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ORIGINAL COMMUNICATION

Factors that influence adherence with disease-modifying therapy in MS

Katherine Treadaway
Gary Cutter
Amber Salter
Sharon Lynch
James Simsarian
John Corboy
Douglas Jeffery
Bruce Cohen
Ken Mankowski
Joseph Guarnaccia
Lawrence Schaeffer
Roy Kanter
David Brandes
Charles Kaufman
David Duncan
Ellen Marder
Arthur Allen
John Harney
Joanna Cooper
Douglas Woo
Olaf Stüve
Michael Racke
Elliot M. Frohman

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E. M. Frohman, MD, PhD (✉) ·
K. Treadaway, LCSW · A. Salter, MPH ·
O. Stüve, MD, PhD
Dept. of Neurology
University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard
Dallas, TX 75235, USA
Tel.: 214-645-0555
Fax: 214-645-0556
E-Mail: elliot.frohman@utsouthwestern.edu

G. Cutter, PhD
University of Alabama at Birmingham
School of Public Health
Birmingham, AL

S. Lynch, MD
University of Kansas Medical Center
Kansas City, KS

J. Simsarian, MD
Neurology Associates of Fairfax
Fairfax, VA

J. Corboy, MD
University of Colorado Health Sciences Center
Denver, CO

D. Jeffery, MD, PhD
Wake Forest University Health Sciences Center
Winston-Salem, NC

B. Cohen, MD
Northwestern University
Chicago, IL

K. Mankowski, DO
Capital Neurology Services and MS Institute, Inc.
Columbus, OH

J. Guarnaccia, MD
Multiple Sclerosis Treatment Center at Griffin Hospital
Derby, CT

L. Schaeffer, MD
Neurology Consultants of Amarillo, TX

R. Kanter, MD
VIA Medical Center
Cheyenne, WA

D. Brandes, MD
Hope Neurology
Knoxville, TN

C. Kaufman, MD
Louisiana Neurologic Consultants
Baton Rouge, LA

D. Duncan, MD
MKMG Neurology MS Center
Mount Kisco, NY

E. Marder, MD
Neurology Specialists of Dallas
Dallas, TX

A. Allen, MD
Neurology Consultants
Overland Park, KS

J. Harney, MD
Dallas Neurological Associates
Richardson, TX

J. Cooper, MD
East Bay Physicians Medical Group
Berkeley, CA

D. Woo, MD
Medical College of Wisconsin
Milwaukee, WI

M. Racke, MD
Ohio State University Medical Center
Columbus, OH

Abstract *Background* The complexity and cost of injection treatment can represent a formidable challenge for patients affected by a chronic illness, particularly those whose treatment is primarily preventative and only modestly effective on the more conspicuous symptomatic aspects of the disease process. The aim of this investigation was to identify which factors most influenced nonadherent behavior with the available disease-modifying injection therapies for multiple sclerosis (MS). *Methods* A multicenter, observational (three-wave) study using surveys was developed and administered to patients with MS through the World Wide Web. Healthcare providers at 17 neurology clinics recruited patients for the study. *Results* A total of 798 patients responded to the baseline wave of the study (708 responded to all three waves). The nonadherence rates for all patients (missing one or more injections) across these waves remained relatively stable at 39 %, 37 %, and 36 %, respectively. The most common reason participants listed for missing injections was that they simply forgot to administer the medication (58 %). Other factors including injection-site reactions, quality of life, patients' perceptions on the injectable medications, hope, depression, and support were also assessed in relation to adherence. *Conclusions* This study characterizes factors that are associated with failure to fully ad-

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here with disease modifying injection therapy for MS and underscores the principles associated with optimizing adherence and its implications for effective treatment of the disease process in MS.

Key words compliance · adherence · multiple sclerosis · disease · modifying therapy · injections

Defining adherence

Maintaining adherence to DMT can be a formidable challenge to those who manage and coordinate care for the MS patient. Treatment benefits derived from these agents are not realized immediately and injectable therapy (along with their associated side effects) may be prescribed when the patient feels well, as in other chronic illness such as diabetes and hypertension [4]. Nevertheless, optimizing the benefits to be achieved from therapy is at least in part contingent upon the ability of patients to correctly and persistently use these medications.

Adherence has been defined by the World Health Organization adherence project for long-term therapy as "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a healthcare provider" [19]. While adherence rates for patients with MS treated with interferon and glatiramer acetate has been high when assessed in the context of controlled drug trials [10, 13], there has been little systematic longitudinal data to corroborate that commensurate adherence rates are achieved in the context of general clinical practice. In addition, there have been no published attempts to assess how much the long-term effectiveness of these DMTs is altered by omitted doses of medication.

