**Medication habit in a prospective cohort study**

**among persons with Multiple Sclerosis;**

**identifying hindrances and opportunities**

Efrat Neter1, Lea Glass-Marmor2, Anat Wolkowitz2, Ariel Miller2,3

1 Ruppin Academic Center, Israel

2 Rappaport Faculty of Medicine, Technion Institute of Technology, Haifa, Israel

3 Multiple Sclerosis Center & Department of Neurology, Carmel Medical Center, Haifa, Israel

Corresponding author:

Efrat Neter, [neter@ruppin.ac.il](mailto:neter@ruppin.ac.il);

3 Bait, Ruppin Academic Center, Emeq Hefer, 4025000, Israel

Phone: +972-54-6462677; Fax:+972-9-8983043

**Key words**: Disease Modifying Therapy; Habit; Medication Adherence; Multiple Sclerosis; Patient Reported Outcomes; Persistence.

**ABSTRACT**

**Background**: Though habitual behavior is part of medication taking behavior, studies on adherence to medication among persons with relapsing remitting multiple sclerosis (PwRRMS) did not prospectively examine habit for disease modifying treatments (DMT).

**Objectives**: 1. Examine habit dimensions - repetition, lack of awareness and lack of control - across time and route of administration (oral vs. injectable). 2. Examine the association between the repetition dimension and habit index to adherence and persistence in medication taking and to medication perceptions.

**Methods**: PwMS (n=140), newly treated with DMT (first year), were prospectively assessed at three time points: baseline, 6 (Time 1) and 12 months later (Time 2). Clinical, demographic information and patient-reported medication habits and medication perceptions were surveyed in-person. Adherence and persistence were assessed by a combination of self-report and retrospective review of medication claims.

**Results**: Repeated measures ANOVA with dimension as the within-subject factor at each time point indicated that the repetition dimensions at all time points were significantly higher than lack of awareness and lack of control dimensions. Repeated measures ANOVA with time as the within-subject factor and route of administration as between-subject factor yielded a significant time effect in repetition and lack of awareness dimensions so that they increased across time but not in lack of control; administration route effects were found nonsignificant in all dimensions. Repetition at Time 1 was positively associated with a patient-reported adherence at this time point (*r*=.20, p=0.035) but not consistently at other time points. Likewise, reported repetition at Time 1 was higher among PwRMS who persisted with their medication a year later than among those who did not persist. Perceptions of medication (concern, harm, overtreatment) were significantly negatively associated with reported repetition.

**Conclusions**: Over time, PwRMS report increase in the two habit dimensions of repetition and lack of awareness in medication taking. No significant differences in habit by administration modality were found. The habit dimension of repetition was significantly associated with perceptions on medications, adherence and prospectively predicted persistence. However, the low values of lack of awareness and lack of control, compared with higher level of repetition, indicate that the habit is not well ingrained. Hence, intervention targeting habit formation and maintenance are a promising venue for enhancing adherence.

**Background**

Effective treatments that modify the course of relapsing remitting multiple sclerosis (RRMS) are available [1]. These Disease Modifying Treatments (DMTs) reduce the number of clinical relapses, MRI activity and seem to slow the progression of disability [2]. Oral formulations, which have been approved in recent years, increased anticipation for enhanced tolerability [3] and consequently potential increased adherence [4, 5] and hence effectiveness. Currently more than a dozen DMTs are available [6] varying in administration modality and scheduling.

The effectiveness of treatments, however, is determined by the extent to which persons with RRMS (PwRRMS) take their medication as prescribed, defined as adherence, and stay on (same) treatment, defined as persistence [7, 8]. Reasons for nonadherence reported by PwMS may be categorized into intentional/deliberative (e.g., side effects, concern about long-term effects [9]) and non-intentional/implicit non-adherence [10], the latter expressed most often among PwMS in forgetfulness [11–13], more prevalent when self-administered medication schedules are more than once-a-day.

The construct theorized to mitigate forgetfulness and contribute the most to long term adherence and persistence is habit. Wood and Neal [14] defined it as a cognitive mechanism whereby behavior is prompted automatically by situational cues, as a result of learned cue-behavior associations. Gardner [15] further specifies that the automatic component is the activation of impulse towards action and not the behavior itself, which may still require deliberate control/regulation. Once instigated, behaviors which have been performed repeatedly and consistently in the past are then enacted with minimal forethought [15]. Habit has been found to be strongly associated with treatment adherence across chronic conditions [16, 17]. It has only been explored in qualitative research among PwMS [11]: youth view medication adherence as dependent on building and maintaining habits related to medication adherence.

