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Patients' preferences and willingness-to-pay for disease-modifying therapies

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ABSTRACT

Background: While disease-modifying therapies (DMTs) for multiple sclerosis (MS) treatments are costly, patient valuation of DMTs has not been examined. The objective of this study was to examine patients' preferences and willingness-to-pay (WTP) for DMTs.

Methods: Six attributes (i.e., number of relapses, percentage of disability progression, percentage of severe adverse events, route of administration, frequency of administration, and out-of-pocket cost) and their levels were used to develop a discrete choice experiment questionnaire. Each questionnaire comprised seven choice sets and each choice set contained two hypothetical DMTs and an opt-out alternative. A total of 1,200 U.S. patients with MS were asked to choose a DMT option or opt-out in each choice set. Multinomial logit model was used to determine relative preferences of each attribute. WTPs for all attributes and DMTs were calculated.

Results: A total of 508 patients were analyzed. Patients preferred DMTs with lower relapse rate, lower disability progression, lower severe adverse event, lower frequency of administration, and lower cost. In addition, they preferred oral DMTs. They were willing to pay $2,768, $289, $292, and $76 a month in exchange for every 1-time decrease in the number of relapses in two years, every 1% decrease in disability progression in two years, every 1% decrease in severe adverse events, and every 1-time decrease in the frequency of administration per month, respectively. The patients were willing to pay, in relation to market prices, between $7,020 and $134,934 per year for all DMTs, but interferon beta-1a SC.

Conclusions: Patients with MS considered relapse rate, disability progression, severe adverse events, route of administration, frequency of administration, and out-of-pocket cost, when they chose DMTs. Their WTPs for DMTs varied widely.

1. Introduction

Approximately 730,000 patients with multiple sclerosis (MS) resided in the U.S. (Wallin et al., 2019) MS has a considerable burden on the healthcare system in the country. (Costello et al., 2017; Campbell et al., 2014; Adelman et al., 2013; Owens et al., 2013; National Institute of Neurological Disorders and Stroke 2017; IMS Institute for Healthcare Informatics 2017) The annual cost of MS was estimated to be approximately $2.5 billion. (National Institute of Neurological Disorders and Stroke 2017) One of several drivers for the costs of MS was the cost of disease-modifying therapies (DMTs). (Ernstsson et al., 2016) The DMT costs had been high and are increasing at accelerated rates. (Hartung et al., 2015) DMT annual sales in the U.S. increased from $4 to $9 billion between 2008 and 2012. (IMS Health 2015) Although there were potential rebates and discounts, they had not risen enough to compensate for price increase (Hartung, 2017)

Even with substantial health insurance coverage and patient-assistance programs in the U.S., patient access to DMTs is still a challenge. Various studies demonstrated that the high DMT prices under the current insurance landscape have a negative impact on DMT use and health outcomes. (Romley et al., 2012; Dor et al., 2010; Ivanova et al., 2012; Oleen-Burkey et al., 2014; Steinberg et al., 2010; Reynolds et al., 2010) While patients are directly affected by DMTs, understanding the ways in which patients with MS value the DMTs has never been rigorously studied. Recently, four studies were conducted by using either conjoint analysis or discrete choice experiment (DCE) to examine

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patient preferences for DMTs in the U.S. (Poulos et al., 2016a; Wilson et al., 2015; Mansfield et al., 2017; Hincapie et al., 2017) These studies focused on only the relative importance among DMT attributes, e.g., effects of DMTs on relapse rate and disease progression, route of administration, and cost. Therefore, the objective of this study was to determine patients' preferences and their willingness-to-pay (WTP) that reflected their value of DMTs for MS.

2. Methods

2.1. Attributes and levels

This study conducted literature review and interviews with neurologists and patients to select DMT attributes, which were important to patients, and their levels for DCE. Clinical literature, economic evaluation and patient preference studies were reviewed to obtain the DMT attributes and their levels. (Costello et al., 2017; Poulos et al., 2016a,b; Tice et al., 2017; Carlin et al., 2017; Lynd et al., 2016; Garcia-Dominguez et al., 2016; Bottomley et al., 2017; Utz et al., 2014; Wicks et al., 2015) Later, five neurologists and five patients with MS were purposively selected for in-depth interviews and a nominal group process, respectively, to verify the DMT attributes that were important to them. Finally, a total of eight DMT attributes, including route of administration, frequency of administration, the effects of DMT on relapse rate, disability progression, gadolinium-enhancing (Gd+) lesion, new or enlarging T2 lesions, adverse events or side effects, and cost, were identified.

