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Examining the Influence of Behavioral Factors on Compliance and Persistence with Glatiramer Acetate Injection for Relapsing-Remitting Multiple Sclerosis

MerriKay Oleen-Burkey[1,2*], Gabriel Pardo[3], Howard Zwibel[4], Douglas Denney[5]

[1]Health Outcomes Research Consulting and Writing, Outcomes Scribe, LLC, Kalamazoo, MI, USA

[2]Formerly, Health Economics and Outcomes Research, Teva Neuroscience, Inc., Kansas City, MO, USA

[3]MS Center of Excellence, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA

[4]Neuroscience Consultants, Comprehensive Multiple Sclerosis Center, Coral Gables, FL, USA

[5]Department of Psychology, University of Kansas, Lawrence, KS, USA

*__Corresponding author:__ MerriKay Oleen-Burkey, PhD, Outcomes Scribe, LLC, 664 Wynding Oaks, Kalamazoo, MI 49006, Tel: 913-302-1211; E-mail: OutcomesScribe@gmail.com

Abstract

Objective: To evaluate the relationship between compliance and persistence with glatiramer acetate (GA) and the behavioral variables in the transtheoretical model of change.

Methods: Patients diagnosed with relapsing-remitting multiple sclerosis and being treated with GA for the first time, whether treatment-naïve (TN) or treatment-experienced (TE), were eligible for this prospective, observational, 12-week study. Institutional Review Board approval was obtained for each of 32 US study sites, and written informed consent was obtained for all patients prior to study procedures. Four office visits were required. Study procedures included baseline self-injection training and patient-reported behavioral variable surveys. Injection competence and medication compliance and persistence were assessed at weeks 4 and 12.

Results: A total of 257 patients were enrolled; 80.9% were female, 81.6% white, and 60.0% TN. The evaluable population included 146 TN patients and 88 TE patients having discontinued beta-interferons. TE patients were at a significantly higher readiness stage, were less concerned about the negative aspects of self-injection, but had lower levels of MS self-efficacy than TN patients. While compliance and persistence rates did not differ between TN and TE groups, there were differences in outcome predictors. For the TN patients both higher self-injection competence at baseline and improvement in self-injection competence over the first month of therapy were predictive of better compliance and persistence with GA. Separate from injection competence, higher levels of functional self-efficacy were directly associated with better persistence in TN patients. None of the behavioral variables appeared to predict compliance or persistence for the TE patients.

Conclusion: Among the TN, injection competency at baseline and improvement over the first month of use were significant predictors of compliance and persistence to GA at 12 weeks. Improving self-injection competence should be a priority when planning interventions for TN patients. Behavioral factors predicting compliance and persistence among TE patients require further study. ClinicalTrials.gov (number NCT00238654)

Keywords: Compliance; Persistence; Injection readiness; Self-injection; Self-efficacy; Injection competence; Transtheoretical model; Multiple sclerosis; Glatiramer acetate; Beta-interferon

Introduction

Compliance and persistence with continuous, life-long therapy for a chronic condition can be difficult for patients, regardless of the specific therapy employed or condition under treatment. Compliance with medication refers to the extent that a patient adheres to the timing, dosage and frequency prescribed by the physician, while persistence is the "act of continuing the treatment for the prescribed duration [1]." The problem of enlisting continued patient cooperation with prescribed therapies requiring self-administration is the most significant threat to the effectiveness of these therapies. When medications must be injected, as is the case with many of the disease-modifying therapies for multiple sclerosis (MS) adherence and compliance may be a barrier to use.

The most common type of multiple sclerosis (MS) is relapsing-remitting; in which patients have episodes of worsening neurologic function, followed by full or partial recovery [2]. Treatment with disease-modifying therapies decreases frequency and severity of relapses and reduces brain lesion development, which in turn may slow disease progression. The Medical Advisory Board of the National Multiple Sclerosis Society recommends that treatment with one of these agents should begin immediately after a definitive diagnosis of relapsing-remitting MS (RRMS) and may also be considered for selected patients with a first attack who are at high risk of MS. Treatment should be continued indefinitely unless there is poor effectiveness or tolerability [3].

The requirement that a disease-modifying MS therapy be self-injected is not the only barrier to treatment compliance and persistence, but may be one of the most daunting for many patients. The injections may be perceived as painful or difficult to perform and patients may experience injection anxiety [4]. Physical impairments associated with MS such as poor hand-eye coordination, tremor, and fatigue may in fact increase the difficulty of performing self-injection, and cognitive deficits may impair the patient's ability to learn the best injection technique [5]. These factors and others may influence patients to decide that they are unwilling or unable to self-inject.