Understanding why patients do not take their medications is a necessary first step to improve adherence in patients with a chronic illness. The issue of adherence in medicine was recently considered in the *New England Journal of Medicine*, in which Osterberg and Blaschke emphasized that adherence rates in chronic illness are often lower than those observed in acute illnesses [17]. Adherence has been studied across many chronic illnesses, such as HIV infection, hypertension, diabetes, epilepsy, asthma, and psychiatric illnesses. The World Health Organization indicates an average rate of only 50 % adherence among patients who have chronic diseases in developed countries [19]. With respect to MS, there has been little prospective data to characterize the factors that influence adherence to DMTs. It does appear that a higher adherence rate is observed when the patient perceives that the treating physician strongly supports the use of the prescribed medication. Other factors that appeared to be important were the patient's sense of control over the disease by using treatment, higher levels of hope, and no previous use of other DMTs [7]. Depression and anxiety have also been found to affect adherence with disease-modifying MS therapy [15, 16]. Ultimately, as underscored by former Surgeon General of the United States, C. Everett Koop, "Drugs don't work in patients who don't take them" [17].

Methods

Study design and objective

A multicenter observational study using on-line questionnaires was developed and administered to patients with MS via the World Wide Web. The primary objective was to identify specific factors that influenced adherent and nonadherent drug-taking behavior in patients with MS. Healthcare providers at 17 neurology clinics recruited patients for the study. Seven of the sites were large academic centers, specializing in the diagnosis and management of MS. Ten sites were community-based neurology clinics where the site investigator had a specific interest in MS.

The survey instruments included demographic information, the validated Multiple Sclerosis Quality of Life-54 (MSQOL-54) Questionnaire [22], the Beck Depression Inventory (BDI)-FastScreen for Medical Patients [1, 2], the Herth Hope Index (HHI) [12], and a patient self-reported adherence survey concerning injection behavior over the previous 4 weeks. The MSQOL-54 consists of 54 questions that incorporates a generic health status questionnaire (Short Form-36) and additional questions that are pertinent to people with MS. The BDI FastScreen for Medical Patients consists of seven questions extracted from the BDI-II to measure the severity of depression. The HHI is a 12-item validated measure that helps examine levels of hope.

Neurologists and medical staff personnel identified eligible patients for participation consecutively as they came in for their regularly scheduled clinic appointments. Participants were provided an information letter which directed them to the study Web site for more information on enrollment and the conduct of the study. A Web-based study was assembled to allow ascertainment of information (patients were prompted to finish each question before moving on) and to eliminate the confounding influence of a patient's interaction with the medical staff. The confidential nature of the study instruments allowed patients to confidently answer questions without any chance of being identified.

Participants completed the survey items during three consecutive assessment periods via the Internet at baseline, Month 1, and Month 2. To ensure the most complete multiwave ascertainment, patients were prompted by e-mail when it was time for them to complete the next survey. The surveys took approximately 30 to 45 minutes to complete. Participants were paid $25 for the first completed survey and $50 if the following two surveys were completed. The study was approved by the University of Texas Southwestern Medical Center's investigational review board (IRB), by each institution's IRB, and by the Western IRB for those sites without an IRB. The study Web site was maintained by an independent outside research organization, TNS Healthcare. TNS collected the study data sets and then transferred them to our biostatistician for analysis.

Patient inclusion criteria

Participants were eligible for the study if they had a relapsing form of MS; were age 18 years or older; had maintained therapy with one of the four FDA-approved injectable disease-modifying agents

(glatiramer acetate [Copaxone®, Teva Neuroscience], interferon β-1b [Betaseron®, Bayer], intramuscular [IM] interferon β-1a [Avonex®, Biogen Idec], or subcutaneous [SC] interferon β-1a [Rebif®, EMD Serono]) for at least 6 months; and had access to the Internet. Full completion of each online survey battery was ensured, given that the assessment session could not be terminated until all questions were answered.

Statistical analysis

The number of respondents necessary for inclusion (power analysis) was derived using a type 1 error of 5% for the hypothesis-testing situation. Adherence is an important factor that is measured in clinical trials. However, there are subjective cutoff levels that are used to establish adequate versus inadequate levels of adherence for any individual trial (the range of which can vary from 80% to greater than 95%) [17]. While there are no data available to determine the impact of a specific number of missed injections on disease course – especially among drugs with different injection regimens – our design was developed to understand, from the patient's perspective, why injections were omitted and whether missing doses (any dose) was a predictor of future nonadherent behavior.

Data were univariately examined with a focus on patient factors such as demographics; adherence with current DMTs; and patient experience, support, and perceptions of the treatment, including side effects, benefits and effectiveness, quality of life, depression, and hope. All analyses were conducted using two-sided tests with an α level of 0.05; no adjustment was made for multiple comparisons and are reported herein with this caveat. Dichotomous and categorical data were analyzed using a chi-square test, and continuous data were analyzed using an analysis of variance (ANOVA) controlling for treatment where appropriate.