The selection of attributes was primarily based on the results of the patient and neurologist views since generally the patient and their neurologist views were important when choosing DMTs. Two study reviews reported that most DCE studies used four to seven attributes to develop their choice sets. (De Bekker-Grob et al., 2012; Marshall et al., 2010) The effect of DMTs on brain lesions, including Gd+ and new or enlarging T2 lesions, was excluded since the brain lesions and relapse rate had a strong correlation and the MRI measures of brain lesions varied across trials. (Goodin et al., 2012; Sormani et al., 2009; Sormani and Bruzzi, 2013) Severe adverse event was selected as it caused the greatest patient and neurologist concern. (Tice et al., 2017) Finally, a total of six DMT attributes, including the effect of DMT on relapse rate, the effect of DMT on disability progression, severe adverse events of DMT, route of administration, frequency of administration, and cost, were selected. Table 1 summarizes the selected attributes and their levels. Generally, literature suggested extreme ranges of the attribute levels for DCE modeling reasons. (Hartung et al., 2002; Johnson et al., 2013) This study identified the extreme ranges of the attribute levels from the literature review of all existing DMTs and their current prices. These levels were equally spaced for designing purposes. All existing routes of administration were included.

2.2. DCE questionnaire development

It was not feasible to present all possible 972 ($3 \times 3 \times 3 \times 4 \times 3 \times 3$) combinations of the selected attributes and levels to patients. An orthogonal and level balance design was used to randomly draw a subset of all combinations by using Ngene® software.

Table 1
Selected attributes and levels.

Attributes	Levels
Number of relapses in 2 years	0, 1, 2
% patients with disability progression in 2 years	0, 15, 30
% patients who have severe adverse events	5, 20, 35
Route of administration	Oral, IM, SC, IV
Frequency of administration per month	Less than 1, 30, 60
Out-of-pocket cost per month	$0, $6000, $12000

A total of 36 choice sets was generated and divided into six blocks. Each block comprised six choice sets that were used to develop a self-administered questionnaire. Therefore, this study had a total of six different questionnaire versions. Each choice set contained three unlabeled alternatives, including two hypothetical DMTs and an opt-out alternative. The opt-out alternative was used to resemble a real-world option since patients might not choose any DMT at all. Another choice set, containing a dominant alternative (lowest relapse rate, lowest disability progression, lowest adverse event, lowest frequency of administration, oral dosage form, and lowest cost), was added to every questionnaire for a validity check. In addition, questions on respondent's characteristics and experiences related to MS and DMT were included in the questionnaire. A think aloud method was conducted with five patients to examine the patient's understanding of the questionnaire. Three clinical and outcome research faculty members were asked to check the content validity of the questionnaire. No major change was made. Then, iConquerMS™, a patient community, was asked to develop a web-based survey, including the developed questionnaires. The survey was piloted with 10 MS patients. No major concern was found.

2.3. Data collection

The study protocol was approved by the Human Subjects Research Committee of South Dakota State University. This study used multiple approaches, including a good DCE research practice and a published practice guide for achieving the statistical power of 80%, to determine the sample size. (Hensher et al., 2007; De Bekker-Grob et al., 2015) Finally, a total of 1,200 patients, who were aged 18 or above, were randomly selected from the iConquerMS™ email list of 2,357 patients residing across the U.S. A pre-notification email was sent to notify all patients five days before the main survey was sent. An invitation email, including the link to the questionnaire, participation code, and the cover letter, were sent in July 2017. Patients, who completed the questionnaire, received a $5 gift card as a token of our appreciation. An email was sent to remind the patients, who did not respond to the questionnaire, two weeks after sending the invitation email. Another reminder was sent to non-responding patients a week after the first reminder.