Despite patients' reservations about self-injecting treatment, research has demonstrated that persistence is improved when patients self-inject as opposed to receiving treatment from another individual, whether at home or in the clinic [4]. Thus patients should be encouraged to learn self-injection techniques, as long as they are physically able to perform them, in order to increase the probability of long-term compliance and persistence.

Because of the importance of regular, continuous treatment for MS and the potential barriers to treatment with a subcutaneous injectable like glatiramer acetate (GA, Copaxone®, Teva Pharmaceutical Industries), we developed a study model to conceptualize and predict behavioral factors that would influence patients' adoption of, and compliance and persistence with self-injected GA for RRMS. This paper will describe the assessment of the model variables in predicting compliance and persistence with GA.

The Study Model

The Transtheoretical Model of Readiness to Change

The study model was predicated on the transtheoretical model (TTM) developed by Prochaska and DiClemente, which conceptualizes intentional behavioral change as a process involving movement through a series of 5 discrete stages that define the "readiness" to adopt a new behavior: i.e., precontemplation, contemplation, preparation, action, and maintenance [6-8]. In this model, processes of change are the covert and overt activities that people use to progress through the stages [9]. Knowledge of the individual's current stage has critical implications for successful intervention because stagespecific interventions accelerate a patient's movement through earlier stages towards action and maintenance of a desired behavior. The TTM has been the basis for developing various instruments that measure stages of change for different health behaviors and effective interventions to promote health behavior change. The strongest empirical database for the model exists for the topic of smoking cessation; however, other areas, such as engaging in an exercise program, weight control, reducing high-fat diets, and medical compliance have also been investigated using this model [7,8]. Specific to MS, Holland et al. proposed that the TTM of behavioral change could be useful in achieving treatment goals [10].

Because our intent was to focus specifically on the adoption of self-injection of GA, we adapted Prochaska's TTM of intentional change for self-injection. Table 1 identifies, in behavioral terms, the person's current stage of change with respect to selfinjection, the processes of change, and interventions to facilitate change. While we believed that readiness to selfinject would have an impact on compliance and persistence with therapy, we also hypothesized that intervening variables might be more directly associated with compliance and persistence to therapy. Borrowing from other elements of the TTM, 3 potential intervening behavioral variables were identified for this study: (1) selfreported decisional balance (pros and cons of self-injection); (2) selfreported self-efficacy; and (3) selfinjection competence as evaluated by the nurse. Figure 1 depicts the proposed relationship among the behavioral variables and adherence in our study model.
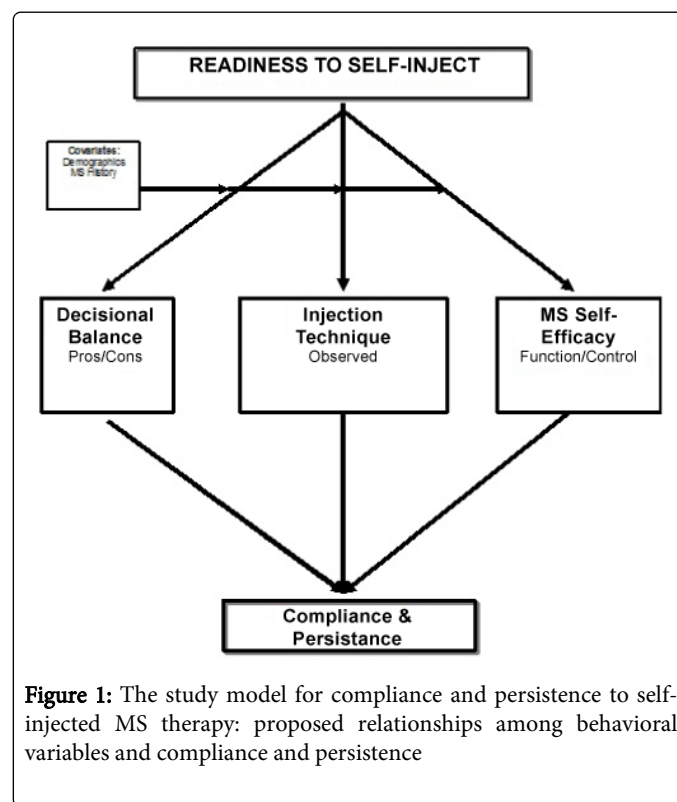

Figure 1: The study model for compliance and persistence to self-injected MS therapy: proposed relationships among behavioral variables and compliance and persistence

Stage of Change	Description	
	Processes of Change	**Interventions**
Precontemplation (Stage 1)	No intention of learning to selfinject in the foreseeable future (i.e., the next 6 months). Patients may be in this stage because they are uninformed or underinformed about the consequences of selfinjecting or they may have tried to start selfinjecting a number of times and become demoralized about their ability to do so. Patients in this stage are often characterized as resistant or unmotivated or as not ready to become selfinjectors.	
	Consciousness Raising	Discussion about RRMS: how it affects the body and the case for treatment. Discussion about the pros (not cons) of selfinjection.

