

Gender Differences in Self-Reported Symptom Awareness and Perceived Ability to Manage Therapy with Disease-Modifying Medication Among Commercially Insured Multiple Sclerosis Patients

Anna Vlahiotis, MA; Rebecca Sedjo, PhD; Emily R. Cox, PhD; Thomas E. Burroughs, PhD; Amy Rauchway, DO; and Rebecca Lich, PharmD

ABSTRACT

BACKGROUND: Multiple sclerosis (MS) is a chronic, neurodegenerative inflammatory disease that affects approximately 400,000 Americans, the majority of whom are female. Although MS prevalence is higher among females, males are more likely to have a more progressive clinical course. For both genders, use of disease-modifying medications (DMMs) in the clinical management of MS is pivotal in altering the natural course and diminishing progressive disability over time.

OBJECTIVES: To evaluate gender differences in self-reported symptom awareness and perceived ability to manage therapy among MS patients taking a DMM.

METHODS: During February 2008, a self-administered, 42-item survey was mailed to 4,700 commercially insured patients taking a DMM to treat MS. Survey items measured self-reported clinical characteristics, symptom awareness, and perceived ability to manage therapy. Bivariate analyses assessed associations of gender with other predictor and outcome variables, including demographic characteristics, clinical disease characteristics, specific DMM used at the time of the survey, self-reported symptom awareness, and perceived ability to manage therapy. Logistic regression analyses further assessed the associations of gender with symptom awareness and perceived ability to manage MS after adjustment for relevant covariates (age at diagnosis, educational level, income, current DMM, type of pharmacy where drug was dispensed, frequency of flare-ups, and clinical course of disease).

RESULTS: The response rate was 44.1% (n=2,074). Of the 2,022 respondents with useable surveys, 80.6% were female; 82.3% had relapsing-remitting MS; and 83.1% were taking one of the most commonly used DMMs (intramuscular interferon beta-1a 33.4%, subcutaneous interferon beta-1a 15.9%, and glatiramer acetate 33.8%). Compared with female patients, males were older and a greater proportion had a more progressive clinical course of disease. In multivariate models, female patients were more likely than males to report recognition of a relapse/exacerbation (odds ratio [OR]=1.37, 95% CI=1.03-1.82) and to report knowing what to do when experiencing a relapse/exacerbation (OR=1.34, 95% CI=1.01-1.77) or if they missed a dose of medication (OR=1.78, 95% CI=1.08-2.43). Females were also more likely to report awareness of treatment options (OR=1.48, 95% CI=1.07-2.07) and to think that DMMs were helping their MS (OR=1.32, 95% CI=1.02-1.77).

CONCLUSIONS: Female MS patients report better awareness of disease symptoms and have more positive perceptions of their ability to manage therapy with DMMs than male MS patients. These findings suggest that

male MS patients may require additional education and support to manage their disease and therapy needs. Knowledge of these gender differences potentially could help managed care organizations to improve therapy adherence by guiding gender-specific patient support programs.

J Manag Care Pharm. 2010;16(3):206-16

Copyright© 2010, Academy of Managed Care Pharmacy. All rights reserved.

What is already known about this subject

- Adherence to disease-modifying medications (DMMs) for multiple sclerosis (MS) is particularly challenging because these drugs are injectable rather than oral medications. Mohr et al. (2001) showed that nonadherence to weekly intramuscular injections of interferon beta-1a was related to patients' low expectations of their ability to self-inject medication and that patients whose medication was administered by another individual, such as a spouse or a visiting nurse, had an increased risk of discontinuation. These medications also have side effects that reduce adherence to therapy.
- Female MS patients are more optimistic and confident about their ability to function with MS than are males. In a study population (n=556) of 124 males (73 with relapsing-remitting MS [RRMS] and 51 with progressive MS) and 432 females (348 with RRMS and 84 with progressive MS), Fraser and Polito (2007) found that females had significantly higher scores than males ($P=0.001$) on a 9-item function subscale of the Multiple Sclerosis Self-Efficacy Scale (MSSE), a validated and reliable tool. Although the MSSE's creators suggested its use in research investigating adherence to treatment and health, the MSSE does not capture information about DMMs or patient perception of ability to manage therapy with DMMs.
- Female MS patients are better able than males to manage the emotions related to MS disabilities. Miller and Dishon (2006) found that the negative correlation between a Health Related Quality of Life (HRQOL) Scale (MSQOL-54 with Fatigue Severity Scale) and physical sequelae of MS as measured by the Expanded Disability Status Scale was smaller for females than for males. However, this survey did not capture information about perceived ability to manage therapy with a DMM.

Gender Differences in Self-Reported Symptom Awareness and Perceived Ability to Manage Therapy with Disease-Modifying Medication Among Commercially Insured Multiple Sclerosis Patients

What this study adds

- Patient perceptions about ability to manage MS therapies and symptom awareness, which are essential for optimal long-term disease management, differ by gender. Female patients have greater self-reported symptom awareness and more positive perceptions of ability to manage therapy.
- Most respondents to a mailed survey of commercially insured MS patients (N=2,022) were female (n=1,629, 80.6%); most had relapsing-remitting MS (n=1,493 of 1,813, 82.3%); and most were using subcutaneous glatiramer acetate (n=680 of 2,011; 33.8%) or intramuscular interferon beta-1a (n=672 of 2,011; 33.4%) to treat MS.
- After controlling for relevant covariates, such as frequency of flare-ups, clinical course of disease, and type of pharmacy where medications were dispensed, female MS patients had greater odds of reporting that they know what to do when experiencing any MS symptom (odds ratio [OR]=1.42, 95% CI=1.08-1.88); that they recognize a disease relapse or exacerbation (OR=1.37, 95% CI=1.03-1.82); and that they know what to do if a relapse or exacerbation occurs (OR=1.34, 95% CI=1.01-1.77). Female patients were also more likely to perceive that the DMM they were taking was helping their MS (OR=1.32, 95% CI=1.02-1.77) and were more likely to report being aware of treatment options (OR=1.48, 95% CI=1.07-2.07).

Multiple sclerosis (MS) is a chronic, neurodegenerative inflammatory disease of the central nervous system that affects an estimated 400,000 Americans.¹ This disease is categorized into 4 forms or subtypes by clinical course: relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive-relapsing MS (PRMS). At the onset of the disease, approximately 85% of all MS patients have RRMS, of whom almost one-half will experience a gradual progression of disability within 10 years of their initial attack,² and 90% will develop worsening disease within 25 years.³ Multiple sclerosis affects females at 2 to 3 times the rate it affects males,^{4,5} but males have a later average onset of disease and a faster progression to disability than do female patients.⁵⁻⁷