2.4. Data analysis

Only data from patients, who correctly chose the right alternative in the validity choice set, were included in the analyses. Patients' characteristics and experiences in MS were descriptively analyzed. Based on Random Utility Theory, patients' responses for each choice set were observed and analyzed in DCE. (McFadden, 1981) The following utility, that a patient i assigns to an alternative j in a choice set s, U_{isj}, was estimated:

$$U_{isj} = \beta_0 + \beta_1 \text{Relapse}_{isj} + \beta_2 \text{Disability}_{isj} + \beta_3 \text{SAE}_{isj} + \beta_4 \text{Route1}_{isj} + \beta_5 \text{Route2}_{isj} + \beta_6 \text{Route3}_{isj} + \beta_7 \text{Frequency}_{isj} + \beta_8 \text{Cost}_{isj} + \varepsilon_{isj}$$

where β_0 is the constant reflecting respondents' preference for using DMT relative to no treatment, β_1, β_2, β_3, β_4, β_5, β_6, β_7, β_8 are the coefficients or the mean attribute weights of number of relapse in 2 years (Relapse),% patients with disability progression in 2 years (Disability),% patients who have severe adverse events (SAE), route of administration (Route, using effect code with IV DMT as a reference), frequency of administration (Frequency), and out-of-pocket cost per month (Cost), respectively, ε_{isj} is error term.

Multinomial logit model (MNL) was used to estimate the utility model by using Nlogit®. The level of statistical significance was set at 0.05. Marginal WTPs of the attributes were calculated by taking the ratio of the mean attribute coefficient to the mean coefficient of cost attribute. Krinsky and Robb method was used to estimate 95%

Table 2
Patient Characteristics and Experiences (N = 508).

Characteristics	
Gender	
Female	397(78.1%)
Age, years old	
Mean ± *S*.D. (N = 501)	52.9 ± 11.0
Race	
White	483(95.6%)
Marital status	
Married	349(68.7%)
Education	
4-year college degree or higher	372(73.2%)
Employment	
Employed at home or outside home	227(44.7%)
Health insurance[1]	
No insurance	2
Private insurance	385
Others	243
Health status	
Excellent	34(6.7%)
Very good	140(27.6%)
Good	195(38.4%)
Fair	122(24.0%)
Poor	17(3.4%)
MS Experiences	
Number of years of MS diagnosis	
Mean ± *S*.D.	13.4 ± 9.4
Type of MS	
Relapsing-remitting MS	336(66.1%)
Secondary-progressive MS	100(19.7%)
Primary-progressive MS	46(9.1%)
Progressive-relapsing MS	10(2.0%)
Do not know	16(3.1%)
Number of relapse during the last 2 years	
Mean ± *S*.D.	1.1 ± 2.4
MS symptoms by PDDS	
Normal	110(21.7%)
Mild disability	80(15.7%)
Moderate disability	51(10.0%)
Gait disability	53(10.4%)
Early cane	72(14.2%)
Late cane	39(7.7%)
Bilateral support	96(18.9%)
Bedridden	7(1.4%)
Current DMT use	
Interferon beta-1a (Avonex®)	11(2.2%)
Interferon beta-1a (Rebif®)	17(3.4%)
Interferon beta-1b (Betaseron®)	6(1.2%)
Interferon beta-1b (Extavia®)	3(0.6%)
Peginterferon beta-1a (Plegridy®)	5(1.0%)
Teriflunomide (Aubagio®)	36(7.1%)
Dimethyl fumarate (Tecfidera®)	64(12.6%)
Glatiramer acetate (Copaxone®)	81(15.9%)
Fingolimod (Gilenya®)	53(10.4%)
Glatiramer acetate (Glatopa®)	3(0.6%)
Alemtuzumab (Lemtrada®)	14(2.8%)
Rituximab (Rituxan®)	32(6.3%)
Natalizumab (Tysabri®)	52(10.2%)
Daclizumab (Zinbryta®)	2(0.4%)
Ocrelizumab (Ocrevus®)	26(5.1%)
None	103(20.3%)

[1] Each patient had multiple insurance types.

confidence intervals of WTPs of the DMT attributes. (Krinsky and Robb, 1986) Finally, WTPs for existing DMTs in the real-world market were calculated by multiplying the marginal WTP for that DMT with the difference between attribute levels, which were obtained from clinical literature.