		Written information about MS and its treatment.
	Dramatic Relief	Recommend Shared Perspectives□a
Contemplation (Stage 2)		Patients are developing awareness of the need for selfinjection and are seriously considering selfinjecting in the next 6 months.
		Patients in this stage are more aware of the pros of selfinjecting but are also acutely aware of the cons. This balance between the costs and benefits of changing can produce profound ambivalence that can keep patients stuck in this stage for long periods of time (i.e., chronic contemplation or behavioral procrastination).
		These patients are not yet ready to become selfinjectors.
	Self-Reevaluation	Discussion about what is required to selfinject.
		Demonstration of selfinjection.
		Hands-on practice with selfinjection, encouragement, coaching.
		Written educational information.
Preparation (Stage 3)		Patients are intending to begin selfinjecting in the immediate future (i.e., the next 4 weeks).
		Patients in this stage have typically taken some significant action towards selfinjecting in the past year and they have a plan of action, such as talking to their physician or nurse.
		These are the people that should be recruited to become selfinjectors.
	Self-Liberation	Setting an appointment to initiate selfinjection.
		Viewing the glatiramer acetate therapy information video.
		Reading the written information in the glatiramer acetate therapy information kit.
		Selfinjection training, followed by observed selfinjection, with coaching as needed.
Action (Stage 4)		Patients have started to selfinject within the past 6 months.
		In the action stage, patients have started to selfinject but selfinjection is being performed at a minimally acceptable level and the patient is not yet at ease with selfinjection.
		The Action stage is the stage where vigilance against relapse is critical.
	Contingency Management	Review of selfinjection training and handson practice followed by observed selfinjection, with coaching as needed.
		Encouraging repeated daily selfinjection to build mastery of the technique.
Maintenance (Stage 5)		Patients may be considered 'long-term selfinjectors'.
		Patients are consistently engaging in selfinjection and are integrating selfinjection into their daily routine.
		Maintenance is the stage in which patients are less likely to relapse and increasingly more confident that they can continue selfinjection.
	Helping Relationships	Review of glatiramer acetate therapy information video.
		Discussion about the pros and cons of selfinjection.
		Professional nurse calls (Shared Solutions®).

Table 1: The Transtheoretical Model's Stages of Change to SelfInject and Processes of Change, [a]Patients who were deciding whether to begin therapy were offered the opportunity to contact a peer with MS (a volunteer) who had relevant experience with injecting glatiramer acetate.

Intervening Behavioral Variables Associated with Compliance and Persistence

Decisional Balance

Part of the decision to move from one stage of readiness to the next is based on the relative weight given to the pros and cons of changing behavior, in this case, moving from no selfinjection to selfinjection several times a week. There is evidence that pros and cons are indicators of an individual's progress from pre contemplation to contemplation and preparation [11-13]. In general, the pros are expected to increase as a function of readiness stage whereas the cons will decrease with a crossover around the contemplation or preparation stage, depending upon the health behavior examined.

Self-efficacy

Selfefficacy is the belief in one's capabilities to organize and execute the action required to manage prospective situations [14]. Bandura's concept applies to individuals facing behaviors or tasks they perceive as novel, unexpected, or stressful. Bandura proposed that if a person is given sufficient motivation to engage in a behavior, it is the person's selfefficacy beliefs that will determine whether that behavior will be started, how much effort will be expended, and how long the effort will be sustained in the face of obstacles and negative experiences. Individuals with stronger selfefficacy are more likely to select challenging tasks, to persist at them longer, and to perform them successfully. According to Bandura, self-efficacy is the highest predictive factor of perseverance in a new behavior. There is considerable evidence that higher selfefficacy is related to greater persistence in diverse contexts ranging from health recommendations for management of diabetes and rheumatoid arthritis, to exercise and

smoking cessation programs, to medication taking in a variety of diseases such as epilepsy, HIV, post-transplantation [15] and RRMS [4,16].

Self-Injection Competence

Patients must be physically and mentally capable of performing an injection in order to initiate and maintain self-injections. Training in self-injection techniques is important during the contemplation, preparation, and action stages of change. To simplify selfinjection, an auto injector device (autoject®2 for glass syringe) and prefilled syringes of GA were used in this study.

Methodology

Patients diagnosed with RRMS and being treated with GA for the first time, whether treatment-naïve (TN) or treatment-experienced (TE), were eligible for this prospective, observational, 12-week study (READY Trial). IRB approval was obtained for each of 32 US study sites and written informed consent was obtained for all patients in the volunteer sample prior to study procedures. The study was listed on ClinicalTrials.gov (NCT00238654).

