/jmcp.2016.22.12.1394>.
- Olek MJ. Disease-modifying treatment of relapsing-remitting multiple sclerosis in adults. UpToDate. 2016. Available at: <https://www.uptodate.com/contents/disease-modifying-treatment-of-relapsing-remitting-multiple-sclerosis-in-adults>. Accessed June 19, 2017.
- Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2006;354(9):899-910.
- Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med*. 2006;354(9):911-23.
- Bridges JF, 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(4):403-13.
- Johnson FR, Van Houtven G, Özdemir S, et al. Multiple sclerosis patients—benefit-risk preferences: serious adverse event risks versus treatment efficacy. *J Neurol*. 2009;256(4):554-62.
- Poulos C, Kinter E, Yang J-C, et al. A discrete-choice experiment to determine patient preferences for injectable multiple sclerosis treatments in Germany. *Ther Adv Neurol Disord*. 2016;9(2):95-104.
- Shingler S, Swinburn P, Ali S, Perard R, Lloyd A. A discrete choice experiment to determine patient preferences for injection devices in multiple sclerosis. *J Med Econ*. 2013;16(8):1036-42.
- Utz KS, Hoog J, Wentrup A, et al. Patient preferences for disease-modifying drugs in multiple sclerosis therapy: a choice-based conjoint analysis. *Ther Adv Neurol Disord*. 2014;7(6):263-75.
- Wicks P, Brandes D, Park J, Liakhovitski D, Koudinova T, Sasane R. 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(1):e6.

17. Wilson L, Loucks A, Bui C, et al. Patient centered decision making: use of conjoint analysis to determine risk–benefit trade-offs for preference sensitive treatment choices. *J Neurol Sci*. 2014;344(1-2):80-87.
18. 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(2):74-82.
19. 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):287-96.
20. Ozminkowski RJ, Marder WD, Hawkins K, et al. The use of disease-modifying new drugs for multiple sclerosis treatment in private-sector health plans. *Clin Ther*. 2004;26(8):1341-54.
21. Rao VR. *Applied Conjoint Analysis*. Basel, Switzerland: Springer; 2014.
22. Johnson FR, Lancsar E, Marshall D, et al. Constructing experimental designs for discrete-choice experiments: report of the ISPOR conjoint analysis experimental design good research practices task force. *Value Health*. 2013;16(1):3-13.
23. Kunze AM, Gunderson BW, Gleason PP, Heaton AH, Johnson SV. Utilization, cost trends, and member cost-share for self-injectable multiple sclerosis drugs-pharmacy and medical benefit spending from 2004 through 2007. *J Manag Care Pharm*. 2007;13(9):799-806. Available at: <http://www.jmcp.org/doi/10.18553/jmcp.2007.13.9.799>.
24. Gleason P, Starner CI, Gunderson BW, Schafer JA, Sarraf HS. Association of prescription abandonment with cost share for high-cost specialty pharmacy medications. *J Manag Care Pharm*. 2009;15(8):648-58. Available at: <http://www.jmcp.org/doi/abs/10.18553/jmcp.2009.15.8.648>.
25. Winkelmann A, Loebermann M, Reisinger E, Zettl U. Multiple sclerosis treatment and infectious issues: update 2013. *Clin Exp Immunol*. 2014;175(3):425-38.
26. Chew LD, Griffin JM, Partin MR, et al. Validation of screening questions for limited health literacy in a large VA outpatient population. *J Gen Intern Med*. 2008;23(5):561-66.
27. Collum JL, Marcy TR, Stevens EL, Burns CF, Miller MJ. Exploring patient expectations for pharmacist-provided literacy-sensitive communication. *Res Social Adm Pharm*. 2013;9(5):626-32.
28. Ryan M, Farrar S. Using conjoint analysis to elicit preferences for health care. *BMJ*. 2000;320(7248):1530.
29. Remington G, Rodriguez Y, Logan D, Williamson C, Treadaway K. Facilitating medication adherence in patients with multiple sclerosis. *Int J MS Care*. 2013;15(1):36-45.
30. Dionne C, R G. Do oral disease modifying agents (DMTs) improve adherence to MS treatment? a comparison of oral and injectable drugs. Paper presented at: Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC) 2015; May 27-30, 2015; Indianapolis, IN. Available at: <https://cmcs.confex.com/cmcs/2015/webprogram/Paper3275.html>. Accessed June 19, 2017.
31. Romley J, Goldman D, Eber M, Dastani H, Kim E, Raparla S. Cost-sharing and initiation of disease-modifying therapy for multiple sclerosis. *Am J Manag Care*. 2012;18(8):460-64.
32. Palmer L, Abouzaid S, Shi N, et al. Impact of patient cost sharing on multiple sclerosis treatment. *Am J Pharm Benefits*. 2012;4(Special Issue):SP28-SP36.
33. Wang G, Marrie RA, Salter AR, et al. Health insurance affects the use of disease-modifying therapy in multiple sclerosis. *Neurology*. 2016;87(4):365-74.
34. Bove R, Secor E, Healy BC, et al. Evaluation of an online platform for multiple sclerosis research: patient description, validation of severity scale, and exploration of BMI effects on disease course. *PloS One*. 2013;8(3):e59707.

APPENDIX Drug Attributes and Corresponding Levels

Attribute	Description of Each Level
Overall efficacy: disease progression stabilization	85% of patients had their disease stabilized for 2 years
	75% of patient had their disease stabilized for 2 years
	65% of patients had their disease stabilized for 2 years
Specific efficacy: no acute increase in disease activity (flare-ups)	40% of patients experienced no flare-ups for 2 years
	33% of patients experienced no flare-ups for 2 years
	20% of patients experienced no flare-ups for 2 years
Safety: respiratory tract infections	14% of patients experienced a respiratory tract infection
	30% of patients experienced a respiratory tract infection
	72% of patients experienced a respiratory tract infection
Safety: infections leading to hospitalizations	No patients were hospitalized
	5% of patients had a serious infection requiring hospitalization
Medication use: route of administration and frequency	One intramuscular injection per week
	One subcutaneous injection twice weekly
	One pill each day
Patient monthly out-of-pocket medication expenses	\$75 per month
	\$150 per month
	\$300 per month
	\$450 per month