3. Results

3.1. Patients' characteristics and MS experiences

Among 595 patients with MS, who entered the questionnaires, 556 completed them. The completion rate and the response rate were 93.4% and 46.3%, respectively. Only responses from 508 patients, who correctly responded to the validity choice set, were included in the study analyses. There was no evidence of non-response bias.

Table 2 shows the characteristics and MS experiences of the patients. The average age of the patients was approximately 53 years old. The majority of patients were female (78.1%), white (95.6%), married (68.7%), and not employed at home or outside home (55.3%). Most of them had a four-year college degree or higher (73.2%) and good health status or better (72.6%). A total of 385 patients had private health insurance. The average number of years that the patients had been diagnosed with MS was approximately 13 years. The majority of them (66.1%) had relapsing-remitting MS. The number of relapses varied largely, but on average the patients had experienced one relapse in the past two years. Based on the Patient Determined Disease Steps (PDDS), 56.8% of these patients lived with their normal life or mild disability or moderate disability or gait disability. A total of 405 patients had used a DMT during the study period. A wide variety of DMTs were used, but most frequent used DMTs were glatiramer acetate, dimethyl fumarate, fingolimod, natalizumab, and teriflunomide.

3.2. Patients' preference for DMT attributes

Table 3 shows the estimated coefficients of all study attributes with their standard errors and p-values. The estimated coefficients of all attributes had expected signs and were statistically significant. The positive constant in the MNL model indicated that the patients preferred DMT use, as compared to no treatment. The negative signs of the number of relapses in two years,% patients with disability progression in two years,% patients who have severe adverse events, frequency of administration, and out-of-pocket cost per month intuitively reflected that the patients preferred DMTs with a lower relapse rate, lower disability progression, lower severe adverse events, lower frequency, and lower out-of-pocket cost. The positive sign of the route of administration implied that the patients preferred the oral DMTs, as compared to the intravenous DMTs.

The estimated coefficient of each attribute represents how much the patient's utility changes for a one-unit or one-level change in the attribute. The study results showed that if the patients still had one relapse or 1% of the patients had disability progression in two years when they used a DMT, their utility decreased by 0.39 and 0.04 units, respectively. Any DMT causing 1% of these patients severe adverse events dropped the patient's utility by 0.04 units. Any increase in one time of administration per month also decreased the patient's utility of the DMT by 0.01 units. Finally, every $1 out-of-pocket decreased the patient's

Table 3
Multinomial logit (MNL) model.

	Coefficient	Standard error	P-value
Constant	2.4371	0.1132	< 0.0001
Relapse rate	− 0.3874	0.0413	< 0.0001
Disability	− 0.0404	0.0027	< 0.0001
Severe side effect	− 0.0408	0.0028	< 0.0001
Route of administration (Reference = IV)			
Oral	0.4534	0.0568	< 0.0001
IM	− 0.2450	0.0635	0.0001
SC	− 0.1720	0.0532	0.0012
Frequency	− 0.0106	0.0014	< 0.0001
Monthly cost	− 0.0001	0.000007	< 0.0001

[1]Log-likelihood = − 2689.65; Akaike information criterion = 1.80, Pseudo-R^2 = 0.171.

Table 4
Willingness-to-pay (WTP) for the attributes of DMTs.

	Average WTP ($) per month (95% confidence interval)
Constant	17,417.0(15,914.0–19,088.6)
Relapse rate	−2,768.1((−3,383.7)-(−2,194.1))
Disability	−289.4((−334.5)-(−246.5))
Severe side effect	−291.9((−338.4)-(−249.5))
Route of administration (Reference = IV)[1]	
Oral	3,246.3(2,439.1–4128.3)
IM	−1,752.3((−2,667.5)-(−883.1))
SC	−1,239.0((−2,020.5)-(−496.4))
Frequency	−76.0((−96.3)-(−56.7))

[1] effect code.

utility of the DMT by 0.0001 units.