Four office visits were required. All enrolled participants were also required to enroll in the Shared Solutions® program for assistance and support during treatment with GA. Study procedures included self-injection training at initiation of GA treatment and patient-reported surveys at each visit. Injection competence evaluation and medication compliance and persistence were assessed at weeks 4 and 12. A complete description of the study methodology has been published previously [17].

Measures

Behavioral Assessments

Readiness Survey

The Readiness Survey, a 16-item TTM-derived instrument, assessed intentions and current selfinjection activities with respect to self-injection of GA. The survey asked the patient to rate each item using a 5point scale, where 1 was "strongly disagree" and 5 was "strongly agree". An algorithm was devised to arrive at a score for each stage of change and the patient was assigned to the stage with the highest score.

Decisional Balance Inventory

The Decisional Balance Inventory was developed to assess positive and negative aspects (pros and cons) of selfinjection. The survey asked the patient to rate 10 items according to their importance to the patient, using a 5point scale where 1 was "not important" and 5 was "extremely important". The inventory yielded two scores, obtained by summing the ratings for the pro and con items separately. Each of these scores ranged from 525. High pro scores and low con scores indicated a favorable attitude toward self-injection. A combined score was obtained by subtracting the con score from the pro score. The combined score thus ranged from 20 to +20 with a higher positive score indicating a more favorable attitude toward selfinjection.

MS SelfEfficacy (MSSE) Scale

The MSSE scale a core construct of the TTM, assesses patients' personal convictions that they will be able to perform specific behaviors in a given situation [18]. It has been shown to be positively related to adherence (persistence) to GA [15,16, 19].

The MSSE scale consisted of two subscales of nine items each, relating to function and control. Patients were asked to rate each item according to how certain they felt that they would be able to perform the behavior (i.e., dressing, taking care of the home) or control the situation (i.e., control disease symptoms, reactions to disease-related limitations) described in the item. Each item was rated on a scale from 10 to 100, where 10 were "very uncertain" and 100 was "very certain". Each subscale score ranged from 90 to 900, with higher scores denoting certainty. The two parts of the scale were scored and reported separately; a combined score was obtained by adding the function score and the control score

SelfInjection Competence

Measurement of the targeted behavior is also a key component of the TTM; therefore, a study nurse evaluated the competence with which the patient performed selfinjection using the SelfInjection Technique Evaluation form designed for this study. Selfinjection competence was rated on a 10point scale ranging from 1 to 10, with "1" representing "poor" and "10" representing "excellent". The form also allowed the rater to check off the key steps that a patient followed for the selfinjection and to note any barriers to learning; however, the score was based on the global competence rating only.

Compliance and Persistence Measures

Compliance was defined by the number of prefilled syringes that were used over the course of the treatment period since the preceding visit. Since the length of time between visits varied, this number was adjusted to the length of the period to yield a "percentage of days compliant."

Persistence was evaluated on the basis of responses to two questions: 1) "Has the patient used the study therapy continuously for the past month [or two months]?" and 2) "If the patient stopped therapy, is the patient willing to restart?" If the patient stopped therapy for a short time during the prior period in question but was willing to restart at this office visit, the subject was considered persistent.

Statistical Analysis

Demographic, disease-related, and behavioral characteristics were compared between patient groups (i.e., TN vs. TE) at the inception of the READY trial. Between-group comparison was performed using a t-test for independent sample means for continuous variables (e.g., age, length of illness, Decisional Balance Inventory scores) or using the Mann-Whitney U test for ordinal variables (e.g., Readiness stage). Chi-square was used to compare the groups on categorical variables such as gender and ethnicity. Additionally, Chi-square and Fisher's Exact Test were used to compare persistence/non-persistence for the TN versus the TE group at the 4 and 12 week visits. Forward stepwise logistic regression analyses were used to assess the relationship between all of the variables and membership in each dichotomous group.

A multiple-group path analysis using LISREL 8.71 software was performed to evaluate the direct and indirect influences of background variables and behavioral variables on compliance and persistence at 12 weeks. The external variables included in this analysis were those background variables shown to be related to compliance and persistence by the prior analyses or by the compliance and persistence literature.