Altering the natural course of MS and diminishing the risk of progressive disability over time are pivotal in the clinical management of MS. Accordingly, the Multiple Sclerosis Council for Clinical Practice Guidelines and the National Multiple Sclerosis Society recommend the early use of disease-modifying medications (DMMs) in patients who have relapsing forms of MS.^{8,9} Of the 6 immunomodulatory therapies approved for treatment in MS patients, there are 3 beta-interferons: intramuscular interferon beta-1a (Avonex, IM IFN β -1a), subcutaneous interferon beta-1a (Rebif, SC IFN β -1a), and subcutaneous interferon beta-1b (Betaseron and newly released Extavia, SC IFN β -1b); glatiramer acetate, a synthetic protein; intravenous natalizumab (Tysabri),

a monoclonal antibody; and the antineoplastic mitoxantrone for intravenous infusion (Novantrone). The interferons and glatiramer acetate are recommended for treatment in patients with RRMS.⁹ Natalizumab is recommended primarily for patients who are unable to tolerate or have not responded adequately to other DMMs.⁹ Mitoxantrone is recommended for worsening relapsing disease but is also used in patients with worsening SPMS with or without relapses.⁹ Although clinical trials of some DMMs in patients with progressive forms of MS have failed to provide conclusive evidence of disease modification, DMMs are still used in these patients.^{10,11} Despite the recommendation for the initiation of treatment after confirmed diagnosis,^{8,9} only about one-half of all MS patients currently use a DMM.¹²

Although DMM use is important for optimal health management, MS patients face many challenges in adhering to the recommendations. These include the chronicity of the disease, high cost of therapies, injection anxiety, injection site and post-injection reactions, and adverse side effects of the DMMs.^{13,14} Reports suggest that the chronic and disabling nature of the disease may lead to depression in some patients,^{15,16} which may be associated with decreased adherence to DMMs.¹⁷ In addition, the costs of DMMs present an additional burden. Unemployment rates of 41% to 60% have been reported in MS patients, which may lead to difficulty affording prescription medications.^{18,19} In a study of MS patients aged 21 to 64 years, Iezzoni et al. (2008) reported that even among patients with prescription drug coverage, 20% reported the level of difficulty in paying for medications as somewhat or very difficult.¹⁹ Furthermore, the interferons and glatiramer acetate are injectable medications, and self-injection is frightening to some patients. Mohr et al. (2001) found injection anxiety in 44% of a survey sample of 101 MS patients and suggested that negative perceptions of injection of DMMs are significantly related to discontinuation of therapy.²⁰ Injections may also lead to injection site reactions ranging from mild bruising to the development of ulcers and granulomas.²¹ The interferons used to prevent disease progression in MS are often also associated with such side effects as flu-like symptoms, muscle spasticity, and fatigue.^{22,23} Such adverse effects are often cited as reasons for discontinuation of therapy.²⁴ Other factors that decrease adherence include perceived lack of efficacy and suboptimal patient-health care provider relationship.^{20,24-26}

In addition to effective management of and adherence to DMM therapy, awareness of MS symptoms and the ability to respond to them appropriately are important factors in the successful self-management of MS.²⁷ Symptom awareness as part of self-monitoring in other chronic diseases has also been associated with fewer physician visits and hospitalizations.^{28,29} Disease self-management is in turn thought to be an important factor in the psychological adjustment or adaptation to being diagnosed and living with a chronic disease.³⁰

It has been well established that, in general, male and female patients experience health and disease differently.^{31,32} Although

Gender Differences in Self-Reported Symptom Awareness and Perceived Ability to Manage Therapy with Disease-Modifying Medication Among Commercially Insured Multiple Sclerosis Patients

some of the gender differences in MS patient health can be attributed to clinical course of disease,^{5,6} these differences may also be attributable to psychological adjustment. Studies have suggested that female MS patients are more optimistic about their ability to function with the disease.^{18,32} In a study by Fraser and Polito (2007) of 556 patients with MS, average scores on the functional subscale of the Multiple Sclerosis Self-Efficacy Scale were significantly higher for females (n=348 with RRMS and 84 with progressive MS) than for males (n=73 with RRMS and 51 with progressive MS).³³ Miller and Dishon (2006) evaluated the impact of gender and disability on quality of life in MS patients. The authors found that the relationship between physical disability and diminished quality of life was weaker among females than males, leading them to conclude that females are better able than males to manage the emotions related to MS disabilities.¹⁸

Although studies using existing survey instruments that measure disability and quality of life have reported gender differences in patient psychology, these existing survey instruments do not capture information about symptom awareness or the perceptions of various aspects of therapy with a DMM. Specifically, no study has addressed the impact of gender on self-reported symptom awareness or perceived ability to manage therapy with DMMs, factors that are essential for optimal long-term disease management. Therefore, the purpose of this study was to examine self-reported symptom awareness and perceived ability to manage therapy with DMMs, comparing females with males in a commercially insured population of MS patients who were currently taking a DMM. We hypothesized that female patients would have greater self-reported symptom awareness and a more positive perception of ability to manage therapy than male patients.

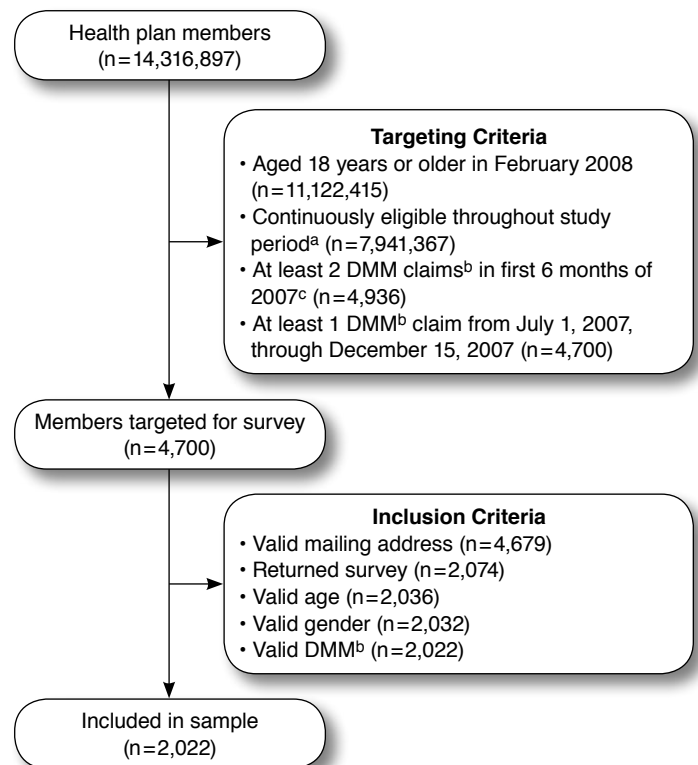
Methods

Patients receiving pharmacy benefits through a large pharmacy benefits management company (PBM) and using a DMM for MS as indicated by the PBM's administrative claims data were asked to complete a survey detailing their perceptions of their overall health, their disease, and the DMMs that they were taking. The survey was designed to identify potential gaps in care upon which managed care organizations (MCOs) could potentially intervene.

Patients

Data were extracted from a 1-year database (2007) constructed for research purposes by Express Scripts, Inc. The database was composed of administrative pharmacy claims and eligibility information (including age, gender, and mailing address) for a random sample of approximately 14 million enrollees, representing all 50 states, from the more than 55 million enrollees in 578 commercially insured (i.e., not Medicare or Medicaid) health plans using the PBM to manage their pharmacy benefits. Health plan sponsors included private and public sector employer groups, MCOs, third-party administrators, self-insured employers, and union groups. The target population consisted of all

FIGURE 1 Flow Chart of Sample Selection



^aFrom January 1, 2007, through January 31, 2008.

