



## Medication beliefs in first-line and second-line treated multiple sclerosis patients



Gesa Elena Albertine Pust (M.Sc.)<sup>a,c,1</sup>, Bente Untiedt (Dipl.)<sup>a,1</sup>,  
 Roland Weierstall-Pust (Prof. Dr.)<sup>b</sup>, Jennifer Randerath (Dr.)<sup>c,d</sup>, Anna Barabasch (M.Sc.)<sup>a</sup>,  
 Anne Christin Rahn (Dr.)<sup>a</sup>, Christoph Heesen (Prof. Dr.)<sup>a,e,\*</sup>

<sup>a</sup> Institut für Neuroimmunologie und Multiple Sklerose (INIMS), Zentrum für Molekulare Neurobiologie Hamburg (ZMNH), Universitätsklinikum Hamburg-Eppendorf (UKE), Hamburg, Germany

<sup>b</sup> Medical School Hamburg (MSH), Department of Psychology, Clinical Psychology and Psychotherapy, Hamburg, Germany

<sup>c</sup> Department of Psychology, University of Konstanz, Constance, Germany

<sup>d</sup> Lurija Institute for Rehabilitation and Health Sciences at the University of Konstanz, Schmieder Foundation for Sciences and Research, Allensbach, Germany

<sup>e</sup> Klinik und Poliklinik für Neurologie, Universitätsklinikum Hamburg-Eppendorf (UKE), Hamburg, Germany

### ARTICLE INFO

#### Keywords:

Multiple Sclerosis  
 Adherence Behaviour  
 First-line treated patients  
 Second-line treated patients

### ABSTRACT

**Background:** Immune treatments of multiple sclerosis (MS) can be classified in first-line and second-line approaches. While in both treatment efficacy is often not easy to assess in the short-term, treatment and illness beliefs may differ in first-line and second-line treated patients. The current study aimed to assess differential beliefs about medicine and illness perception between these groups based on the hypothesis that they are closely connected to adherence behaviour.

**Methods:** An online survey through the website of the German MS Society was performed investigating beliefs about immune treatments as well as the patients' illness perceptions with validated questionnaires. Demographic factors, disability and self-reported adherence rates were studied as moderator variables.

**Results:** In total, 630 patients participated. Data of 433 first-line treated and 192 second-line treated patients with MS (PwMS) were analysed. Necessity beliefs and also concerns beliefs were significantly higher in second-line treated PwMS (MANCOVA  $p = .001$  and  $p = .006$ ) and generally in patients with higher disability, while illness perception did not differ between groups. Self-assessed adherence rates were around 70% for oral treatments and injectables irrespective of first-line or second-line. Nonadherence was below 5% for infusion treatments. However, most patients reported only single omissions.

**Conclusion:** The current study reveals differential behavioural attitudes between first-line versus second-line-treated PwMS. However, follow-up studies are needed to further unravel the relationship between behavioural attitudes and treatment adherence.

### 1. Introduction

In recent years, the number of immune treatment options for multiple sclerosis (MS) has substantially grown with now 18 licensed immune treatments in many European countries. In other chronic diseases, adherence to pharmacological treatments can significantly affect treatment outcomes as well as costs (1, 2). In people with MS (PwMS), relapse or disease progression seems more prevalent among patients non-adherent to treatment (3). Additionally, lower medication adherence is associated with increased healthcare resource utilization (4, 5). Like in other chronic conditions, studies on adherence rates in

PwMS rates report rates not higher than 50-70% (5, 6).

While some work has been performed in revealing moderating factors for non-adherence in MS, most of the studies have addressed injectable treatments and most studies have focused on perceived effects and side-effects as well as on convenience of the application (3). Psychosocial factors have been rarely addressed. This is surprising, since there is evidence for illness and treatment beliefs to be more relevant for self-management competences of patients than disease associated parameters as severity, course and duration of MS (7). Aloisai and colleagues (8) recently argued based on a dataset of 129 Saudi Arabian patients, most of them on injectable MS treatments that

\* Corresponding author: Heesen, C. Prof. Dr. Institute for Neuroimmunology and Multiple Sclerosis (INIMS), Martinistr. 52, 20246 Hamburg  
 E-mail address: [heesen@uke.de](mailto:heesen@uke.de) (C. Heesen).

<sup>1</sup> Equally contributing

<https://doi.org/10.1016/j.msard.2020.102144>

Received 17 September 2019; Received in revised form 6 February 2020; Accepted 21 April 2020

2211-0348/ © 2020 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

illness beliefs, e.g. considering MS as “due to supernatural forces”, were negatively associated to medication adherence. In fact, illness and medication beliefs might be the most predictive psychological factors for adherence (9). Given that patient-related factors as beliefs are amenable to change through interventions, illness and medication beliefs should be part of any analysis of adherence mitigating factors.