3.3. Patients' WTP for DMT attributes and DMTs

Table 4 shows the patients' WTP for each individual attribute. Marginal WTP for each attribute reflected how much the patients with MS were willing to pay for a unit or a level change of each attribute. The results showed that the patients were willing to pay approximately $2,768 per month if the DMT use could reduce the number of relapses to one time in two years. They were willing to pay approximately $289 per month if only one in 100 patients, who used that DMT, had disability progression in two years. The patients were willing to pay approximately $292 per month for one person in 100 persons to avoid severe adverse events from using a DMT. Also, they were willing to pay approximately $76 per month for every one-administration time less in one month. In addition, the patients were willing to pay $3,246 per month for an oral DMT. Although they were not willing to pay for the IM, SC, and IV DMT, they were willing to pay highest in order to avoid the IM DMT, followed by SC, and IV DMTs.

Table 5 shows the patients' WTP for DMTs. The results showed the patients' WTP for DMTs varied widely. They were not willing to pay for interferon beta-1a SC, while they valued pegylated interferon beta-1a (approximately $100,199 per year), glatiramer acetate (approximately $100,034 per year), and ocrelizumab (approximately $134,934 per year) relatively high. The patients were willing to pay between $7020 to $85,741 per year for the rest of the DMTs.

4. Discussions

Generally, the characteristics of the patients in this study were similar to those of the patients in previous studies on MS patients' preference for DMTs in the U.S. (Poulos et al., 2016a; Wilson et al., 2015; Mansfield et al., 2017; Hincapie et al., 2017; Carlin et al., 2017; Wicks et al., 2015; Wilson et al., 2014; Johnson et al., 2009) Expectedly, the majority of patients had relapsing-remitting MS. The average years of MS diagnosis and the average number of relapses during the last two years reflected that the patients in this study understood MS well.

Table 5
Willingness-to-pay (WTP) for DMTs.

	Average WTP per year($)
Interferon beta-1b	12,670.0
Interferon beta-1a (Intramuscular)	14,715.6
Interferon beta-1a (Subcutaneous)	−32,588.4
Pegylated interferon beta-1a	100,199.5
Glatiramer acetate 20 mg	7,020.9
Glatiramer acetate 40 mg	100,034.4
Fingolimod	85,741.1
Teriflunomide	80,322.3
Dimethyl fumarate	59,997.3
Daclizumab	45,975.1
Alemtuzumab	27,925.3
Natalizumab	64,154.9
Ocrelizumab	134,934.3

Large positive mean estimates for the constant reflected the strong preference for having DMTs over not having DMT. This result was intuitive since the patients had experienced MS symptoms and used DMTs. They thus would recognize the benefits of DMTs. All attributes were statistically significant. It reflected that the selected attributes in this study were truly important to the patients with MS. Intuitively, the patients preferred the DMTs with the lower levels of the number of relapses in two years, the% patients with disability progression in two years, the% patients who have severe adverse events, the frequency of administration, and the out-of-pocket cost per month. The results were consistent with the results of previous studies on MS patients' preference for DMTs in the U.S. in which the patients preferred an improvement in outcomes and convenience. (Poulos et al., 2016a; Wilson et al., 2015; Mansfield et al., 2017; Hincapie et al., 2017; Carlin et al., 2017; Wicks et al., 2015; Wilson et al., 2014; Johnson et al., 2009) The results from the coefficients of the route of administration were also sensible in which the oral DMTs were preferred to other dosage forms of DMTs.