Results

Demographic and Disease-Related Characteristics

Two hundred and fifty-seven patients were enrolled in the study and included in the intent-to-treat population. The majority was female (80.9%) and White (81.6%), as is consistent with the MS population in general [20-22]. The patients ranged in age from 19 to 69 years (Mean [M] = 43.7; Standard Deviation [SD] = 10.6). Age at diagnosis ranged from 18 to 61 years (M = 39.6; SD = 10.2), and duration of MS ranged from less than a year to 29 years (M = 4.1; SD = 6.0). Since patients were recruited, for the most part, from community neurology clinics where Expanded Disability Status Scale (EDSS) assessment is not routinely done, investigators were asked to record the most recent EDSS scores from the charts, if available. Last recorded EDSS scores were available for 63 of the patients; these ranged from 0 to 7 (Median (Mdn) = 1.5). Sixty percent of patients (155/257) were TN. Among the 102 patients who had been previously treated, interferon beta-1a IM was the most common first-line treatment (received by 54.9%), followed by interferon beta-1b SC, (received by 34.3%). Poor tolerability was the primary reason for previous treatment discontinuation. Flu-like symptoms, mood disorders, and hepatobiliary intolerance were the most commonly reported adverse events.

Comparisons between Treatment-Naïve and Treatment-Experienced Patients

Table 2 provides a comparison of the TN patients and TE patients in terms of each of the variables in this study. TE patients were somewhat older, had been diagnosed at a younger age (p< .05), had a longer duration of MS (p< .001), and were more disabled (p< .001, among the subset of patients who had an EDSS score).

Readiness Stage

At the inception of the study, the readiness stage tended to be higher for TE patients (Mdn = 3.0) compared with TN patients (Mdn = 2.0, p< .001). The majority of TN patients were in the contemplative stage (57.8%) as compared with only 39.0% of the TE patients (Figure 2). Nearly one quarter of TE patients were in the action or maintenance phases because of their recent experience injecting a beta-interferon therapy. The single TN patient who was in the action phase (0.7% of group) had just begun therapy with GA.

Characteristic	Statistic/ Category	Treatment-Naïve (n = 155)	Treatment - Experienced (n = 102)	p
Gender	n Female Male	155 123 (79.4%) 32 (20.7%)	102 85 (83.3%) 17 (16.7%)	.52a
Race	n Minority Non-minority	154 26 (16.9%)b 128 (83.1%)	102 21 (20.6%)c 81 (79.4%)	.51a
BMI	n M ± SD	155 27.3 ± 6.1	101 27.5 ± 6.2	.78d
	Range	15, 49	12, 44	
Age (years)	n M ± SD Range	155 43.2 ± 10.2 19, 64	102 44.4 ± 11.1 21, 69	.38d
Age at diagnosis (years)	n M ± SD Range	155 40.7 ± 10.1 19, 61	102 37.8 ± 10.1 18, 61	.03d
Duration of MS (years)	n M ± SD Range	155 2.5 ± 5.4 0, 26	102 6.6† ± 6.0 0, 29	<.001d
Last recorded EDSS	n Mdn Range	40 1.5 0, 6	23 3.0 1, 7	<.001e
Readiness Survey	n Mdn Range	153 2.0 1, 4	102 3.0 1, 5	<.001e
Decisional Balance Pro score	n M ± SD Range	154 21.8 ± 3.7 8, 25	102 21.9 ± 3.5 9, 25	.78d
Con score	n M ± SD Range	154 9.4 ± 4.1 5, 25	102 8.4 ± 3.3 5, 19	.04d
Combined	n M ± SD Range	154 12.4 ± 6.0 -6, 20	102 13.5 ± 4.8 -3, 20	.11d
MS Self-Efficacy Function subscale	n M ± SD Range	154 795.5 ± 141.2 100, 900	102 711.1 ± 157.0 290, 900	<.001d
Control subscale	n M ± SD Range	154 650.3 ± 192.3 90, 900	102 554.7 ± 194.3 110, 900	<.001d
Combined	n M ± SD Range	154 1445.7 ± 315.0 210, 1800	102 1265.8 ±306.0 550, 1800	<.001d
Self-Injection Competence	n M ± SD Range	146 7.9 ± 2.1 1, 10	88 8.0 ± 1.9 3, 10	.59d