Positive and negative experiences substantially affect expectations and specifically pain research has repeatedly shown that a failed first treatment substantially lowers the chance of a benefit of a second-choice treatment in treating pain (10). In chronic conditions such as MS, a failed first-line treatment may substantially alter patients' attitudes towards medication, i.e. treatment and illness beliefs. Therefore, comparing adherence mitigating factors and especially illness and medication beliefs in first-line and second-line treatment seems highly reasonable to develop stage-adapted treatment decision making and adherence counselling strategies.

Our earlier qualitative work has shown that the main reason for non-adherence reported by patients on first-line therapies was “burdensome side effects”. For adherence “belief in medication effectiveness” was given the highest priority. In second-line patients, a “lack of perceived medication effectiveness” was the main reason for changes to or discontinuation of a treatment regimen. Reasons for adherence were “positive illness beliefs/perceptions” and “the belief in a highly active disease” (11). Thus, it seems that in second-line treated patients an illness concept of MS as treatable disease was relevant to adhere to medication.

Based on this work, the current online survey study aimed at comparing illness and medication beliefs in first-line and second-line treated PwMS in relation to their treatment adherence profiles. We followed the hypothesis that based on the experience of a failed first-line therapy, patients who decided to go on a second-line treatment had a stronger idea of medication necessity than first-line treated patients.

## 2. Material and Methods

### 2.1. Participants

The survey was presented to PwMS as a study on factors relevant for adhering or not adhering to an immune therapy for MS. PwMS were recruited via advertisements at the website of the German Society for Multiple Sclerosis (DMSG) as well as through the quarterly E-newsletter of the MS outpatient clinic, University Medical Centre Hamburg-Eppendorf, from November 2016 to February 2017. Additionally, PwMS from the Rehabilitation Clinics Schmieder, Konstanz were invited to participate via leaflets and brief verbal communications. Inclusion criteria were: 1) age  $\geq 18$ , 2) a self-reported relapsing-remitting MS (RRMS) diagnosis, 3) current immunotherapy. A total of 1318 individuals accessed the online questionnaires. 625 full data sets were obtained for the present study. Only full data sets were considered, as also individual items were analyzed, which precludes the application of an imputation method for missing data. All patients gave informed consent via the web-based survey. The study was approved by the Ethical Review Board of the Hamburg Chamber of Physicians (PV5236).

### 2.2. Measures

Adherence questions (see appendix 1) referred to the last 4 weeks for oral treatments and self-injectables, while questions about natalizumab and alemtuzumab referred to the past 6 months.

#### 2.2.1. Patient determined Disease Steps (PDDS)

Disability was assessed according to the disease steps defined by Hohol and colleagues (12), ranging from “no disability” to “confined to wheelchair or worse”. Due to the online presentation of the survey, the participation of bedridden participants was not expected, so that the

original version was preferred over the Patient Determined Disease Steps (PDDS; NARCOMS) scale, which suggests a further distinction of the severely impaired patients. Responses are coded between “0” and “8”, with higher values indicating more disability.

#### 2.2.2. Beliefs about medicines questionnaire (BMQ) (see appendix 2)

The 10-item Beliefs about medicines questionnaire (BMQ; 13) was used in its German version (14) to assess the PwMS' beliefs about their medication specifying the clinical condition as MS. The BMQ is based on the Necessity-Concerns-Framework balancing patients' beliefs about the necessity to take a medication against concerns about adverse effects. Each of the five items assesses patients' beliefs about the necessity of their medication (*BMQ Specific Necessity Beliefs*) as well as specific concerns about the current medication (*BMQ Specific Concerns Beliefs*). The BMQ has been shown to be associated with medication adherence, with patients that belief in a strong necessity of their medication demonstrating higher adherence behavior (9). All items were scored on a 5-point Likert-scale, ranging from “0” (totally disagree) to “4” (totally agree). For both sub-scales, item-scores were summed.

#### 2.2.3. Brief Illness Perception Questionnaire

The BIPQ (Brief illness perception questionnaire; 15) was administered to assess the patients' illness perceptions and adaptation to MS. The BIPQ is a valid a reliable measure that has demonstrated its good psychometric properties in various diseases and has also already been evaluated in a meta-analysis (16). Contrary to other questionnaires and surveys, the BIPQ assess each of its eight dimensions with only a single item and with individual anchor labels. The dimensions cover “perceived consequences” (the short- and long-term effects of the illness, and its physical, social, economic, and emotional effects), “timeline” (the expected duration and course of the illness), “perceived personal control” (what the individual believes they themselves can do), “treatment control” (what the treatment can do to control or bring about recovery from the illness), “identity” (label attributed by the affected person to the illness and the symptoms he/she associates with it), “concerns about the illness” (specific worries), “coherence of the illness” (coherence of patients concept of the condition) and “emotional representation” (emotions elicited about the disease). In its original version, item responses are scored on a scale ranging from 0 to 10, where higher scores indicate stronger perceptions along that dimension. For the present study, a 10-point scale was used to reduce the risk of central tendency bias.