^bMedi-Span GPI code beginning 62-40, including intramuscular interferon β -1a, subcutaneous interferon β -1b, subcutaneous glatiramer acetate, mitoxantrone, subcutaneous interferon β -1a, and intravenous natalizumab.

^cJanuary 1, 2007, through June 30, 2007.

DMM = disease-modifying medication; GPI = generic product identifier.

patients identified as having MS as indicated by the purchase of at least 2 prescriptions for 1 of the 6 biologic agents used to treat the disease during the first 6 months of 2007, identified by generic product identifier (GPI, Medi-Span, Inc., Indianapolis, IN) code beginning with 62-40. These drugs included IM IFN β -1a, SC IFN β -1b, SC glatiramer acetate, mitoxantrone, SC IFN β -1a, and IV natalizumab.

Additional study inclusion criteria were (a) at least 1 pharmacy claim for a DMM between July 1, 2007, and December 15, 2007; (b) aged 18 years or older when the survey was mailed; and (c) continuous enrollment with the study PBM for pharmacy benefits between January 1, 2007, and January 31, 2008 (Figure 1). This study protocol was determined to be exempt by the Institutional Review Board at Saint Louis University in Saint Louis, Missouri.

Survey Development and Administration

A single, self-administered survey was mailed to each targeted

Gender Differences in Self-Reported Symptom Awareness and Perceived Ability to Manage Therapy with Disease-Modifying Medication Among Commercially Insured Multiple Sclerosis Patients

patient during the first week of February 2008. Because the survey was anonymous, it was not possible to identify initial nonrespondents. Thus, no follow-up with nonrespondents was performed. Responses were captured through April 25, 2008.

The 42-item self-report survey collected standard demographic and MS-specific clinical characteristics, such as clinical course of disease and frequency of exacerbations or relapses, in addition to information about therapy with DMMs and utilization of physician services. Although a previously validated MS-specific survey instrument has been used to measure some constructs of patient perception of disease impact and ability to function with the disease,³⁴ the instrument was not used for this study because it did not specifically capture information about DMMs. Our survey measured self-reported physical and mental health status using the Medical Outcomes Short Form 12 (SF-12), a validated health outcomes instrument that has been used in previous MS surveys.³⁵

Additional questions about utilization of physician services and reasons for lack of physician care were also asked in an attempt to capture information about potential gaps in care. These questions were not part of a previously validated instrument. The survey also captured information about symptom awareness, which DMMs were currently being used, where the medications were being obtained (through a mail order pharmacy, specialty pharmacy, or community pharmacy), and how positively or negatively the patients perceived their ability to manage therapy with those medications. The perception questions included items measuring the perceived efficacy of medications, drug administration skill and knowledge, and adherence to prescribed drug therapy. Factual and behavioral questions involving clinical disease characteristics, physician care, MS medications, and demographic characteristics were measured with multiple-choice responses tailored for each question. Knowledge and attitudinal questions (e.g., perceived self-care ability) were measured on 5-point Likert scales ranging from 1 (strongly agree) to 5 (strongly disagree) to provide a representative set of response options, maximize discrimination, and maintain a consistent number of response options with the SF-12 that served as a foundation for the current instrument.

The survey was developed through an iterative process that involved 6 experts in neurology, pharmacy, epidemiology, and survey design and validation, following the industry standard approach developed by Dillman and colleagues and recommended in survey methodology textbooks.³⁶ This multi-step process included (a) definition of the primary aims of the study; (b) identification and operational definition of the relevant constructs to be measured; (c) detailed literature search for existing validated instruments; (d) interviews with patients, family members, and clinicians caring for patients with MS to establish core survey content; (e) drafting the initial item set, including any questions from existing instruments; (f) structured review for appropriateness of response options and understandable terminology by 2

external survey methodologists who were not associated with the current study; (g) item revisions or reductions; (h) pilot testing in a convenience sample of 8 individual MS patients; (i) additional item revisions; and (j) administration of instrument to the full study sample. The revisions to the survey instrument included a reordering of the survey to include general health questions from the SF-12 as the first set of questions and moving questions about physician care to the middle of the instrument; changing the clinical terminology from “exacerbation” to “flare-up” in all questions asking about disease exacerbations; and deletion of the term “benign MS” as a clinical subtype of the disease. Questions were worded at the sixth-grade reading level, with the exception of commonly used MS clinical terminology. The questionnaire is available by request from the corresponding author.

Measurement of Outcomes

The primary outcomes for this study were self-reported symptom awareness and perceived ability to manage therapy. Questions were designed to capture information about perceptions of disease and therapy with DMM in order to identify where managed care pharmacy could intervene on behalf of the patient. Three items on the survey measured self-reported symptom awareness, that is, whether patients felt they could recognize when disease relapses or exacerbations were occurring and how to respond to these and other general disease symptoms. Additional questions measured perceived ability to manage therapy and included 2 questions about patient perception of managing dosing regimens, a single question about perception of adverse effects, 3 questions about medication adherence, and 2 questions measuring perceived efficacy of DMMs. Questions also asked about the perceived ease of self-administering, obtaining, and paying for medications, and another question measured whether or not patients were aware of the treatment options for MS.

Statistical Analysis

Post hoc reliability analyses using the Cronbach's alpha coefficient were performed to determine the internal consistency of identified constructs. The constructs tested for reliability included symptom awareness (relapse recognition, management of relapses, and management of general MS symptoms); dosing regimens; adherence; and perceived efficacy of DMMs.

The responses to all statements measuring symptom awareness and perceived ability to manage therapy were dichotomized by combining the responses “strongly agree” or “agree” into the category “agree” versus any other response (i.e., “neither agree nor disagree,” “disagree,” or “strongly disagree”) as “did not agree.” Bivariate analyses assessing the relationship between gender and a number of survey measures, including clinical course of disease, DMM, self-reported health status, self-reported symptom awareness, and perceived ability to manage therapy, were computed using the Pearson chi-square test.

Separate multivariate logistic regression models were

Gender Differences in Self-Reported Symptom Awareness and Perceived Ability to Manage Therapy with Disease-Modifying Medication Among Commercially Insured Multiple Sclerosis Patients

developed to further assess the relationship of gender with measures of symptom awareness and perceived ability to manage therapy after adjustment for other covariates. Bivariate comparisons with gender with P values less than 0.25 and variables that theoretically would be expected to affect measured outcomes were included as covariates in the multivariate models. A more liberal critical value than the traditional value of $P < 0.05$ was used as a criterion for covariate inclusion to account for complex relationships or variables that may become significant only in the presence of other variables. All models controlled for educational level (high school diploma or less as the referent category, associates' degree, bachelor's degree, post-graduate education); age at the time of the survey (less than 43 years of age as the referent category, ages 43 through 49 years, ages 50 through 55 years, age 56 years or older); annual household income (less than \$50,000 as referent category, \$50,000 to \$74,999, \$75,000 to \$99,999, \$100,000 to \$149,999, \$150,000 or more); type of pharmacy where DMM was dispensed (mail order pharmacy as the referent category, retail pharmacy, specialty pharmacy); clinical course of disease (RRMS disease type as the referent category, SPMS, PPMS, PRMS); frequency of flare-ups or exacerbations in the previous 12 months (none as the referent category, 1 to 2, 3 to 5, 6 or more); and DMM used by the patient at the time of the survey (IM IFN β -1a as the referent category, SC IFN β -1b, SC glatiramer acetate, SC IFN β -1a). Patients using natalizumab or mitoxantrone were excluded from the models because of small patient counts.