Table 2: Baseline Characteristics: Treatment-Naïve vs. Treatment-Experienced Patients M = Mean; SD = Standard Deviation; Mdn = Median; [a]Based on chi-square and Fisher's Exact Test. [b]Includes 15 African-American, 9 Hispanic, 1 Native American, and 1 "Other" patient. [c]Includes 16 African-American, 2 Hispanic, 2 Native American, and 1 Asian patient. [d]Based on independent t test. eBased on Mann-Whitney U test
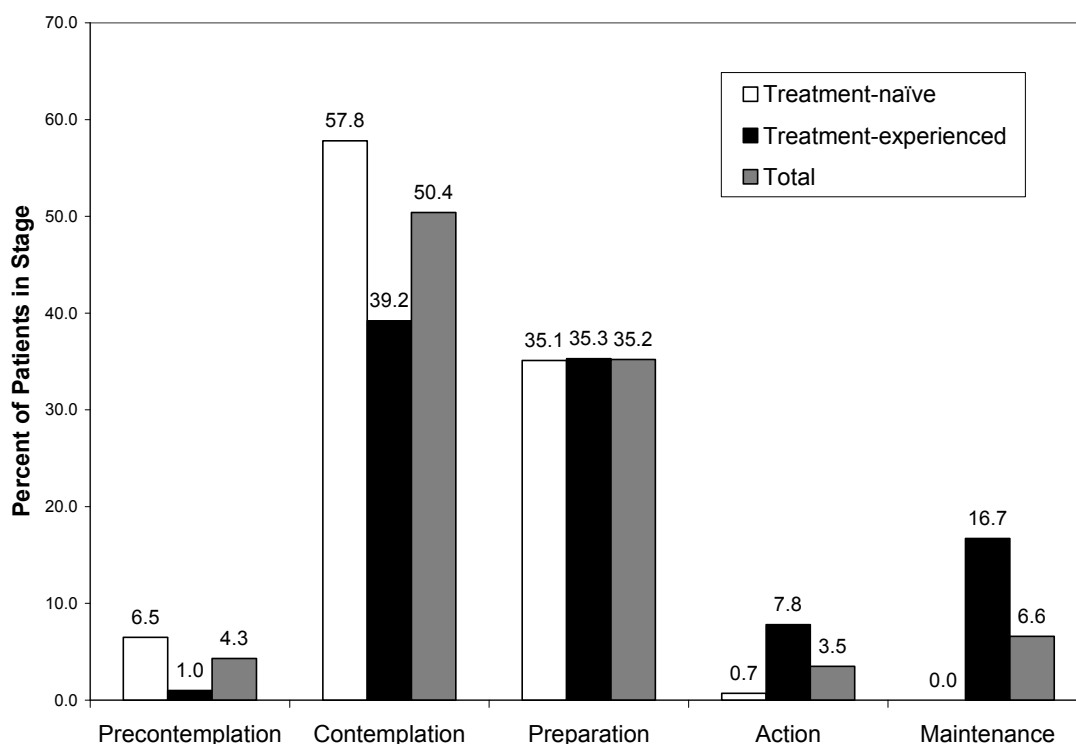
Figure 2: Readiness stage at baseline for the treatment-naïve, treatment-experienced, and total patient (combined) groups. Median readiness stage was higher in the treatment-experienced group than in the treatment-naïve group (p< .001).

Decisional Balance, MS Self-Efficacy, and Self Injection Competence

The two groups also differed on decisional balance and MS self-efficacy at baseline. TN patients had significantly higher con scores on the Decisional Balance Inventory than the TE patients (p = .03), but did not differ on the pro or combined scores. TN patients also had significantly higher scores on the function, control, and combined scales of the MSSE (p< .001). Mean scores on self-injection competence at baseline did not differ between the TN and TE groups.

Of the 257 enrolled patients, 234 (91.1%) actually initiated therapy with GA and had post-baseline data reported; 146 were TN and 88 were TE. There were 32 patients who did not complete the 12 weeks of the study and represented the non-persistent patients (13.7%) in the study. The most common reasons for stopping therapy included patient's decision to stop (12), adverse experiences (7), and loss to follow-up (6). There were 202 persistent patients (86.3%) who completed the 12 weeks of study. The percentage of days compliant with GA during the first month of therapy was 95.7% and it improved over the 12 weeks to 97.4%.

Table 3 presents the compliance and persistence results at 4 weeks and 12 weeks. There were no statistically significant differences in either compliance or persistence between the TN and TE groups at either time point.

Study Visit	Variable	Statistic	Group A	Group B	Total	p-value

			(Treatment naïve)	(Treatment experienced)		
			(N = 155)	(N = 102)	(N = 257)	
Persistence						
All Subjects Enrolled		N	155	102	257	
	Never started treatment 1	N	9 (5.8%)	14 (13.7%)	23 (9.0%)	-
30-Day	Persistent	Yes No	132 (85.2%) 14 (9.0%)	82 (80.4%) 6 (5.9%)	214 (83.3%) 20 (7.8%)	.0720 Chi-Square test
90-Day	Persistent	Yes No	126 (81.3%) 20 (12.9%)	76 (74.5%) 12 (11.8%)	202 (78.6%) 32 (12.5%)	.0937 Chi-Square test
All Subjects Starting Treatment 1		N	146	88	234	-
30-Day	Persistent	Yes No	132 (90.4%) 14 (9.6%)	82 (93.2%) 6 (6.8%)	214 (91.5%) 20 (8.6%)	.4627 Chi-Square test