### 2.3. Procedure

A specified link was provided on the DMSG website to get direct access to the survey. The link was also printed on the leaflets provided to patients. PwMS gave their informed consent online prior to participation. After pushing the “agree” button referring to the terms of participation, the questionnaires outlined above were presented. Relevant patients characteristics were assessed (sex, age, MS duration, past and ongoing immunotherapy, education, family status, patient determined disability and adherence behavior). Subsequently, the specific questionnaires on disability and illness beliefs were presented. It took about 20 minutes to complete the entire survey. The web presentation of the study was programmed using Unipark EFS survey software (17). An invitation teaser, study instructions, data protection regulations as well as the questionnaires were presented. Participant responses were provided anonymously. It was not possible to access the survey with the same IP address twice. The Questback server farm is reliably protected against external access. The BSI-certified data center is subject to extremely high data protection and security requirements according to ISO 27001 based on IT basic protection.

## 2.4. Statistical Analyses

Interferon-beta preparations, glatiramer acetate as well as teriflunomide and dimethylfumarate were classified as first-line treatments while fingolimod, natalizumab and alemtuzumab were considered second-line. Differences in demographic variables were calculated by using *t*-tests for independent samples as well as chi-square-tests. To examine potential differences in illness and medication beliefs between first-line and second-line patients, two multivariate analyses of covariance (MANCOVAs) were calculated for 1) the two BMQ subscales and 2) the eight BIPQ items. In all analyses, *age*, *PDDS* and *disease duration* were considered as co-variables and *group* as well as *gender* as fixed factors. In addition, post hoc analyses were performed comparing adherent and non-adherent PwMS by defining non-adherence through at least one omitted treatment. Mann-Whitney U tests were applied for comparisons between groups, when assumptions for the application of parametric tests were violated. All analyses were conducted using SPSS 24.0 for windows. The level of significance was set to alpha .05.

## 3. Results

PwMS included in the study had a mean age of 37 years, a mean disease duration of 6.4 years and their mean PDDS score was 2.4 (see table 1 for details). 124 of the PwMS treated with first-line medication used Interferon-beta-1a or -b preparations, 96 used glatiramer acetate, 165 dimethylfumarate and 48 teriflunomide. Among the second-line treated PwMS, 70 used natalizumab, 113 fingolimod and nine alemtuzumab. There was no difference in age or gender distribution between first-line and second-line treated PwMS. Second-line PwMS reported a longer disease duration ( $p = .005$ ) and higher PDDS scores ( $p < .001$ ). There was no significant difference in rates of adherence or non-adherence between the two groups ( $p = .950$ ). Analyses on BMQ scale reliabilities revealed satisfying results: Cronbach's Alpha in the present sample was  $\alpha = .84$  for the BMQ Specific Necessity Beliefs scale and  $\alpha = .69$  for the BMQ Specific Concern Beliefs scale.

Among first-line treated patients, self-reported non-adherence during the past four weeks ranged from 0 to 30 times (25% quartile: 0; median: 0; 75% quartile: 2; oral medications: 25% quartile: 0; median: 0; 75% quartile: 1; injectables: 25% quartile: 0; median: 0; 75% quartile: 0). 18% (91 patients) of PwMS reported not having been non-adherent more often than once. In those 79 PwMS taking infusions, self-reported non-adherence in the past six months ranged from 0 to 6 times (25% quartile: 0; median: 0; 75% quartile: 0). Two of four PwMS did omit more than one infusion (see also table 1).

### 3.1. Beliefs about medicine (BMQ) specific beliefs

Comparing BMQ data between first-line and second-line treated PwMS, there was a significant difference (BMQ specific necessity

beliefs; first-line PwMS:  $M = 11.5$ ,  $SD = 4.0$ ; second-line PwMS:  $M = 13.7$ ,  $SD = 3.7$ ; BMQ specific concerns beliefs; first-line PwMS:  $M = 6.7$ ,  $SD = 3.9$ ; second-line PwMS:  $M = 7.4$ ,  $SD = 3.6$ , see figure 1) with more necessity beliefs and also more concerns beliefs in second-line treated PwMS, as indicated by the significant effect for the fixed factor *group* (BMQ specific necessity beliefs:  $p < .001$ ; BMQ specific concerns beliefs:  $p = .006$ ).

As indicated by the significant regression coefficients of the covariates included in the MANCOVAs, PwMS with higher PDDS scores also scored higher in both BMQ scales (BMQ specific necessity beliefs:  $p = .005$ ; BMQ specific concerns beliefs:  $p = .011$ ). Likewise, the covariate disease duration reached statistical significance only for the specific concerns beliefs ( $p = .001$ ). Neither the factors gender and age reach statistical significance. However, there was a significant interaction between gender and the group for the specific concerns beliefs ( $p = .039$ ) indicating that specific concerns beliefs were higher among females in the group of first-line treated PwMS but lower among females in second-line treated PwMS compared to males from the same group (for more data see appendix 3). Post-hoc analyses were calculated for differences in the BMQ scales between full adherent and non-adherent PwMS. In the group of PwMS on second-line treatment, there was neither a significant difference in the BMQ specific necessity beliefs, nor in the BMQ specific concerns beliefs (both Mann-Whitney-U-test,  $p > .05$ ). In the group of first-line treated PwMS, there was no statistically significant difference in the BMQ specific concerns beliefs (Mann-Whitney-U-test,  $p > .05$ ) but non-adherent PwMS had lower BMQ specific necessity beliefs (*t*-test,  $p < .05$ ). This effect remained stable, even after adding a first-line vs. second-line group variable as well as the interaction term (two-way ANOVA, adherence effect  $< .05$ ).