Two variables meeting the covariate inclusion criteria were excluded from the models. First, because age at the time of diagnosis and age at the time of the survey were strongly correlated (Pearson's $r = 0.60$, $P < 0.01$), only age at time of survey was included as a covariate. Second, although theoretically important, self-reported health status was strongly correlated with number of flare-ups (Spearman's $\rho = 0.78$, $P < 0.001$) and was therefore excluded from the models.

Although we computed models evaluating the relationship between gender and all of the items measuring symptom awareness and perceived ability to manage therapy, model results are reported only for outcomes in which gender was a statistically significant predictor. All analyses were conducted using a 2-sided alpha of 0.05 in SPSS 17.0 (SPSS Inc., Chicago, IL). Other data captured by the survey but not significantly related to gender and self-reported symptom awareness or perceived ability to manage therapy are available by request from the authors.

Results

Of the 4,700 patients who were mailed a survey in February 2008, 2,074 (44.1%) returned a survey by April 25, 2008 (Figure 1). Of those who returned a survey, respondents with invalid or missing values for age at the time of the study ($n = 38$), gender ($n = 4$), or type of DMM ($n = 10$) were excluded. The final analytic sample included 2,022 respondents. Respondents who were using natalizumab ($n = 37$) or mitoxantrone ($n = 2$) were included

in the analytic sample but were excluded from multivariate analysis because of small sample size.

Assessments of Questionnaire Response Rates and Reliability

Some respondents did not answer all of the questions, and rates of item nonresponse differed by question but were less than 2% of the responses for most survey items. An error in a questionnaire skip pattern, intended to direct respondents not to complete items about lack of physician care if they were currently seeing a physician for their MS, also directed respondents who were seeing a physician not to answer questions about use of physician services. However, nearly all (98.7%) respondents reported being under a physician's care in responding to the questions in that section, and only those who reported that they were not currently under a physician's care responded to questions about why they were not receiving care.

There were no significant differences in age, gender, DMM, disease type, or frequency of relapses or exacerbations between respondents included in the final analysis sample and the 52 respondents who were excluded. As survey participation was anonymous, making analysis of nonrespondents impossible, potential nonresponse bias was measured only by comparing the 4,700 targeted patients with the 2,022 respondents on key demographic and clinical characteristics. The total targeted sample and the respondents were similar with respect to distributions of gender, DMM type, DMM-related monthly out-of-pocket costs, and the average age of patients by gender (data not shown but available from authors on request).

In post hoc reliability tests, the Cronbach's alpha coefficient for measures of symptom awareness (relapse recognition, management of relapses, and management of general MS symptoms) was 0.88, indicating that the constructs consistently measured the same concept. Post hoc reliability tests suggested some internal consistency on questions related to the concept of dosing regimens ($\alpha = 0.64$), low internal consistency on questions related to adherence ($\alpha = 0.35$), and sufficient internal consistency on questions related to perceived efficacy of DMMs ($\alpha = 0.76$).

Patient Characteristics

The majority (80.6%) of respondents were female (Table 1). Compared with female respondents, male respondents were older when the survey was completed ($P = 0.009$), were diagnosed with MS at an older age ($P = 0.006$), and were more likely to have a progressive clinical course of disease ($P < 0.001$), although the majority of respondents, regardless of gender, did not have the more progressive forms of MS. In addition, a greater portion of male respondents were taking SC IFN β -1a at the time of the study (19.5% vs. 15.0% for males and females, respectively), and a smaller portion were taking IM IFN β -1a, (25.7% vs. 35.3%, $P = 0.008$). Differences in the proportions of males and females filling prescriptions for DMMs through retail pharmacies, the

Gender Differences in Self-Reported Symptom Awareness and Perceived Ability to Manage Therapy with Disease-Modifying Medication Among Commercially Insured Multiple Sclerosis Patients

TABLE 1 Characteristics of Female and Male Patients Using Disease-Modifying Medication for Multiple Sclerosis

Characteristics	Females	Males	P Value ^a
Whole sample n (percent of sample)	1,629 (80.6)	393 (19.4)	
Number of years since diagnosis mean [SD]	10.8 [9.0]	10.7 [8.8]	0.747
	n (%)^b	n (%)^b	
Age at time of diagnosis (years)			
1 to 31	419 (26.7)	71 (18.6)	0.006
32 to 38	370 (23.6)	91 (23.8)	
39 to 45	409 (26.0)	108 (28.3)	
46 or older	373 (23.7)	112 (29.3)	
Age at time of survey (years)			
18 to 42	405 (24.9)	81 (20.6)	0.009
43 to 49	401 (24.6)	78 (19.8)	
50 to 55	405 (24.9)	106 (27.0)	
56 or older	418 (25.7)	128 (32.6)	
Race			
Caucasian	1,498 (92.1)	361 (92.6)	0.927
African-American	74 (4.6)	16 (4.1)	
Other	54 (3.3)	13 (3.3)	
Educational attainment			
HS/GED or less	651 (40.5)	148 (38.2)	0.130
Associate's degree	279 (17.4)	54 (14.0)	
Bachelor's degree	376 (23.4)	96 (24.8)	
Post-graduate degree	302 (18.8)	89 (23.0)	
Annual household income			
\$49,999 or less	498 (32.8)	102 (27.5)	0.169
\$50,000 to \$74,999	395 (26.0)	102 (27.5)	
\$75,000 to \$99,999	263 (17.3)	73 (19.7)	
\$100,000 to \$149,999	243 (16.0)	55 (14.8)	
\$150,000 or more	121 (8.0)	39 (10.5)	
Clinical course of disease			
Relapsing-remitting	1,238 (84.5)	255 (73.3)	<0.001
Secondary progressive	166 (11.3)	47 (13.5)	
Primary progressive	45 (3.1)	33 (9.5)	
Progressive relapsing	16 (1.1)	13 (3.7)	
Flare-ups experienced in previous year			
None	661 (42.5)	169 (44.5)	0.225
1 to 2	636 (40.9)	140 (36.8)	
3 to 5	199 (12.8)	49 (12.9)	
6 or more	59 (3.8)	22 (5.8)	
Self-reported overall health status			
Excellent, very good, or good	1,324 (84.0)	296 (78.1)	0.008
Fair or poor	252 (16.0)	83 (21.9)	
Steroids to treat symptoms			
Not using steroids	976 (80.9)	229 (79.5)	0.726
Oral steroids (scheduled or for flare-ups)	135 (11.2)	37 (12.8)	
Intravenous steroids (scheduled or for flare-ups)	96 (8.0)	22 (7.6)	
DMM currently used by patient			
IM interferon beta-1a	572 (35.3)	100 (25.7)	0.008
SC interferon beta-1a	244 (15.0)	76 (19.5)	
IV natalizumab	28 (1.7)	9 (2.3)	
SC interferon beta-1b	233 (14.4)	67 (17.2)	
SC glatiramer acetate	543 (33.5)	137 (35.2)	
IV mitoxantrone	2 (0.1)	0 (0.0)	