90-Day	Persistent	Yes	126 (86.3%)	76 (86.4%)	202 (86.3%)	.9893
		No	20 (13.7%)	12 (13.6%)	32 (13.7%)	Chi-Square test
Compliance						
30-Day	Percentage of days compliant	N	134	79	213	.5307
		M ± SD	95.3 ± 14.7	96.5 ± 11.7	95.7 ± 13.7	
		Range	5, 100	8, 100	5, 100	Unpaired t-test
		Mdn	100.0	100.0	100.0	
90-Day	Percentage of days compliant	N	121	75	196	.6707
		M ± SD	97.2 ± 8.6	97.6 ± 4.2	97.4 ± 7.3	
		Range	45, 100	80, 100	45, 100	Unpaired t-test
		Mdn	100.0	100.0	100.0	

Table 3: Compliance and Persistence, M = Mean; SD = Standard Deviation; Mdn = Median; 1 Of the 257 subjects who were enrolled in this study, 23 subjects discontinued the study prior to starting glatiramer acetate treatment.

Regression Analysis

Prior to path analysis model building, two preliminary stepwise analyses were performed to identify the best overall predictors of compliance and persistence. Logistical regression analysis was applied to the persistence outcome and multiple regression analysis was applied to the compliance outcome. All of the demographic, disease-specific and behavioral variables were included in these regressions. Preliminary analysis showed the combined Decision Balance score to have better predictive power than the individual pro and con scores, and therefore, only the combined score on this inventory was used. In contrast, on the basis of similar preliminary analyses, the control and function scores, but not the combined scores from the MSSE were included. The first analysis yielded three significant predictors of persistence to GA: (1) duration of MS; (2) injection competence at baseline; and (3) change in injection competence at 1 month. Longer duration of MS, higher injection competence at baseline, and positive change in injection competence at 1 month was associated with membership in the persistent group. The second analysis yielded significant predictors for compliance with GA: (1) higher pro decisional balance; (2) higher injection competence at baseline; and (3) being female. Persons who were TN were less compliant than persons who were TE.
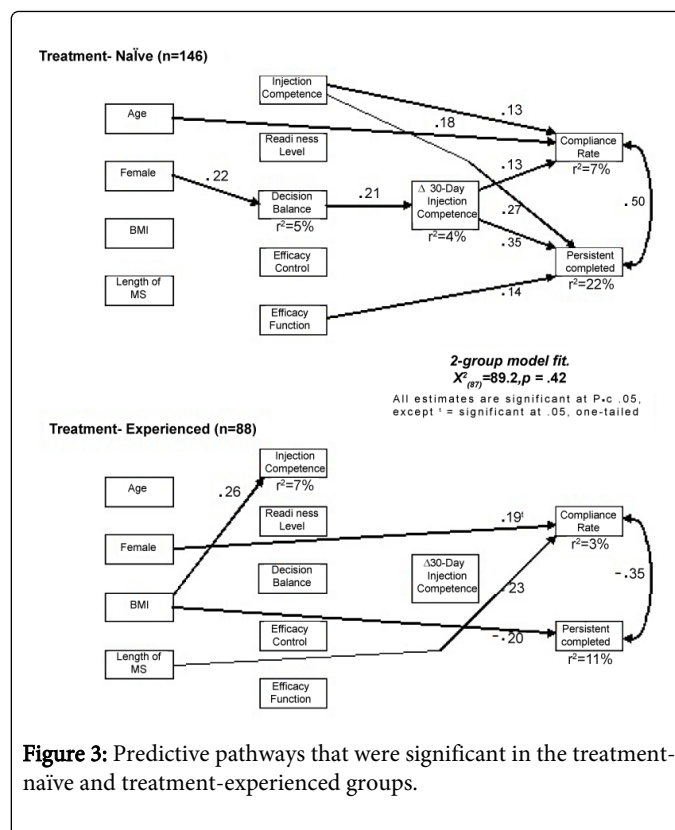

Figure 3: Predictive pathways that were significant in the treatment-naïve and treatment-experienced groups.

Path Analysis

Figure 3 presents the results of the path analyses that predict compliance with and persistence to GA for the TN and TE groups. The values next to each line of prediction are the standardized regression estimates. The values next to the double-head lines linking compliance and persistence are the correlations between these two factors after controlling for the regression effects. This correlation showed marked differences between the TN and TE groups. In the TN group, compliance and persistence showed a strong positive correlation while this correlation was moderately negative in the TE group.

A number of noteworthy relationships emerged from the path analysis. First, for the TN group, both baseline injection competence and the change in injection competence at 1 month were significant predictors of compliance and persistence with GA. The change in injection competence at 1 month served as a mediator of the effects of decision balance as well as the effect of gender on compliance and persistence in the TN group. Independent of injection competence, higher levels of functional self-efficacy were directly associated with better persistence in TN patients. In the TE group neither injection competence nor self-efficacy had an effect on compliance and persistence with GA.