#### 3.1.2 Illness beliefs

**3.1.2.1. Brief Illness Perception Questionnaire (BIPQ) - beliefs.** Results on illness beliefs are displayed in figure 2. While PwMS demonstrated only weak agreement to the items *dealing with perceived consequences* and *identity*, highest values were obtained for the variable *timeline (acute – chronic)*. There was no significant difference between first-line and second-line treated PwMS in any of the items, except for the item *perceived consequences* ( $p = .013$ ), where second line treated PwMS expected worse consequences. *Self-rated disability* was associated with illness beliefs in most items, except for the item focusing on *coherence of the illness*, where none of the variables had a statistically significant impact. Thus, PwMS with higher scores in the covariate PDDS scores also reported stronger illness beliefs in the respective measures. The obtained effect sizes of differences in the BIPQ subscales were largest for the items focusing on *perceived consequences* and *identity*, exceeding all other effect sizes found in the data. Gender did not impact on the results but illness duration had an effect on the amount of *perceived personal control*, the *concerns about the illness* and the *perceived consequences* (all  $p < .05$ ): PwMS with a longer illness duration

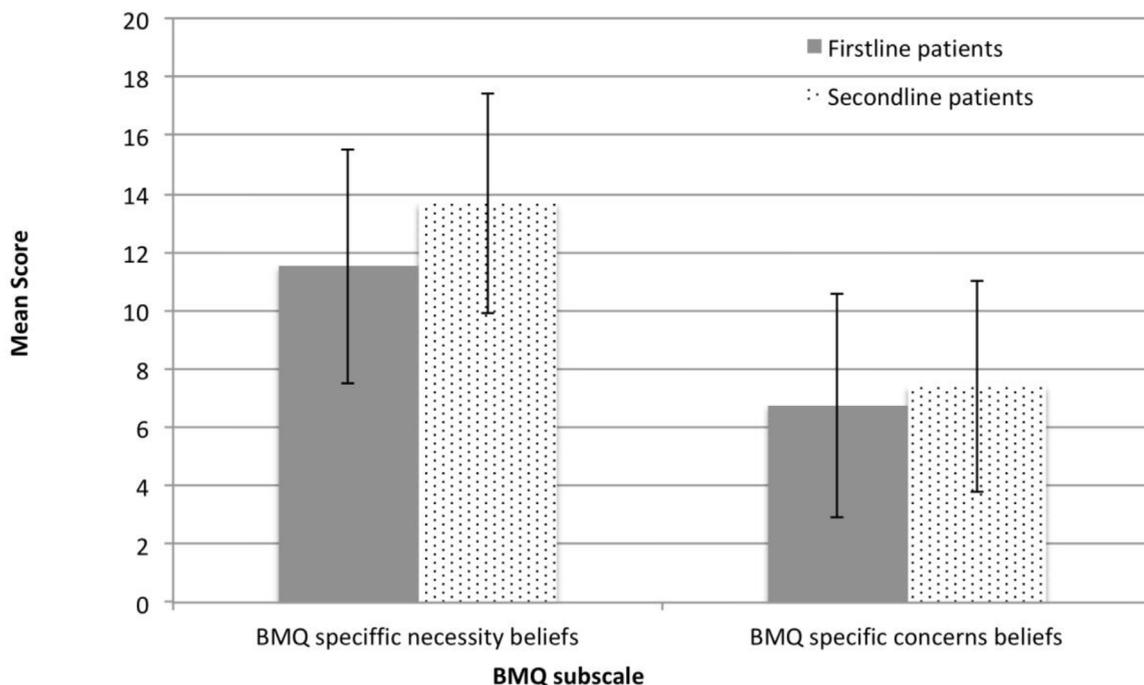
**Table 1**

Demographic and clinical data in first-line and second-line PwMS.

		First-line treatment	Second-line treatment	Total
<i>N</i>		433	192	625
Female/male (%)		76/24	74/26	75/25
Age in years ( <i>SD</i> ) <sup>†</sup>		37.8 (9.6)	36.6 (9.2)	37.4 (9.5)
disease duration in years ( <i>SD</i> ) <sup>†</sup>		6.0 (5.6)	7.4 (5.6)	6.4 (5.6)
PDDS* ( <i>SD</i> ) <sup>†</sup>		2.3 (1.3)	2.7 (1.5)	2.4 (1.4)
<b>Medication Type and Adherence</b>				
oral/self-injectable medication (4 weeks)	full-adherent	303 (70%)§	78 (69%)§	381
	non adherent	131 (30%)§	34 (31%)§	165
Infusions (6 months)	full-adherent	-	75 (95%)§	-
	non adherent	-	4 (5%)	-

<sup>†</sup> Data as mean and standard deviation (SD).