Gender Differences in Self-Reported Symptom Awareness and Perceived Ability to Manage Therapy with Disease-Modifying Medication Among Commercially Insured Multiple Sclerosis Patients

TABLE 1 Characteristics of Female and Male Patients Using Disease-Modifying Medication for Multiple Sclerosis (continued)

Characteristics	Females	Males	P Value ^a
Type of pharmacy where DMM is dispensed			
Community retail	102 (6.6)	18 (4.8)	0.442
Mail order pharmacy	348 (22.5)	86 (23.1)	
Specialty	1,095 (70.9)	269 (72.1)	
Survey Items			
Self-reported symptom awareness^c			
I know when I am experiencing a relapse or exacerbation.	1,159/1,538 (75.4)	255/370 (68.9)	0.011
I know what to do when I am experiencing a relapse or exacerbation.	1,124/1,534 (73.3)	244/367 (66.5)	0.009
I know what to do when I experience any MS symptom.	1,164/1,541 (75.5)	257/371 (69.3)	0.013
Perceived ability to manage therapy^c			
I know what to do if I miss a dose.	1,462/1,583 (92.4)	338/374 (90.4)	0.204
I know what to do if there is an injection site reaction.	1,347/1,572 (85.7)	312/373 (83.6)	0.317
I take my medication as prescribed by my physician.	1,517/1,584 (95.8)	363/376 (96.5)	0.496
I forget to take my medications.	348/1,566 (22.2)	85/375 (22.7)	0.853
I take medications only when symptoms appear.	19/1,578 (1.2)	9/376 (2.4)	0.081
The benefits I receive from taking the medication are worth the costs.	1,202/1,582 (76.0)	255/372 (68.5)	0.003
I believe that the medication helps my MS.	1,250/1,580 (79.1)	270/376 (71.8)	0.002
The medication gives me unwanted side effects.	740/1,579 (46.9)	157/375 (41.9)	0.081
I have trouble administering the medication to myself.	464/1,578 (29.4)	95/376 (25.3)	0.111
I have trouble paying for my medication.	336/1,576 (21.3)	80/376 (21.3)	0.985
I have trouble getting the medications I need for my MS.	87/1,580 (5.5)	26/375 (6.9)	0.287
I am aware of my treatment options for MS.	1,327/1,562 (85.0)	303/378 (80.2)	0.022

^aFor categorical variables, P values are derived from Pearson's chi-square test. For number of years since diagnosis, P values are derived from Student's t-test. All tests compared males with females.

^bBecause of item nonresponse, the total number of respondents answering each question does not always sum to the total number of cases in the sample.

^cFor these survey items, numerators are counts of respondents who answered "strongly agree" or "agree" on a 5-point Likert-type scale, on which the remaining options were "neither agree nor disagree," "disagree," and "strongly disagree." Denominators are counts of respondents answering the question.

DMM = disease-modifying medication; HS/GED = high school/general education diploma; IM = intramuscular; IV = intravenous; MS = multiple sclerosis; SC = subcutaneous; SD = standard deviation.

PBM's mail order pharmacy, or specialty pharmacies were not significant ($P=0.442$). A significantly greater proportion of male respondents reported fair or poor overall health compared with females (21.9% vs. 16.0%, respectively, $P=0.008$).

Relationship of Gender with Measures of Symptom Awareness and Perceived Ability to Manage Therapy

Multivariate models controlling for clinical course of disease, frequency of flare-ups or exacerbations, DMM type, pharmacy where medications were dispensed, income, age, and educational attainment reflected significant differences in self-reported symptom awareness and some perceptions of ability to manage therapy between males and females (Table 2). Compared with male respondents, females had 42% greater odds of agreeing with the statement "I know what to do when I experience any MS symptom" (odds ratio [OR]=1.42, 95% confidence interval [CI]=1.08-1.88). Female respondents also had greater odds of reporting that they know when they are experiencing a disease exacerbation (OR=1.37, 95% CI=1.03-1.82) and that they know what to do when they experience a disease exacerbation (OR=1.34, 95% CI=1.01-1.77). In addition, female respondents had greater odds

of responding optimistically to several statements related to perception of ability to manage therapy. They had 78% greater odds of reporting that they know what to do if they miss a dose of medication (OR=1.78, 95% CI=1.08-2.43), 32% greater odds of believing that the medications they were taking were helping their disease (OR=1.32, 95% CI=1.02-1.77), and 38% greater odds of believing that the benefits of taking the medications were worth the costs (OR=1.38, 95% CI=1.04-1.84). Finally, female respondents also had 48% greater odds of reporting awareness of all treatment options for MS (OR=1.48, 95% CI=1.07-2.07). Measures that were not significantly associated with gender included taking prescriptions as prescribed, forgetting to take medications, taking medications only when symptoms appeared, having trouble self-administering medications, having trouble paying for medications, perceiving unwanted side effects from the medications, and having trouble obtaining the medications.

Discussion

Among commercially insured MS patients who were currently taking a DMM, the results of this survey suggest that a gender

Gender Differences in Self-Reported Symptom Awareness and Perceived Ability to Manage Therapy with Disease-Modifying Medication Among Commercially Insured Multiple Sclerosis Patients

TABLE 2 Logistic Regression Analyses: Measures of Self-Reported Symptom Awareness and Perceived Ability to Manage Therapy^a