Discussion

The study model presented here was developed to investigate the behavioral factors that may be influencing compliance and persistence to self-injected GA. Analysis of disease-related characteristics and behavioral variables revealed baseline differences between patient groups. As might be expected, TE patients had a longer duration of MS, and for those with EDSS scores available, it appears that they may

have had higher disability levels than TN patients. TE patients were also diagnosed with MS at a younger age. Differences in behavioral variables appeared to reflect differences in the length of experience with injectable treatment and with MS in general. TE patients were at a higher stage of readiness at baseline - probably due to their past experiences with self-injection. However, their scores on self-efficacy (MSSE) were lower than those of TN patients. The lower self-efficacy scores among the TE patients may be related to the length of their MS experience and how well they have been able to cope with the disease in general; symptoms and uncertainty are hallmarks of MS and having lived with them for a number of years they had knowledge of MS that was considerably greater than those who were TN. In addition, the TE patients had been self-injecting but had to discontinue and change therapy due to intolerance or suboptimal effectiveness. Their self-injection competence at baseline was no better than that of the TN patients. The experience of having to discontinue one of a limited number of treatments available to them may have contributed to the lower self-efficacy of some TE patients. They may have been uncertain about how they would respond to the new therapy, and in turn, they may have questioned whether they would be able to manage their symptoms in order to participate in daily activities. Scores on the con portion of the Decisional Balance Inventory at baseline were consistent with readiness stage scores in that TN patients held less favorable attitudes towards self-injection than TE patients – again, possibly reflecting differences in experience with injections.

The results of the path analyses suggest that for the TN group, either starting out with injection competence or gaining that competence within the first month of therapy with GA is an important accomplishment that cans predict compliance and persistence at 12 weeks. Those who are lower on injection competence at the beginning of therapy with GA or do not develop it within the first month may not be resilient enough to comply with the injection regimen.

However, for those who are TN and do not have high levels of injection competence at the beginning of therapy, positive decisional balance can compensate and lead to increases in the level of injection competence at 1 month. Furthermore, quite separate from injection competence, higher levels of functional self-efficacy are directly associated with better persistence in TN patients.

The prediction of compliance and persistence with GA in the TE group was much less successful than in the TN group. None of the behavioral variables examined in the present study emerged as significant predictors of compliance or persistence. This unsuccessful outcome is consistent with clinical impressions that compliance and persistence encompass more complicated issues for patients who have experienced previous treatment failures. Further investigation of this topic is needed.

The READY Trial was a prospective observational study and that poses some methodological limitations as recently discussed by Marrie [23]. Lack of randomization is commonly cited but it is an inherent feature of observational studies. Lack of standardized data collection is sometimes a limitation of observational studies; however, the READY Trial was designed around standardized case report forms that assured data for each patient was recorded using the same questions at each office visit and over time.

While not directly assessed in this study, disability may be a potentially important characteristic to differentiate TN from TE patients and should be assessed comprehensively in future studies. Patients provided self-reports about their persistence to therapy,

though patients were instructed to bring unused medication syringes to each visit that offered an objective measure of drug compliance. A high rate of persistence and compliance achieved by both treatment groups in this study limited the variability of the outcome measure and may have reduced the opportunity to identify predictors of these drug use outcomes.

Our original model in which the behavioral variables, decisional balance and MS self-efficacy functioned in a mediating role between injection readiness and compliance and persistence with GA was not supported. The readiness variable itself was not a predictor for either the TN or the TE groups. However, injection competence at the beginning of therapy and improved injection competence over the first month of therapy were significant predictors of compliance and persistence at 12 weeks among the TN group of GA users. In addition, in the absence of high injection competence at the beginning of therapy, high decisional balance scores predicted increases in injection competence at 1 month for TN patients on GA therapy. Higher functional self-efficacy scores were directly associated with better persistence to GA.

In summary, for those patients with RRMS who are being treated with GA, long-term compliance and persistence is a necessity in order to reduce the number and severity of relapses and potentially slow MS progression. If clinicians are able to convince patients about the benefits of treatment and can motivate them to begin treatment, it will enhance patients' functional self-efficacy. Patients need to know what will be required of them to maintain treatment with GA, and self-injection training and support early in treatment will be helpful in shifting their decisional balance from negative to positive and building their injection competence. Due to the long-term treatment required for MS, ongoing patient encouragement from clinicians to continue treatment with GA despite any obstacles they may face will be keenly important for patients' long-term compliance and persistence with GA.

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