\* PDDS = Patient Determined Disease Steps (description see below). All other numbers indicate absolute frequencies and percentages in brackets. §referring to 100% of the group on oral/self-injectable treatments or on 100% or infusion treatments



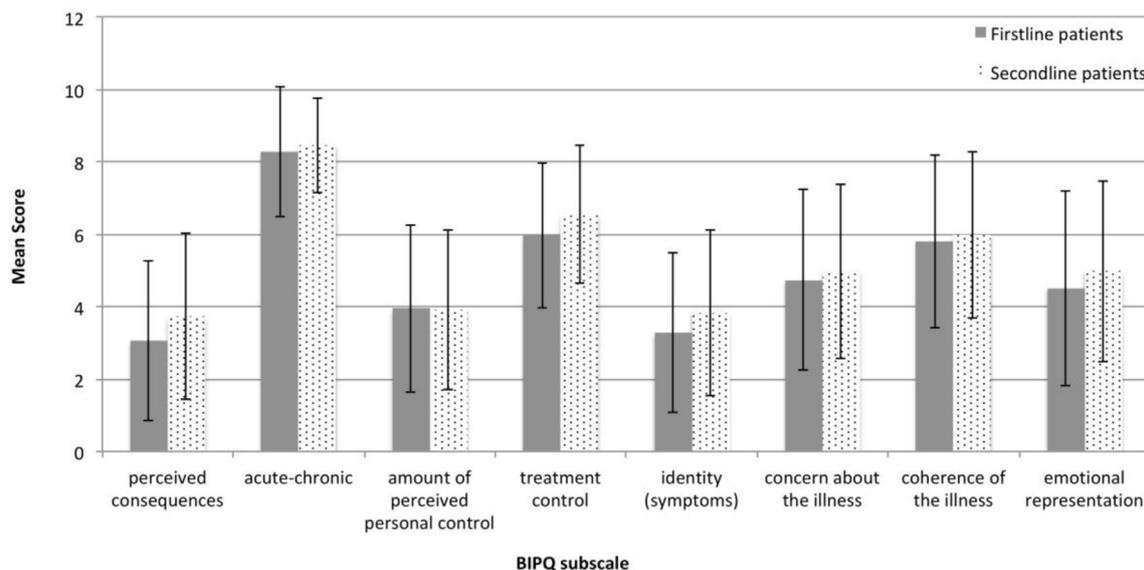
**Figure 1.** Differences in the Belief about Medicine Questionnaire (BMQ) subscales between first-line and second-line PwMS; 0 = low level, 20 = high level. Means and standard deviations are displayed.

reported higher perceived personal control, more concerns about their illness and expected more serious consequences. Age was another significant covariate ( $p < .05$ ), with older PwMS reporting worse *illness perceptions* and higher scores in the dimension *timeline (acute-chronic)*. More detailed information about the statistics is reported in [appendix 3](#). Post-hoc analyses for differences between full-adherent and non-adherent PwMS did not reach statistical significance (all Mann-Whitney-U-tests and t-tests  $p < .05$ ).

**4. Discussion**

This survey was performed to better understand illness and treatment beliefs in first-line and second-line treated MS patients in relation

to treatment adherence. Contrary to our hypothesis of relevant differences of behavioral attitudes between first-line- and second-line-treated PwMS, among the 10 studied dimensions from both questionnaires, only the necessity belief of treatment was different indicating stronger necessity beliefs in second-line PwMS. This finding indicates face validity of the scale. For patients having experienced treatment failure, the need for another treatment is more obvious than for treatment-naïve patients reflecting on any treatment. In the only other published study on BMQ scores in PwMS, Thach and colleagues (2018) reported scores of 13.3 for necessities and 5.6 for concerns in a NARCOMS registry subcohort with  $N = 489$  PwMS, thus in a similar range as in our data (data adjusted to 0-20 scale). Interestingly, concerns were somewhat higher in our sample, maybe indicating a more critical



**Figure 2.** Differences in the Brief Illness Perception Questionnaire (BIPQ) subscales between first-line and second-line PwMS; 0 = low agreement, 9 = high agreement. Means and standard deviations are displayed.

attitude towards medication side-effects in German PwMS in contrast to US PwMS investigated.

Reported adherence rates in the NARCOMS subcohort were even higher than in the present study indicating that an online study might not be the ideal strategy to sample a cohort with real life adherence rates. However, the necessity-concerns framework was considered of high relevance in analyzing adherence prediction based on a meta-analysis from more than 25.000 patients of diverse conditions (9): high necessity beliefs and low concerns are strong predictors of adherence. This pattern of beliefs and concerns applies also for the actual study. However, association to adherence patterns was not possible based on the lack of substantial non-adherence. Adherence rates were around 70% for oral treatments and injectables irrespective if first-line or second-line. Non-adherence was below 5% for infusion treatments. However, most patients reported just single omissions.