	I know when I am experiencing a relapse or exacerbation	I know what to do when I am experiencing a relapse or exacerbation	I know what to do when I experience any MS symptom	I know what to do when I miss a dose	I believe the benefits of the medication are worth the costs	I believe the medications help my MS	I am aware of the treatment options for MS
Male	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Female	1.37 (1.03-1.82)	1.34 (1.01-1.77)	1.42 (1.08-1.88)	1.78 (1.08-2.43)	1.38 (1.04-1.84)	1.32 (1.02-1.77)	1.48 (1.07-2.07)
Clinical course of disease							
Relapsing-remitting	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Secondary progressive	0.72 (0.49-1.04)	0.77 (0.53-1.10)	1.04 (0.71-1.53)	1.61 (0.79-3.31)	0.57 (0.40-0.82)	0.54 (0.38-0.78)	1.02 (0.65-1.61)
Primary progressive	0.40 (0.23-0.70)	0.45 (0.26-0.79)	0.71 (0.39-1.27)	2.58 (0.61-10.93)	0.53 (0.29-0.94)	0.28 (0.28-0.92)	0.96 (0.47-1.99)
Progressive relapsing	0.45 (0.18-1.10)	0.57 (0.23-1.38)	0.80 (0.31-2.03)	N/A	1.97 (0.62-6.23)	1.51 (0.52-4.36)	1.15 (0.37-3.63)
Flare-ups experienced in previous year							
None	Reference	Reference	Reference	Reference	Reference	Reference	Reference
1 to 2	1.49 (1.16-1.93)	1.32 (1.03-1.69)	0.89 (0.69-1.14)	0.92 (0.61-1.39)	0.88 (0.67-1.14)	0.91 (0.69-1.19)	0.76 (0.56-2.03)
3 to 5	1.76 (1.19-2.60)	1.41 (0.98-2.04)	0.94 (0.65-1.36)	0.68 (0.39-1.19)	0.49 (0.35-0.70)	0.52 (0.36-0.74)	0.64 (0.42-0.97)
6 or more	1.91 (1.00-3.65)	1.65 (0.89-3.05)	1.01 (0.55-1.84)	1.02 (0.35-3.01)	0.31 (0.18-0.55)	0.29 (0.17-0.51)	0.67 (0.35-1.30)
Age (years)							
42 or younger	Reference	Reference	Reference	Reference	Reference	Reference	Reference
43-49	1.23 (0.87-1.74)	1.23 (0.88-1.71)	1.12 (0.81-1.56)	1.28 (0.76-2.15)	0.81 (0.58-1.14)	0.89 (0.67-1.37)	1.45 (0.98-2.15)
50-55	0.95 (0.68-1.32)	1.08 (0.73-1.39)	1.07 (0.78-1.48)	1.15 (0.69-1.91)	0.85 (0.61-1.19)	1.04 (0.72-1.46)	1.64 (1.10-2.44)
56 or older	1.01 (0.72-1.41)	0.93 (0.68-1.28)	1.06 (0.77-1.47)	1.39 (0.82-2.35)	0.91 (0.65-1.28)	0.82 (0.54-1.08)	1.13 (0.78-1.64)
Educational attainment							
High school diploma/GED or less	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Associate's degree	0.94 (0.67-1.32)	1.04 (0.75-1.45)	1.13 (0.81-1.59)	1.15 (0.65-2.03)	0.58 (0.41-0.81)	0.95 (0.66-1.36)	1.13 (0.77-1.68)
Bachelor's degree	0.90 (0.66-1.23)	1.06 (0.79-1.43)	1.00 (0.74-1.35)	1.09 (0.66-1.79)	0.47 (0.53-0.87)	0.81 (0.59-1.11)	1.25 (0.87-1.79)
Post-graduate degree	1.02 (0.73-1.44)	1.14 (0.82-1.58)	1.34 (0.87-1.70)	0.88 (0.52-1.48)	0.71 (0.50-1.00)	0.93 (0.65-1.33)	1.89 (1.22-2.93)
Annual household income							
\$49,999 or less	Reference	Reference	Reference	Reference	Reference	Reference	Reference
\$50,000 to \$74,999	1.29 (0.96-1.74)	1.23 (0.92-1.64)	1.39 (1.03-1.86)	1.17 (0.72-1.89)	0.99 (0.73-1.34)	1.29 (0.94-1.77)	1.54 (1.09-2.17)
\$75,000 to \$99,999	1.88 (1.31-2.69)	1.64 (1.16-2.32)	1.66 (1.17-2.36)	1.34 (0.76-2.35)	1.22 (0.86-1.74)	1.28 (0.88-1.85)	2.14 (1.38-3.32)
\$100,000 to \$149,999	1.97 (1.34-2.88)	1.74 (1.20-2.52)	1.34 (0.93-1.91)	1.52 (0.82-2.85)	1.56 (1.06-2.29)	1.29 (0.87-1.89)	1.72 (1.10-2.67)
\$150,000 or more	1.93 (1.19-3.13)	1.27 (0.81-1.98)	1.55 (0.97-2.48)	0.96 (0.49-1.90)	1.45 (0.90-2.35)	1.11 (0.69-1.79)	1.78 (0.99-3.22)
DMM currently used by patient^b							
IM interferon beta-1a	Reference	Reference	Reference	Reference	Reference	Reference	Reference
SC interferon beta-1a	0.93 (0.65-1.33)	0.88 (0.63-1.23)	0.89 (0.61-1.20)	2.38 (1.29-4.40)	0.62 (0.44-0.87)	0.49 (0.65-0.68)	1.04 (0.69-1.60)
SC interferon beta-1b	1.27 (0.87-1.86)	1.38 (0.96-1.99)	1.10 (0.80-1.65)	2.86 (1.43-5.72)	0.96 (0.66-1.39)	0.81 (0.58-1.20)	0.91 (0.60-1.39)
SC glatiramer acetate	0.85 (0.64-1.12)	0.89 (0.69-1.17)	0.92 (0.70-1.20)	1.55 (1.02-2.36)	0.88 (0.66-1.17)	0.76 (0.54-0.96)	0.86 (0.62-1.20)
Type of pharmacy where DMM is dispensed							
Retail	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Mail order	1.15 (0.69-2.13)	1.33 (0.81-2.18)	1.23 (0.74-2.03)	0.99 (0.43-2.27)	1.57 (0.95-2.59)	1.35 (0.58-1.20)	1.23 (0.70-2.16)
Specialty	1.34 (0.84-2.13)	1.17 (0.74-1.84)	1.17 (0.74-1.86)	0.97 (0.45-2.09)	1.36 (0.87-2.14)	1.26 (0.54-0.96)	1.49 (0.89-2.49)
Model statistics							
C-statistics	0.629	0.610	0.583	0.658	0.654	0.647	0.646
Number of cases	1,908	1,901	1,912	1,957	1,954	1,956	1,940

^aCells show odds ratios and 95% confidence intervals. Cells in bold font indicate statistically significant results.

^bPatients using natalizumab or mitoxantrone were excluded from all models because of small patient counts.

DMM = disease-modifying medication; GED = general education diploma; IM = intramuscular; MS = multiple sclerosis; SC = subcutaneous.

difference may exist in self-reported symptom awareness and perceived ability to manage DMM therapy among MS patients. The present study is the first, to our knowledge, to report that female MS patients had significantly greater self-reported symptom

awareness than males, even after controlling for clinical course of disease and frequency of flare-ups. Female survey respondents also had more optimistic perceptions of efficacy with DMMs compared with male respondents and reported greater awareness

Gender Differences in Self-Reported Symptom Awareness and Perceived Ability to Manage Therapy with Disease-Modifying Medication Among Commercially Insured Multiple Sclerosis Patients

of treatment options, both of which are important factors in the perception of ability to manage therapy. Such factors have been shown to be important for long-term adherence to drug therapy in a variety of disease states.^{25,37,38}

Our findings are consistent with those of previous research that reported gender differences in illness perception and symptom awareness among females as compared with males. Previous research suggests that female patients, because of greater selective attention to their bodies and an increased attribution of bodily sensations to physical illness, have historically perceived an excess of symptoms compared with males, even when both sexes are healthy.³⁹ Coping skills are also an important factor in patients' adaptation to and self-management of their chronic diseases, including MS. Structured interviews with male and female patients and their partners suggested that the ability to integrate various dimensions of the disease into their daily lives is associated with gender. Female patients had greater coping skills compared with male patients.⁴⁰ In similar studies of patients with heart failure, females scored higher on measures of health satisfaction and generally had more positive perceptions of the impairment, limitations, loss, and emotional burden associated with living with heart failure.⁴¹

The present study's findings may play an important role in enhancing patients' adherence to DMMs. The perception of lack of efficacy accounts for as many as one-half of treatment discontinuations,²⁶ and perceiving efficacy from DMM therapy may be associated with better adherence.^{20,42,43} Patients may also assume that their DMM is ineffective when their current MS symptoms persist or new symptoms arise.⁴⁴ Although this perceived lack of efficacy may be accurate in patients who develop neutralizing antibodies after beginning therapy or in patients with nonresponsive disease,⁴⁵ it may also be the result of unrealistic treatment expectations or lack of symptom awareness⁴⁶ and may lead to detrimental discontinuations, nonadherence, or costly medication waste.