Results

A total of 798 patients responded on the website to the baseline study, and 708 (89%) of those completed the subsequent two waves of the survey (three separate periods of ascertainment were conducted). Each DMT group had the following number of respondents in the baseline wave: IM interferon β-1a, n = 223 (28%); interferon β-1b, n = 203 (25%); glatiramer acetate, n = 223 (28%); and SC interferon β-1a, n = 149 (19%).

Patient characteristics

Table 1 outlines the patient characteristics from the baseline survey. The majority of respondents were female (77%), consistent with the known gender prevalence of MS. The average age of respondents was 43. Over half of patients were employed and 65% had some college courses or graduated from college. Most of the participants were recruited from academic sites (66%), and the remaining 34% from the community. No significant differences were seen in adherence rates between the larger and smaller sites. Over 90% of the participant population was Caucasian and over 70% married.

The age at diagnosis of MS had an impact on adherence rates, with patients who were older at disease onset having better adherence (ANOVA p value = 0.0002 between adherent and nonadherent groups). The duration of disease was significantly different between adherent and nonadherent patients. Specifically, higher adherence rates were observed for patients with MS with a disease duration of less than 3 years ($p = 0.0185$), whereas the length of time on therapy (any therapy) did not predict higher or lower adherence rates. While participants were assessed as using their current therapy for a minimum of 6 months, the majority of our respondents had been on their current treatment for over 2 years (63%). Compared to patients with MS who had previously used other injection therapy, participants administering their first treatment were more likely to be fully adherent ($p = 0.0013$).

Adherence rates and drug-specific adherence rates

During the three waves of the study, the nonadherence rates (defined as missing any injection within the last 4 weeks) for all patients on all treatments remained relatively stable at 39%, 37%, and 36%, respectively. There is no consensus for each individual medication regarding what constitutes adequate adherence. When reading this report it is important to remember that the different DMA's involve different regimens and will not carry the same implications when injections are missed. Individually, the data showed non-adherence rates (defined as missing any of the prescribed doses) for Interferon- β 1a IM to be 21%, Interferon β 1a SC to be 32%, Glatiramer acetate 51% and Interferon β1-b 51%. There were few patients, irrespective of treatment group, who missed more than four injections for any wave of ascertainment. The percent of missed injections was correlated across the three waves ($r = 0.51$ for baseline to Wave 2, $p < 0.0001$; $r = 0.46$ for Wave 2 to Wave 3, $p < 0.0001$), with 85% of those compliant (i.e., taking their medication correctly) at baseline remaining compliant at Wave 2. Of those noncompliant at baseline, 28% reported compliance at Wave 2. Similarly, of those compliant at Wave 2, 85% reported compliance in Wave 3, and of those noncompliant at Wave 2, 27% reported being compliant at Wave 3. Overall, 48% of those assessed in all three waves were compliant on all three surveys, and 22% were noncompliant on all three surveys, suggesting a consistency in responses.

Since we are primarily reporting a cross sectional baseline survey we have limited information on the differences by which patients were selected for various therapies. What we do know is whether there are significant differences in exposure to prior drugs that might impact upon adherence with the current therapy. That is, are poorer compliers selectively moving from one drug to another in a consistent pattern. Random switching of a particular behavior type would make the groups

Table 1 Clinical characteristics of participants

Variable	All patients	Adherent	Non-adherent	P value
N	798	489	309	
Age, yrs				
Mean ± SD (Range)	43.4 ± 9.65 (19–67)	44.2 ± 9.58 (21–67)	42.2 ± 9.64 (19–67)	**0.0034***
Age at diagnosis, yrs				
Mean ± SD (Range)	36.1 ± 9.05 (4–64)	37.0 ± 9.16 (4–60)	34.6 ± 8.69 (15–64)	**0.0002***
Disease duration, yrs				
Mean ± SD (Range)	7.3 ± 6.28 (0.5–36)	6.41 ± 5.0 (0.5–35)	7.6 ± 6.08 (0.5–36)	**0.4355***
Disease duration by category (%)				**0.0185****
≤ 3 yrs	34.2	38.2	27.8	
4–6 yrs	23.7	21.5	27.2	
7–10 yrs	17.9	16.6	20.1	
> 10 yrs	24.2	23.7	24.9	
Gender (%, Female)	76.7	76.3	77.3	**0.2781****
Employment status (%)				
Employed	55	56.1	53.4	**0.5101****
Not employed	25.4	23.5	28.5	
Retired/disability	17.4	17.4	15.9	
Student	2.2	2.0	2.3	
Education (%)				
< 12 yrs	13.8	14.3	12.9	**0.5976****
12 to 16 yrs	64.5	63.4	66.4	
> 16 yrs	21.7	22.2	20.7	
Site (%)				
Academic	66.3	65.4	67.6	**0.5223****
Community	33.7	34.6	32.4	
Other medical illness (%)	60.7	58.3	64.7	**0.5941****
Marital status (%)				
Married	71.9	72.8	70.6	**0.2632****
Single	14.3	13.5	15.5	
Divorced	12.9	13.3	12.3	
Widowed	0.9	0.4	1.6	
Prior disease modifying therapy use (%)	**66.2**	**70.5**	**59.4**	**0.0013****
No prior use	**33.8**	**29.5**	**40.6**	
Prior use				