In line with our survey the few studies on behavioural factors and adherence in MS studied samples with high adherence rates. In the above cited study by Thach (18) medication beliefs were not associated with adherence. While only 8%, i.e. less than 50 patients of the cohort showed non-adherence this finding needs further investigation. In the study by Alosaimi and colleagues (19) belief in MS as supernaturally given was significantly associated with non-adherence in a cohort of 160 patents, most taking injectables and about 80% classified as adherent.

Some studies have addressed illness perception in MS outside the context of adherence. Jopson (20) found in a cross-sectional sample that patients' illness representations were the most significant predictors of levels of social dysfunction, fatigue, anxiety, depression and self-esteem. Vaughan (21) showed in another cross-sectional study that a strong illness identity, chronic time-line view and perception of low control were related to more serious consequences, i.e. a worse disease stage. Dennison, Moss-Morris, Silber, Galea, & Chalder (22) however reported that unhelpful beliefs about the self were the strongest predictors of distress. Illness associated factors were not substantially relevant indicating that premorbid priming through early experiences is more relevant for distress. This seemed also to account for anxiety and depression in the study by Dennison and colleagues (22). Wilski et al. (7) emphasized in their recent study of 210 patients from a rehabilitation center that illness perceptions and treatment beliefs are larger determinants of self-management capabilities. Especially acceptance of the disease as a long-term condition and belief in treatment efficacy turned out to be relevant, but not disease factors as disease course type, disease duration or severity. This has as well been shown in other chronic conditions as cardiovascular diseases (23). Therefore, these factors need to be addressed to maximize self-management abilities. They might range from educational approaches delivering evidence-based patient information and shared decision making to cognitive behavioral techniques analyzing typical cognitive patterns eliciting helplessness but also acceptance-oriented approaches (24).

## 5. Limitations

Participation in the study was based on personal interest of

## Appendix 1. Adherence questions

*People with MS often have difficulty taking their medication for a variety of reasons.*

*For people taking infusions: How often have you missed your current MS medication in the last 6 months? Free field (0 to 12 possible)*

*For people taking pills or subcutaneous injections: In the last 4 weeks, how often have you forgotten to take your current MS medication? Free field (0-63 possible)*

## Appendix 2. Beliefs about medicine questionnaire

*BMQ-Specific - your views about medicines prescribed to you.*

- I would like to ask you about your personal views about medicines prescribed for your MS.

participants and therefore biased towards more self-reflective individuals and presumably also more adherent pwMS. We were not able to correlate adherence patterns with psychosocial factors as reported non-adherence rates were very low. Comparison of full-adherent and non-adherent PwMS did not show clear differences in the illness beliefs. There was only a significant difference in the BMQ specific necessity beliefs scale, in first-line treated patients. This may indicate that first-line treated patients with less necessity beliefs for treatment are at higher risk for non-adherence. But further work is necessary for studying attitudes towards medication in consecutive patients and trying to engage patients with ambivalent adherence or even explicitly addressing non-adherent patients.

## 6. Conclusions

First- and second-line patients seem to differ in their beliefs about their disease and medicines effect, which, in turn, may impact our understanding of treatment adherence. Specifying differential behavioural attitudes may contribute to the development of effective motivational interventions. Focused work in non-adherent patients is needed to better understand the impact of these factors.

## Data Statement

Due to data protection regulations for clinical data, data files can only be made available upon request to the corresponding author.

## CRedit authorship contribution statement

**Gesa Elena Albertine Pust:** Investigation, Formal analysis, Data curation, Writing - original draft, Visualization. **Benthe Untiedt:** Investigation, Writing - review & editing. **Roland Weierstall-Pust:** Methodology, Formal analysis. **Jennifer Randerath:** Writing - review & editing. **Anna Barabasch:** Methodology, Writing - review & editing. **Anne Christin Rahn:** Writing - review & editing. **Christoph Heesen:** Conceptualization, Methodology, Supervision, Writing - review & editing, Funding acquisition.

## Declaration of Competing Interest

GEAP and BU received speaker honoraria and project funding from Genzyme Sanofi. CH received speaker honoraria and project funding from Genzyme Sanofi, Roche, Merck, Biogen. AB received funding from Roche. All remaining authors have no conflict of interest to declare. This study was supported by a grant from Sanofi Genzyme Pharma.

## Acknowledgement

This study was supported by a grant from Sanofi Genzyme Pharma.

- These are statements other people have made about their MS medication.
- Please indicate the extent to which you agree or disagree with them by placing a cross in the appropriate box.
- There are no right or wrong answers. I am interested in your personal views.
- Please only cross one box per question.

Format: Strongly agree - agree - uncertain - disagree - strongly disagree

- 1) My health at present depends on my MS medication.
- 2) Having to take MS medication worries me.
- 3) My life would be impossible without my MS medication.
- 4) Without my MS medication I would be very ill.
- 5) I sometimes worry about the long-term effects of my MS medication.
- 6) My MS medication is mystery to me.
- 7) My health in the future will depend on my MS medication.
- 8) My MS medication disrupts my life.
- 9) I sometimes worry about becoming too dependent on my MS medication.
- 10) My MS medication protects me from becoming worse.