Eliminating barriers to adherence with DMM is therefore key in the clinical management of MS patients, as is increasing awareness of relapses and disease symptoms. In MS, patients' awareness of symptoms and appropriate expectations of treatment are an important part of the patient-provider relationship.^{46,47} While the causes of patient nonadherence are still an area of study and debate, it has been suggested that health care providers play a critical role in recognizing medication nonadherence and identifying solutions that improve patient adherence.²⁶

Findings of the present study suggest that it may be necessary for health care providers and MCOs to tailor messages and programs to male and female MS patients differently in order to optimize therapy. Health care providers and MCOs should consider offering male MS patients additional education on the clinical course of their disease and the benefits of taking a DMM, in addition to steering them toward clinical support programs that teach them to identify when an exacerbation is occurring and how to

handle exacerbations and other disease symptoms. Although the MS literature contains no studies of the effectiveness of such gender-tailored psychosocial interventions, a patient education program for males that better explains the goals of treatment with DMMs, emphasizing delay or prevention of disease progression, may have potential success.

Limitations

First, the potential for reporting biases and misclassification is always present in surveys, especially when gathering self-reported medication use data from patients. In this study, responses were anonymous to minimize any social desirability response bias; however, it is possible that some patients reported better symptom awareness or perceived ability to manage DMM therapy partly because of social desirability concerns. Second, potential self-selection bias may have led to selective reporting of results; that is, more optimistic patients or patients with less disability might have been more likely to respond to the survey. Third, the *c*-statistics for the logistic regression analyses were modest, ranging from 0.58 to 0.66 on a scale of 0.5 to 1.0 where 0.5 indicates predictive ability no better than random assignment.

A fourth limitation was the absence of medical claims data to confirm a diagnosis of MS. Although the DMMs used to treat MS are not often cited as medications with common off-label uses,⁴⁸ patients could have been incorrectly identified as MS patients from inclusion criteria based solely on pharmacy claims. Fifth, an error in survey construction may have prevented the capture of important information about the use of physicians for MS care and potentially threatened the results of the survey. Specifically, a section of the survey contained questions about whether or not a patient was receiving physician care and reasons for lack of physician care, but the survey instructed patients not to answer any of the questions in the section if they were currently being seen by a physician. However, the vast majority of respondents (98.7%) positively answered the question of whether they were currently under care, suggesting that the erroneous instruction did not affect survey responses. Sixth, the sample of patients was identified from a commercially insured population of patients currently using DMMs, whose outcomes may not represent those of the general population of MS patients in the United States or of commercially insured patients not taking DMMs.

Conclusions

This survey of a commercially insured sample of MS patients using DMMs found that female respondents had greater self-reported symptom awareness and more positive perceptions of their ability to manage therapy with DMMs than did male MS patients. These data suggest that males with MS may benefit from additional education and support to manage their disease and therapy needs. Increased education about drug administration and appropriate efficacy expectations may lead to increased adherence, which can prevent disease progression.

Gender Differences in Self-Reported Symptom Awareness and Perceived Ability to Manage Therapy with Disease-Modifying Medication Among Commercially Insured Multiple Sclerosis Patients

Authors

ANNA VLAHIOTIS, MA, is Senior Manager, Research & Clinical Services; REBECCA SEDJO, PhD, is Research Contractor, Research & Clinical Services; EMILY R. COX, PhD, is Senior Director, Research & Clinical Services; and REBECCA LICH, PharmD, is Director, Specialty Product Management, Express Scripts, Inc., St. Louis, Missouri. THOMAS E. BURROUGHES, PhD, is Professor and Executive Director, Saint Louis University Center for Outcomes Research; and AMY RAUCHWAY, DO, is Assistant Professor, Neurology and Psychiatry, St. Louis University, St. Louis, Missouri.

AUTHOR CORRESPONDENCE: Anna Vlahiotis, MA, Express Scripts, Inc., 1 Express Way, St. Louis, MO 63121. Tel.: 314.684.6170; Fax: 800.839.3580; E-mail: avlahiotis@express-scripts.com.

DISCLOSURES

There was no external funding for this research. Rauchway has received compensation for previous work performed for EMD Serono, Inc./Pfizer, Inc., Teva Neuroscience, and Bayer HealthCare Pharmaceuticals.

Cox was responsible for concept and design, with the assistance of Burroughs and Rauchway. Data collection was performed by Cox and Vlahiotis, with the assistance of Burroughs and Rauchway. Cox, Lich, Sedjo, and Vlahiotis shared in the data interpretation. The manuscript was written primarily by Vlahiotis and Sedjo and revised primarily by Vlahiotis and Lich.