* P values were calculated from ANOVA analysis; ** P values were calculated from Chi-square analysis

seem more similar. For instance, we do know that current Avonex, Betaseron, Copaxone and Rebif users responded that they had previously utilized a different disease modifying therapy in the past, at rates of 5.3 % 29.1 %, 44.4 % , 53.0 %, respectively. While the basis upon which a decision was made to start the various drugs differed significantly among groups (28.3 %, 47.3 %, 26.0 %, 32.9 %), we did learn that the choice of current therapy utilized was not significantly related to employment status, education, age at onset of disease, or marital status. However, our analysis of the data supports the contention that nonadherence to disease modifying therapy is a pretext for trying additional agents, and underscores the need to further explore factors that influence drug taking behavior in systematic longitudinal studies.

Factors influencing adherence

According to patient reporting, a variety of factors were identified as being responsible for missed injections (Fig. 1). The most common reason participants listed for missing their injection was that they simply forgot to administer the medication (58 %). Respondents also missed shots because they did not feel like taking the medication (22 %) or were tired of taking the injections (16 %). Nonadherent behavior was also linked to factors directly related to the performance of injection therapy, such as being tired of taking injections (16 %); skin reactions (5 %); pain at injection sites (7 %); not feeling like taking injections (22 %); injection-related anxiety (3 %); and the absence of someone to help administer the medication (4 %). Collectively, these factors represented 32 % of the reported reasons why injections were missed.

Reasons for nonadherence were also divided up between the drugs for comparison. Four of these reasons were significantly different among the drug groups (injection anxiety, forgot to take shot, flu-like symptoms, no one to administer shots) (Fig. 2). While flu-like side effects were a complaint in interferon-treated patients in general, none of the nonadherent participants taking glatiramer acetate listed this as a side effect of treatment. An "other" category was listed for patients to report a reason for missing injections (23 % responded in this category). These included traveling (reported most often 24 %), change in insurance, pharmacy delivery issues, other medical illness or MS exacerbation, falling asleep before administering injection, and family emergencies, among others.

When considered as a percentage of all patients surveyed, the rates of reasons were still highest for 'forgot to administer' at 22 %, which remained statistically significant across the drug groups (41 %, 54 %, 66 % and 60 % for Avonex, Betaseron, Copaxone and Rebif, respectively).

Three groups were defined for adherence to adjust for differences in dosing schedule: patients who took less than or equal to 75 % of their prescribed doses; those who took more than 75 % but less than 100 %; and those reporting 100 % compliance. The groups showed similar trends, with a few notable differences. In the group taking less than or equal to 75 % of their doses (what we may call truly noncompliant patients), only 43 % reported forgetting as the reason for noncompliance, compared with 11 % reporting injection anxiety and 29 % reporting that they did not feel like taking the injection.

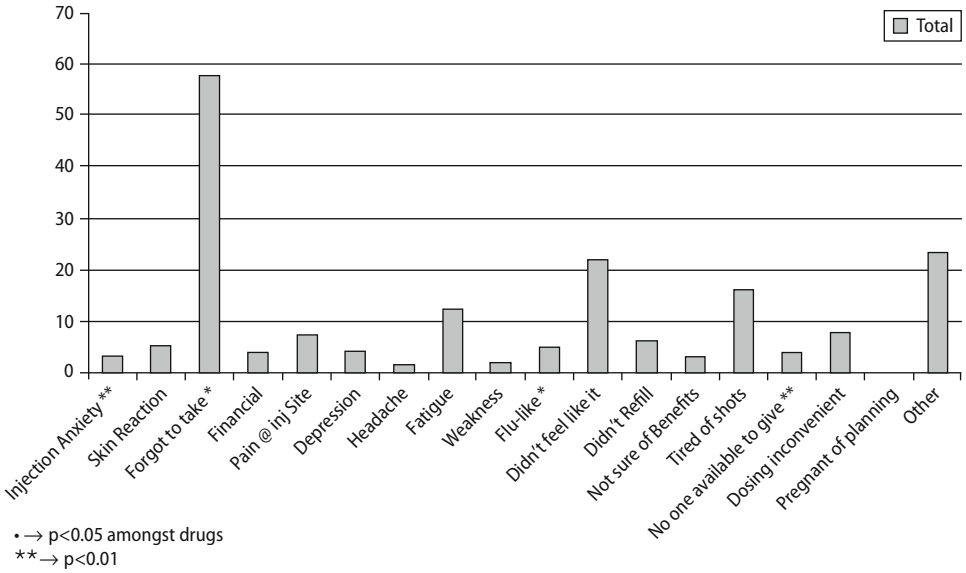

Fig. 1 The distribution (by percent) of the reasons described for missing injections by those patients who were non-adherent are presented. Forgetting to take injections represented the most common explanation for missing any doses of the medication, irrespective of which disease modifying therapy was being utilized. By percentages, about one-third of the reasons offered for missing shots was in some way related to injection therapy itself (i. e., pain, side effects)