**Appendix 3. Statistics for the Multivariate analyses of covariance (MANCOVAs) calculated for the two BMQ<sup>†</sup> sub-scales as well as the eight illness beliefs items**

BMQ <sup>†</sup> specific necessity beliefs				
Variable	F	df	p	$\eta_p^2$
PDDS <sup>‡</sup>	6.70	1, 618	.010**	.01
group	25.99	1, 618	< .001***	.04
disease duration	2.52	1, 618	.113	.003
age	.21	1, 618	.650	< .001
gender	.89	1, 618	.346	.001
group * gender	.05	1, 618	.831	< .001
BMQ <sup>†</sup> specific concerns beliefs				
Variable	F	df	p	$\eta_p^2$
PDDS <sup>‡</sup>	6.72	1, 618	.010**	.01
group	6.57	1, 618	.011*	.01
disease duration	11.10	1, 618	.001***	.02
age	3.76	1, 618	.053	.01
gender	.03	1, 618	.872	< .01
group * gender	3.59	1, 618	.058	.01
illness beliefs - perceived consequences				
Variable	F	df	p	$\eta_p^2$
PDDS <sup>‡</sup>	423.74	1, 618	< .001***	.41
group	.08	1, 618	.772	< .01
disease duration	.02	1, 618	.878	< .01
age	2.43	1, 618	.120	< .01
gender	.42	1, 618	.517	< .01
group * gender	1.10	1, 618	.296	< .01
illness beliefs - acute-chronic				
Variable	F	df	p	$\eta_p^2$
PDDS <sup>‡</sup>	5.47	1, 618	.020*	.01
group	.03	1, 618	.861	< .01
disease duration	2.57	1, 618	.110	< .01
age	9.87	1, 618	.002**	.02
gender	.61	1, 618	.437	< .01
group * gender	1.88	1, 618	.171	< .01
illness beliefs - amount of perceived personal control				
Variable	F	df	p	$\eta_p^2$
PDDS <sup>‡</sup>	11.73	1, 618	.001***	.02
group	.39	1, 618	.534	< .01
disease duration	4.43	1, 618	.036*	.01
age	< .01	1, 618	.963	< .01
gender	.15	1, 618	.695	< .01
group * gender	1.95	1, 618	.163	< .01
illness beliefs - treatment control				
Variable	F	df	p	$\eta_p^2$
PDDS <sup>‡</sup>	4.29	1, 618	.039*	.01
group	8.23	1, 618	.004**	.01
disease duration	8.44	1, 618	.004**	.01
age	3.78	1, 618	.052	.01
gender	.34	1, 618	.559	< .01
group * gender	.48	1, 618	.485	< .01
illness beliefs - identity (symptoms)				
Variable	F	df	p	$\eta_p^2$
PDDS <sup>‡</sup>	526.80	1, 618	< .001***	.46
group	.25	1, 618	.618	< .01

disease duration	.37	1, 618	.542	< .01
age	4.35	1, 618	.037*	.01
gender	1.46	1, 618	.228	< .01
group * gender	.40	1, 618	.528	< .01
illness beliefs - concern about the illness				
Variable	F	df	p	$\eta_p^2$
PDDS <sup>‡</sup>	7.35	1, 618	.007**	.01
group	1.71	1, 618	.141	< .01
disease duration	11.96	1, 618	< .001***	.02
age	2.23	1, 618	.180	< .01
gender	.54	1, 618	.396	< .01
group * gender	.93	1, 618	.289	< .01
illness beliefs - coherence of the illness				
Variable	F	df	p	$\eta_p^2$
PDDS <sup>‡</sup>	2.05	1, 618	.153	< .01
group	.12	1, 618	.735	< .01
disease duration	2.61	1, 618	.106	< .01
age	1.56	1, 618	.212	< .01
gender	1.99	1, 618	.158	< .01
group * gender	.12	1, 618	.734	< .01
illness beliefs - emotional representation				
Variable	F	df	p	$\eta_p^2$
PDDS <sup>‡</sup>	26.19	1, 618	< .001***	.04
group	1.89	1, 618	.170	< .01
disease duration	1.69	1, 618	.194	< .01
age	12.83	1, 618	< .001***	.02
gender	.43	1, 618	.513	< .01
group * gender	.72	1, 618	.398	< .01

<sup>†</sup> BMQ = Beliefs about Medicine Questionnaire.

<sup>‡</sup> PDDS = Patient Determined Disease Steps.

\*  $p < .05$ .

\*\*  $p < .01$ .

\*\*\*  $p < .001$ .