The relative sizes of the impacts of one level change of each attribute reflected the relative preference across attributes. Some changes in one of the DMT attributes could be as important to the patients as changes in other attributes. For instance, the patients could tolerate any DMT causing approximately 10% of them severe adverse events if the DMT could prevent one relapse in two years. This was the maximum acceptable severe adverse event risk for the patients if they could avoid one relapse in two years. We did not compare these coefficients and their relative importance to the results of the previous studies since those studies tended to define or operationalize the DMT attributes differently. (Poulos et al., 2016a,b; Wilson et al., 2015; Mansfield et al., 2017; Hincapie et al., 2017; Carlin et al., 2017; Wicks et al., 2015; Wilson et al., 2014; Johnson et al., 2009)

For the route of administration, intuitively, the results showed that the patients preferred oral DMTs. Their next preference was intravenous DMTs, followed by subcutaneous and intramuscular DMTs. Most of previous studies on patients' preferences of DMTs combined the route of administration and the frequency of administration. (Poulos et al., 2016a,b; Wilson et al., 2015; Mansfield et al., 2017; Hincapie et al., 2017; Carlin et al., 2017; Lynd et al., 2016; Garcia-Dominguez et al., 2016; Bottomley et al., 2017; Wicks et al., 2015; Wilson et al., 2014) Only two previous studies examined the route of administration and the frequency of administration separately and as in this study they both showed that the oral DMTs were preferred to injectable. (Utz et al., 2014; Arroyo et al., 2017) However, one of these studies also reported an opposite result to this study result in which either subcutaneous or intramuscular DMTs were preferred to intravenous DMTs. (Arroyo et al., 2017) One of the reasons could be that the study was conducted in Spain and the patients in that study might have different experience of getting intravenous DMTs in that country.

To our knowledge, this is the first study examining patients' WTPs for DMTs. The WTPs for DMTs were the "maximum" amount of money that the patients were willing to forfeit from their out-of-pocket money, based on the DMT attributes. In this study, they only reflected how patients valued DMTs in relation to their "market prices". The study result showed that the patients were not willing to pay for interferon beta-1a SC. Part of its lower value and WTP was based on the relatively high relapse rate and disability progression compared to other DMTs. Its benefits on relapse rate and disability progression might not be high enough for patients to value it over its risk of adverse events or its route and frequency of administration. Patients did not put a high value on its three times a week and SC administration.

When the patients' WTPs for DMTs were compared to wholesale acquisition cost (WAC) and the value-based prices calculated in a previous report (Tice et al., 2017), interesting results were found. The

value-based prices report indicated that the WAC prices of all DMTs, except alemtuzumab, should be discounted at the range of 37% to 91%. (Institute for Clinical and Economic Review 2018) If the pharmaceutical companies agreed with the value-based prices, the costs of DMTs would decrease dramatically. However, after we estimated the cost saving based on the patients' WTPs from the use of the 13 DMTs by a total of 372 patients in this study, the overall DMT costs would decrease by approximately $11 million or 36% of their WAC costs and by approximately $6.5 million or 25% of their discounted WACs. (Reynolds et al., 2010) Therefore, the WTP-based DMT prices may be another policy option that abates costs and still supports innovation.

There were various limitations in this study. First, the DCE in this study could capture only patients' stated preferences, not revealed preferences, of DMTs. However, this study tried to resemble real-world decision by including an opt-out alternative in each choice set. The second limitation was that the DCE in this study included only a limited number of DMT attributes in order to minimize the complexity of the choice sets. However, the study ensured that the important attributes were already included. The third limitation was the linear continuous specifications of all attributes, except the route of administration, might be inappropriate in the DCE models. We had to treat these variables as continuous variables since this study intended to determine how the patients with MS valued the existing DMTs. We tested whether a linear specification of a continuous variable was appropriate, as a prior study suggested. (Hauber et al., 2016) We found that the linear continuous specifications were acceptable. Finally, this study examined preferences among the patients from iConquerMS™ community. The results should not be directly generalized to all other patients with MS in the U.S. Especially, they seemed to have higher educational background. However, the patients' average age, gender, and race in this study were similar to those of overall patients with MS in the U.S.

5. Conclusions

This study revealed that patients with MS valued the number of relapses in two years, the% patients with disability progression in two years, the% patients who have severe adverse events, the route of administration, the frequency of administration, and the out-of-pocket cost per when they chose their preferred DMTs. The impacts of these DMT attributes were relative, meaning that the patients needed some improvements of other attributes to compensate their utility or preference weights when another attribute became inferior. In addition, they were willing to pay for every existing DMT, except interferon beta-1a SC. However, their WTPs in relation to market prices for the DMTs varied widely.

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Declarations of interest

None

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