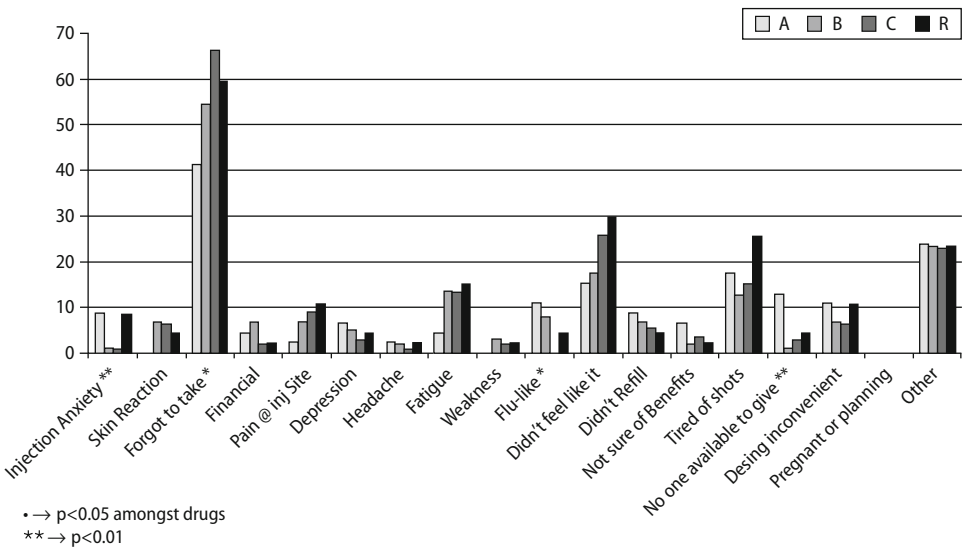

Fig. 2 Data concerning the reasons for non-adherence, in those patients missing injections, and stratified by the use of individual disease modifying agents are presented. Four of these reasons were significantly different among the drug groups (injection anxiety, forgot to take shot, flu-like symptoms, no one to administer shots)

In the group taking more than 75 % but less than 100 % of their doses, 63 % reported forgetting, compared with less than 1 % reporting injection anxiety and 20 % reporting that they did not feel like taking the injection.

While the four considered dosing regimens are so different making direct comparisons highly problematic, we did attempt to evaluate the impact of missing injections across these treatment groups. Of course, we cannot make any comment about how missing a particular injection (or series of them for that matter) impacts upon treatment efficacy and the MS disease course, we did make the observation that missing injections in one wave of study ascertainment was a predictor for missing future injections. Over time, a pattern of nonadherent drug taking behavior would likely negatively impact upon effectiveness of MS disease modifying therapy. Despite these limitations, we did consider the different regimens according to injection frequency in an attempt to understand the potential impact of missing individual injections as a normalization scheme of each individual regimen.

If one assumes a missed injection is counted as per the equivalent number of days per week as a daily injection (i.e., one missed Avonex injection counts for 7 days), the following average number of days per month were found: Avonex mean = 1.8 days per month (SD = 3.9); Betaseron = 3.6 (SD = 6.1); Copaxone = 1.5 (SD = 2.6) and Rebif = 1.5 (SD = 2.9). Only Betaseron was significantly different ($p < 0.001$) from the others using Duncan's multiple range test, which is unadjusted for multiple comparisons.

Perceived effectiveness and benefits with therapy

While most respondents described having a favorable opinion of their DMT, there was a relationship between level of adherence and perception of benefit. In the group taking less than or equal to 75 % of their doses, 6.6 % felt they were not sure about the benefits of their DMT, compared with only 2.2 % in the group taking more than 75 % but less than 100 % of their doses. Interestingly, participants who were more adherent with therapy were more likely than less adherent patients to perceive that their treatment exerted benefits on cognitive problems. The two most important benefits derived from taking the medication as identified by patients was slowing the progression of MS-related disability (83 %) and reducing neurologic attacks (73 %). Patients also indicated that tolerability of the treatment and minimal side effects were important features to be associated with the high fidelity use of injectable DMTs.

Quality of life, depression, hope and satisfaction

Table 2 outlines results for questions measuring quality of life, depression, hope and satisfaction. Adherent patients had higher scores on the majority of the physical and emotional well-being sections of the MSQOL-54 compared with those who reported nonadherent behavior. Those sections on the MSQOL-54 that statistically differentiated between adherent and nonadherent patients included role limitations–physical ($p = 0.0079$), emotional problems ($p < 0.0001$), pain ($p = 0.0095$), emotional well-being ($p = 0.0012$), energy ($p = 0.0042$), health perceptions ($p = 0.0016$), social function ($p = 0.0227$), cognitive function ($p = 0.0005$), change in health ($p = 0.0027$), overall quality of life perception ($p = 0.0001$), and both the physical ($p = 0.0020$) and mental ($p < 0.0001$) health composite scores.