REFERENCES

1. National Multiple Sclerosis Society. Who gets MS? Available at: <http://www1.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/who-gets-ms/index.aspx>. Accessed February 25, 2010.
2. Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. *Brain*. 2006;129(Pt 3):606-16.
3. National Multiple Sclerosis Society. Four disease courses of MS. Available at: <http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/what-is-ms/four-disease-courses-of-MS/index.aspx>. Accessed February 25, 2010.
4. Duquette P, Pleines J, Girard M, Charest L, Senecal-Quevillon M, Masse C. The increased susceptibility of women to multiple sclerosis. *Can J Neurol Sci*. 1992;19(4):466-71.
5. Coyle PK. Gender issues. *Neurol Clin*. 2005;23(1):39-60, v-vi.
6. Voskuhl RR. Gender issues and multiple sclerosis. *Curr Neurol Neurosci Rep*. 2002;2(3):277-86.
7. Trojano M, Pellegrini F, Paolicelli D, et al. Post-marketing of disease-modifying drugs in multiple sclerosis: an exploratory analysis of gender effect in interferon beta treatment. *J Neurol Sci*. 2009;286(1-2):109-13.
8. Goodin DS, Frohman EM, Garmany GP, Jr., et al. Disease-modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology*. 2002;58(2):169-78.
9. National Clinical Advisory Board of the National Multiple Sclerosis Society. Disease management consensus statement. 2007. Available at: <http://www1.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/download.aspx?id=8>. Accessed February 25, 2010.
10. Leary SM, Thompson AJ. Primary progressive multiple sclerosis: current and future treatment options. *CNS Drugs*. 2005;19(5):369-76.
11. McCormack PL, Scott LJ. Interferon-beta-1b: a review of its use in relapsing-remitting and secondary progressive multiple sclerosis. *CNS Drugs*. 2004;18(8):521-46.
12. Minden S, Hoaglin D, Jureidini S, et al. Disease-modifying agents in the Sonya Slifka Longitudinal Multiple Sclerosis Study. *Mult Scler*. 2008;14(5):640-55.
13. Langer-Gould A, Moses HH, Murray TJ. Strategies for managing the side effects of treatments for multiple sclerosis. *Neurology*. 2004;63(11 Suppl 5):S35-41.
14. Brandes DW, Callender T, Lathi E, O'Leary S. A review of disease-modifying therapies for MS: maximizing adherence and minimizing adverse events. *Curr Med Res Opin*. 2009;25(1):77-92.
15. Whitlock FA, Siskind MM. Depression as a major symptom of multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 1980;43(10):861-65.
16. Sadovnick AD, Remick RA, Allen J, et al. Depression and multiple sclerosis. *Neurology*. 1996;46(3):628-32.
17. Mohr DC, Goodkin DE, Likosky W, Gatto N, Baumann KA, Rudick RA. Treatment of depression improves adherence to interferon beta-1b therapy for multiple sclerosis. *Arch Neurol*. 1997;54(5):531-33.
18. Miller A, Dishon S. Health-related quality of life in multiple sclerosis: the impact of disability, gender and employment status. *Qual Life Res*. 2006;15(2):259-71.
19. Iezzoni LI, Ngo LH, Kinkel RP. Working-age persons with multiple sclerosis and access to disease-modifying medications. *Mult Scler*. 2008;14(1):112-22.
20. Mohr DC, Boudewyn AC, Likosky W, Levine E, Goodkin DE. Injectable medication for the treatment of multiple sclerosis: the influence of self-efficacy expectations and injection anxiety on adherence and ability to self-inject. *Ann Behav Med*. 2001;23(2):125-32.
21. Gaines AR, Varricchio F. Interferon beta-1b injection site reactions and necroses. *Mult Scler*. 1998;4(2):70-73.
22. Hartung HP, Gonsette R, Konig N, et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multi-centre trial. *Lancet*. 2002;360(9350):2018-25.
23. Frohman E, Phillips T, Kokel K, et al. Disease-modifying therapy in multiple sclerosis: strategies for optimizing management. *Neurologist*. 2002;8(4):227-36.
24. Daugherty KK, Butler JS, Mattingly M, Ryan M. Factors leading patients to discontinue multiple sclerosis therapies. *J Am Pharm Assoc*. 2005;45(3):371-75.
25. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353(5):487-97.
26. Costello K, Kennedy P, Scanzillo J. Recognizing nonadherence in patients with multiple sclerosis and maintaining treatment adherence in the long term. *Medscape J Med*. 2008;10(9):225.
27. McLaughlin J, Zeeberg I. Self-care and multiple sclerosis: a view from two cultures. *Soc Sci Med*. 1993;37(3):315-29.
28. Gulick EE. Self-assessed health and use of health services. *West J Nurs Res*. 1991;13(2):195-211; discussion 212-199.
29. Lorig KR, Ritter P, Stewart AL, et al. Chronic disease self-management program: 2-year health status and health care utilization outcomes. *Med Care*. 2001;39(11):1217-23.
30. de Ridder D, Geenen R, Kuijper R, van Middendorp H. Psychological adjustment to chronic disease. *Lancet*. 2008;372(9634):246-55.
31. Verbrugge LM. Sex differentials in health. *Public Health Rep*. 1982;97(5):417-37.

Gender Differences in Self-Reported Symptom Awareness and Perceived Ability to Manage Therapy with Disease-Modifying Medication Among Commercially Insured Multiple Sclerosis Patients

32. Bird CE, Rieker PP. Gender matters: an integrated model for understanding men's and women's health. *Soc Sci Med*. 1999;48(6):745-55.
33. Fraser C, Polito S. A comparative study of self-efficacy in men and women with multiple sclerosis. *J Neurosci Nurs*. 2007;39(2):102-06.
34. Schwartz CE, Coulthard-Morris L, Zeng Q, Retzlaff P. Measuring self-efficacy in people with multiple sclerosis: a validation study. *Arch Phys Med Rehabil*. 1996;77(4):394-98.
35. Minden SL, Frankel D, Hadden L, Perloff J, Srinath KP, Hoaglin DC. The Sonya Slifka Longitudinal Multiple Sclerosis Study: methods and sample characteristics. *Mult Scler*. 2006;12(1):24-38.
36. de Leeuw E, Hox J, Dillman D. *International Handbook of Survey Methodology*. New York: Lawrence Erlbaum Associates; 2008.
37. Miller LG, Liu H, Hays RD, et al. Knowledge of antiretroviral regimen dosing and adherence: a longitudinal study. *Clin Infect Dis*. 2003;36(4):514-18.
38. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther*. 2001;26(5):331-42.
39. Gijsbers van Wijk CM, van Vliet KP, Kolk AM, Everaerd WT. Symptom sensitivity and sex differences in physical morbidity: a review of health surveys in the United States and The Netherlands. *Women Health*. 1991;17(1):91-124.
40. Steck B, Amsler F, Kappos L, Burgin D. Gender-specific differences coping with chronic somatic disease. *Arch Womens Ment Health*. 2000;3(1):15-21.
41. Evangelista LS, Kagawa-Singer M, Dracup K. Gender differences in health perceptions and meaning in persons living with heart failure. *Heart Lung*. 2001;30(3):167-76.
42. Fraser C, Hadjimichael O, Vollmer T. Predictors of adherence to Copaxone therapy in individuals with relapsing-remitting multiple sclerosis. *J Neurosci Nurs*. 2001;33(5):231-39.
43. Turner AP, Kivlahan DR, Sloan AP, Haselkorn JK. Predicting ongoing adherence to disease-modifying therapies in multiple sclerosis: utility of the health beliefs model. *Mult Scler*. 2007;13(9):1146-52.
44. Lublin FD, Whitaker JN, Eidelman BH, Miller AE, Arnason BG, Burks JS. Management of patients receiving interferon beta-1b for multiple sclerosis: report of a consensus conference. *Neurology*. 1996;46(1):12-18.
45. Cohen JA, Carter JL, Kinkel RP, Schwid SR. Therapy of relapsing multiple sclerosis. Treatment approaches for nonresponders. *J Neuroimmunol*. 1999;98(1):29-36.
46. Cohen BA. Identification, causation, alleviation, and prevention of complications (ICAP): an approach to symptom and disability management in multiple sclerosis. *Neurology*. 2008;71(24 Suppl 3):S14-20.
47. Elwyn G, Edwards A, Britten N. What information do patients need about medicines? "Doing prescribing": how doctors can be more effective. *BMJ*. 2003;327(7419):864-67.
48. Stern D, Reissman D. Specialty pharmacy cost management strategies of private health care payers. *J Manag Care Pharm*. 2006;12(9):736-44. Available at: <http://www.amcp.org/data/jmcp/736-744.pdf>.