## References

- Haynes, RB, Yao, X, Degani, A, Kripalani, S, Garg, A, McDonald, HP, 2005. Interventions to enhance medication adherence. *Cochrane Database Syst Rev* (4), CD00011.
- World Health Organization, 2003. Adherence to long-term therapies: evidence for action. Annex 1, 143.
- Menzin, J, Caon, C, Nichols, C, White, LA, Friedman, M, Pill, MW, 2013. Narrative review of the literature on adherence to disease-modifying therapies among patients with multiple sclerosis. *Journal of managed care pharmacy* 19, 24–40.
- Burks, J, Marshall, TS, Ye, X, 2017. Adherence to disease-modifying therapies and its impact on relapse, health resource utilization, and costs among patients with multiple sclerosis. *ClinicoEconomics and outcomes research* 9, 251.
- Gerber, B, Cowling, T, Chen, G, Yeung, M, Duquette, P, Haddad, P, 2017. The impact of treatment adherence on clinical and economic outcomes in multiple sclerosis: Real world evidence from Alberta, Canada. *Multiple sclerosis and related disorders* 18, 218–224.
- Hansen, K, Schüssel, K, Kieble, M, Werning, J, Schulz, M, Friis, R, Kugler, J, 2015. Adherence to disease modifying drugs among patients with multiple sclerosis in Germany: a retrospective cohort study. *PLoS one* 10, e0133279.
- Wilski, M, Tasiemski, Illness, T., 2016. perception, treatment beliefs, self-esteem, and self-efficacy as correlates of self-management in multiple sclerosis. *Acta Neurologica Scandinavica* 133, 338–345.
- Alosaimi, FD, AlMulhem, A, AlShalan, H, Alqazlan, M, Aldaif, A, Kowgier, M, Sockalingam, S, 2017. Psychosocial predictors of patient adherence to disease-modifying therapies for multiple sclerosis. *Patient preference and adherence* 11, 513.
- Horne, R, Chapman, SC, Parham, R, Freemantle, N, Forbes, A, Cooper, V, 2013. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework. *PLoS One* 8 (12), e80633 Dec 2.
- Kleine-Borgmann, J, Bingel, U, 2018. Nocebo effects: neurobiological mechanisms and strategies for prevention and optimizing treatment. *International review of neurobiology* 138, 271–283.
- Untiedt, B, Pust, GEA, Liethmann, K, Rholoff, T, Koepke, S, Rahn, A, Heesen, C, 2017. Adherence in multiple sclerosis: A qualitative study comparing firstline and second-line immunotherapies. *Multiple Sclerosis Journal* 23, 890.
- Hohol, MJ, Orav, EJ, Weiner, HL, 1995. Disease steps in multiple sclerosis: a simple approach to evaluate disease progression. *Neurology* 42, 251–255.
- Horne, R, Weinman, J., 1999. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *J Psychosom Res* 47, 555–567.
- Glombiewski, JA, Nestoriuc, Y, Rief, W, Glaesmer, H, Braehler, E, 2012. Medication adherence in the general population. *PLoS One* 7, e50537.
- Broadbent, E, Petrie, KJ, Main, J, Weinman, J, 2006. The brief illness perception questionnaire. *Journal of psychosomatic research* 60, 631–637.
- Broadbent, E, Wilkes, C, Koschwanez, H, Weinman, J, Norton, S, Petrie, KJ, 2015. A systematic review and meta-analysis of the Brief Illness Perception Questionnaire. *Psychology & health* 30, 1361–1385.
- QuestBack Unipark. [www.unipark.com](http://www.unipark.com) Accessed 2016.
- Thach, AV, Brown, CM, Herrera, V, Sasane, R, Barner, JC, Ford, KC, Lawson, KA, 2018. Associations between treatment satisfaction, medication beliefs, and adherence to disease-modifying therapies in patients with multiple sclerosis. *International journal of MS care* 20, 251–259.
- Alosaimi, FD, AlMulhem, A, Moscovici, M, AlShalan, H, Alqazlan, M, Aldaif, A, Sockalingam, S. The relationship between psychosocial factors and cognition in multiple sclerosis. *Behavioural neurology* 2017:1–6.
- Jopson, NM, Moss-Morris, R., 2003. The role of illness severity and illness representations in adjusting to multiple sclerosis. *J Psychosom Res* 54, 503–511.
- Vaughan, R, Morrison, L, Miller, E, 2003. The illness representations of multiple sclerosis and their relations to outcome. *Br J Health Psych* 8, 287–301.
- Dennison, L, Moss-Morris, R, Silber, E, Galea, I, Chalder, T, 2011. Cognitive and behavioural correlates of different domains of psychological adjustment in early-stage multiple sclerosis. *Journal of psychosomatic research* 69, 353–361.
- Lau-Walker, M, 2006. Predicting self-efficacy using illness perception components: A patient survey. *British journal of health psychology* 11, 643–661.
- Heesen, C, Köpke, S, Kasper, J, Poettgen, J, Tallner, A, Mohr, DC, Gold, SM, 2012. Behavioral interventions in multiple sclerosis: a biopsychosocial perspective. *Expert review of neurotherapeutics* 12, 1089–1100.