Analysis of depression across all patient groups revealed low scores (less depression) as measured by the BDI FastScreen for Medical Patients for adherent patients, a 7-item instrument used in medical settings. The average score for adherent patients was 2.7, and for nonadherent patients was 3.5 (a score of 0–3 indicates minimal depression; a score of 4–8 indicates mild depression). Depression is a common accompaniment of MS and represents an important comorbidity that can be effectively treated [14, 20, 25]. Observation of low depression scores in the participants may signal some confounders. In particular, patients who are willing to participate in research studies may be less likely to be afflicted by depression and its cardinal features (e.g., poor initiative). Significantly depressed patients may have been underrepresented in this study, and adher-

Table 2 Participant responses for outcome measures for groups

Measure	Adherent	Non-adherent	P-value**
N	489	309	
MSQOL-54*			
Mean ± SD			
Physical	59.7 ± 20.7	55.2 ± 19.7	0.0020
Mental	69.5 ± 20.5	63.1 ± 21.6	< 0.0001
Beck's Depression Index			
Mean ± SD	2.7 ± 3.1	3.5 ± 3.3	0.0009
Hope Herth Index			
Mean ± SD	39.5 ± 5.7	38.2 ± 5.9	0.0024
Perceived satisfaction (%)			< 0.0001
Very satisfied	52.8	38.8	
Somewhat satisfied	35.2	36.6	
Neither satisfied or dissatisfied	10.0	18.4	
Somewhat dissatisfied	1.8	5.5	
Very dissatisfied	0.2	0.6	

* MS Quality of Life – 54: Comprised of two composite scores, Physical and Mental Health, with 100 being the highest possible score; ** ANOVA analysis was used to determine P-values for MSQOL-54, Beck's Depression Index, and Hope Herth Index. Chi-square analysis was used for Perceived Satisfaction

ence rates may be even lower in this population than reported here. Notwithstanding this potential ascertainment bias, a significant relationship between high depression scores and lower reported adherence rates was observed ($p = 0.0009$).

The Herth Hope Index (HHI) was used to determine whether hope influenced injection-taking behavior. The HHI is a 12-item adapted version of the Herth Hope Scale to assess hope in clinical settings. Irrespective of the specific treatment, we detected high levels of hope across all patient groups. As with the case of low depression scores, the study is likely confounded by a respondent bias with respect to the domain of hope. Patients with substantially less hope, and potentially less confidence in the value of therapy and its impact on their future, may have been less likely to enter our study. Nevertheless, a discrimination between adherent and nonadherent patient groups was observed, based on the level of hope reported with this measure ($p = 0.0024$).

Nonadherent patients reported less satisfaction with their treatment compared with those who were adherent ($p < 0.0001$) (Table 2).

Psychosocial support and the 'administrator' of injection therapy

The study queried patients about the various sources and level of support available to them for dealing with MS. Patients (adherent and nonadherent) listed their strongest source of support as being derived from their treating physician. In contrast to nonadherent patients, those who were highly adherent perceived greater support from their spouse ($p < 0.0001$). It should be noted that people who perceive greater support may have a more positive outlook on life, and not necessarily have greater support.

Discussion

Effective treatment for any condition is contingent upon the ability of patients to take their medication correctly (compliance) over time (persistence). Together these two features of injection-taking behavior represent adherence. The objective of this study was to characterize those factors that are associated with adherent versus less adherent drug-taking behavioral patterns. The identification of such factors provides us with opportunities to anticipate difficulties that patients may have with specific therapeutic regimens and for disease-modifying injection therapies in general. Providers who are equipped with such knowledge can better identify patients at higher risk for nonadherent drug-taking behavior and thereby preemptively develop strategies to optimize the benefits of treatment.

The four injectable treatments and their routes of administration produce different challenges with respect to patient tolerance. At any given time, a number of patients across all treatment groups were missing injections. The application of a three-wave ascertainment protocol was adopted in order to determine whether missed injections during the first cross-sectional assessment was a predictor for future nonadherent behavior. Patients initially nonadherent were more likely to remain nonadherent and those adherent tended to maintain their injection behavior, possibly suggesting either consistency over time in reporting and/or behavior and reliability of a snapshot it time.

We examined several rules: adherence as prescribed implying all doses must be taken as well as more than 75 %, so that missing one of four injections is equivalent to missing seven of 28 for daily injections, and found similar patterns. However, there are no data to help us understand the impact of missing one or more injections on the efficacy of DMTs. If missing a prescribed dose of medication is a predictor of future nonadherent behavior, then we should at least attempt to emphasize the importance of complete (or nearly so) adherence to treatment regimens. Since treatment does favorably affect the course of disease in MS and adherence rates have been very high in the context of clinical trials, emphasizing drug adherence would seem important in clinical practice.

The most common explanation for missed injections was that patients simply forgot to take the dose (58 %), but this is a lesser explanation among the least adherent patients. Forgetting to take medications has also typically been reported by patients with other illness such as depression, diabetes, HIV, transplant recipients, inflammatory bowel disease, hypertension, lupus and rheumatoid arthritis [3, 4, 9, 11, 18, 23, 24, 26]. This observation raises more questions than it answers. Why in fact did patients forget to take the medication? Was it related to simple forgetfulness, or cognitive dysfunction? Perhaps procrastination with taking the dose was subsequently followed by forgetfulness. Forgetting to take a medication should be carefully explored to develop strategies that can effectively prompt patients (and perhaps family members) to develop routines that prevent this occurrence. Findings similar to ours were observed by the Global Adherence Project (GAP) [6], where more than 2500 patients with MS have been recruited from 26 countries. In this worldwide study, the most common reason reported for missing an injection was also forgetting, cited by half of patient respondents. The National MS Society recently published a new expert opinion paper on the assessment and management of cognitive impairment in MS. Given that cognitive abnormalities may affect drug-taking behavior and adherence, periodic screenings and interventions may prove helpful in ensuring full adherence to medications [21].

An important finding in our study was that factors related to the injection procedure itself influenced the predilection of missed injections (about one-third of the reported reasons). Anticipation anxiety, pain, site reactions, and difficulty with the route of administration were reported as germane to missing injections. Patient perceptions about how injections affected their personal appearance (particularly with subcutaneous routes of administration) also figured prominently in whether adherence was compromised. Close attention to discussing these issues with patients at the time of clinic visits provides the opportunity for the patient to reveal such problems and to begin the process of further education and intervention to improve compliance, especially with partially effective therapies [8].

Patient expectations concerning treatment and its influence on their disease course was a predictor for drug-taking behavior. Specifically, those who reported a more favorable and optimistic outlook on the impact of MS treatment on their disease process were more likely to report higher rates of adherence. It is extremely important for healthcare providers to recognize the pivotal role they play in influencing adherence through education and advocacy. Patients with higher levels of depression and less hope were more likely to report nonadherent behavior, suggesting that physicians must be vigilant in the early recognition of mood disorders. Whether this is a consequence or predictor of compliance is unknown, but it is an indicator.

Therapy expectations clearly have an impact on the psychology of having a chronic disease. Education on disease course, treatment rationale, realistic treatment expectations, adverse effects to be expected, treating depression, providing cues for prompting drug administration, and enlisting the support of family members or significant others represent some of the most important strategies for optimizing adherence and thereby treatment efficacy and quality of life [5].

There are a number of limitations of our study. One limitation of the study is that we do not know how many patients were approached in the clinics for the study. Clearly we have analyzed factors influencing self-reported adherence and not observed drug-taking behavior. Nevertheless, the structure of our questionnaire was to focus on many aspects of therapy as experienced by the patient over a defined time period of recollection (1 and 4 weeks). Second, this is not a randomized trial and thus, we may have recruited patients more likely to be comfortable reporting on drug-taking behavior, which may tend to overstate the overall adherence estimates we have reported herein. The stability of the rates from wave to wave, and the consistency reported by the patients across waves, suggests that some level of comfort with the treatments has settled in. Conversely, this is possibly a better representation of the cross-section seen in clinical practice.

As the number and complexity of treatments expand for chronic illnesses, members of the care team will be faced with the formidable challenge of providing more time and resources focused on education and the identification of factors that have impaired adherence in their individual patients. Nevertheless, the substantial progress being achieved in our capability to modify chronic illness can only benefit patients if they receive sufficient education and ongoing support both before and after the initiation of treatment. The responsibility for adherently taking prescribed medication ultimately rests with our patients. The healthcare team, however, is responsible for ensuring that patients can understand what treatment entails, how to correctly take medication, establishing reasonable expectations with respect to the benefits to be derived from therapy, and outlining plans for recognizing and modifying factors that affect adherence.

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References

1. Beck A, Steer R, Ball R, Ciervo C, Kabat M (1997b) Use of the Beck Anxiety and Depression Inventories for Primary Care with medical outpatients. Assessments 4:211–219
2. Benedict RHB, Fishman I, McClellan MM, Bakshi R, Weinstock-Guttman B (2003) Validity of the Beck Depression Inventory-Fast Screen in multiple sclerosis. Mult Scler 9:393–396
3. Bernal I, Domenech E, Garcia-Planella E, Marin L, Manosa M, Navarro M, Cabre E, Gassull MA (2006) Medication-taking behavior in a cohort of patients with inflammatory bowel disease. Dig Dis Sci 51:2165–2169
4. Bulloch AG, Adair CE, Patten SB (2006) Forgetfulness: a role in noncompliance with antidepressant treatment. Can J Psychiatry – Revue Canadienne de Psychiatrie 51:719–722
5. Cohen B (2006) Adherence to disease-modifying therapy for multiple sclerosis. Int J MS Care 8:32–37
6. Devonshire V, Lapierre Y, MacDonell R, Ramo Tello C, Patti F, Fontoura P, Suchet L, Hyde R, Balla I, Kieseier B, Frohman E, Group obotGS (2006) The Global Adherence Project – A multicentre observational study on adherence to disease-modifying therapies in patients suffering from relapsing-remitting multiple sclerosis. In: European Committee for Treatment and Research in Multiple Sclerosis. Madrid, Spain
7. Fraser C, Hadjimichael O, Vollmer T (2003) Predictors of adherence to glatiramer acetate therapy in individuals with self-reported progressive forms of multiple sclerosis. J Neurosci Nursing 35:163–170
8. Frohman EMDP, Phillips TMDP, Kokel KPAC, Van Pelt JPA, O'Leary SRN, Gross SMSW, Hawker KMD, Racke MMD (2002) Disease-Modifying Therapy in Multiple Sclerosis: Strategies For Optimizing Management (Article). Neurologist 8(4):227–236
9. Garcia-Gonzalez A, Richardson M, Popa-Lisseanu MG, Cox V, Kallen MA, Janssen N, Ng B, Marcus DM, Reveille JD, Suarez-Almazor M (2008) Treatment adherence in patients with rheumatoid arthritis and systemic lupus erythematosus. Clin Rheumatol 27(7):883–889 (Epub 2008 Jan 8)
10. Group TIMSS (1993) Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 43:655–661
11. Harzke AJ, Williams ML, Nilsson-Schonnesson L, Ross MW, Timpson S, Keel KB (2004) Psychosocial factors associated with adherence to antiretroviral medications in a sample of HIV-positive African American drug users. AIDS Care 16:458–470
12. Herth K (1992) Abbreviated instrument to measure hope: development and psychometric evaluation. J Adv Nursing 17:1251–1259
13. Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, Myers LW, Panitch HS, Rose JW, Schiffer RB, Vollmer T, Weiner LP, Wolinsky JS, Copolymer 1 Multiple Sclerosis Study G (2001) Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial. 1995. Neurology 57:S16–S24
14. Krupp LB, Rizvi SA (2002) Symptomatic therapy for underrecognized manifestations of multiple sclerosis. Neurology 58:S32–S39
15. Mohr DC, Boudewyn AC, Likosky W, Levine E, Goodkin DE (2001) 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 23:125–132
16. Mohr DC, Goodkin DE, Likosky W, Gatto N, Baumann KA, Rudick RA (1997) Treatment of depression improves adherence to interferon beta-1b therapy for multiple sclerosis. Arch Neurol 54:531–533
17. Osterberg L, Blaschke T (2005) Adherence to medication (see comment). N Engl J Med 353:487–497
18. Russell CL, Kilburn E, Conn VS, Libbus MK, Ashbaugh C (2003) Medication-taking beliefs of adult renal transplant recipients. Clinical Nurse Specialist 17:200–208; quiz 209–230
19. Sabate E (2003) Adherence to Long-Term therapies – Evidence for Action. World Health Organization, Geneva Switzerland
20. Sadovnick AD, Remick RA, Allen J, Swartz E, Yee IM, Eisen K, Farquhar R, Hashimoto SA, Hooge J, Kastrukoff LF, Morrison W, Nelson J, Oger J, Paty DW (1996) Depression and multiple sclerosis. Neurology 46:628–632
21. The National Clinical Advisory Board of the National Multiple Sclerosis Society (2008) Assessment Management of Cognitive Impairment in MS. www.nationalmssociety.org. Exput Opinion Papus
22. Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW (1995) A health-related quality of life measure for multiple sclerosis. Qual Life Res 4: 187–206
23. Viswanathan H, Lambert BL (2005) An inquiry into medication meanings, illness, medication use, and the transformative potential of chronic illness among African Americans with hypertension. Research in Social & Administrative Pharmacy: RSAP 1:21–39
24. Walker EA, Molitch M, Kramer MK, Kahn S, Ma Y, Edelstein S, Smith K, Johnson MK, Kitabchi A, Crandall J (2006) Adherence to preventive medications: predictors and outcomes in the Diabetes Prevention Program. Diabetes Care 29:1997–2002
25. Wallin MT, Wilken JA, Turner AP, Williams RM, Kane R (2006) Depression and multiple sclerosis: Review of a lethal combination. J Rehabil Res Dev 43:45–62
26. Wray J, Waters S, Radley-Smith R, Sensky T (2006) Adherence in adolescents and young adults following heart or heart-lung transplantation. Pediatr Transplant 10:694–700