The majority of studies measured habit strength using the self-report habit index (SRHI, [18]) or sub-sets of items, e.g., self-report behavioral automaticity index [19]. Recent work suggests that the SRHI is a multi-dimensional construct consisting of (1) history of behavioral repetition, expressed as frequent or repeated behavior, (2) performed without awareness (i.e., lack of awareness) and (3) experienced as difficult to control (i.e., lack of control) [20].

As a habit-based approach has a potential to promote the repetition of the target behavior of medication taking, the present work aims to examine habit in medication taking among persons with relapsing-remitting multiple sclerosis (PwRRMS) during the first year of a prescription, differentiating between repetition and the other two dimensions which may occur less in the context of medication, especially if it involves injections. Previous work [21]on this sample examined habit as an index (and not its dimensions) and found it was associated with persistence and not adherence; this previous work also operationalized adherence in dichotomous terms (yes/no), thus decreasing variance and potential association [22]. It also found that adherence was consistently associated with perceptions on medication, specifically concern, overtreatment and harm perceptions. Accordingly, the aims and hypotheses of the current study were the following:

1. To examine the three habit dimensions (repetition, lack of awareness, lack of control) of the SRHI among PwRRMS newly initiated on DMT across a span of a year in three measurement points. We hypothesized that repetition will be higher than lack of control and lack of awareness and that all dimensions of habit will increase over time, as an expression of increased adaptation to the medication.
2. To examine the above dimensions by mode of DMT route administration – oral vs. injectable; we hypothesized that lack of awareness and lack of control will be lower in injectable DMTs compared to oral administration.
3. To examine the association between the repetition dimension and habit index of medication taking (adherence and persistence), hypothesizing that higher repetition will be associated with more medication taking.
4. To examine the association between the repetition dimension and beliefs about medication, hypothesized a negative association so that the higher concerns, perception of overtreatment and harm in medication, the lower will be the repetition in medication taking.

A research question pertaining to a possible association between habit dimensions and index with clinical characteristics of MS duration and physical disability was posed.

**Methods**

**Participants**

PwRRMS treated with DMTs at Carmel Medical Center’s specialized MS clinic in Haifa, Israel responded at baseline, 6 months later (Time 1) and 12 months (Time 2) since baseline. This analysis includes only those in their first year of DMT medication (n=140); those who were just initiated for new medication did not fill out the habit measure at baseline (n=50) are hence included in only some of the analyses. Recruitment is depicted at Figure 1.

A prospective observational study design was used. Data were collected in a large single center between February 2016 and February 2019. Inclusion criteria were: R, RMS diagnosis, being at baseline on DMT of Fingolimod, Dimethyl Fumarate, Interferon beta-1a and Glatiramer Acetate, the most often self-administered medication prescribed at the clinic at the time. Exclusion criteria at recruitment were: language literacy, cognitive impairment, disinclination to participate and moving to another clinic. The surveys were administered prospectively at the clinic at baseline, 6 months (Time 1, median length of 6.9 months) and 12 months later (Time 2, median length of 6.8 months from Time 1) using a tablet. Neurological evaluations were made during respective clinic visits. Medication possession data were retrieved retrospectively for the same periods.

The study was approved by an Internal Review Board of Carmel Medical Center (#0061-14-CMC) and registered (clinical trials registry #NCT02488343). All participants were provided written informed consent forms confirming that they were free to leave the study at any time and that their data may be published without identifying information.

**Measures**

**Adherence and Persistence**. Medication withdrawal records were retrieved from the computerized dataset of 'Clalit Health Services'; these were available for 103 PwMS in the prospective study who are members of this Health Maintenance Organization (HMO) but not for 37 PwMS treated at the clinic yet are members of other HMOs. Based on medication withdrawal data, Medication Possession Ratio (MPR) was computed for each PwMS based on her/his medication type and the initial prescription: it was estimated as the total days with index medication supply within the refill interval (six months between baseline and Time 1 and six months between Time 1 and Time 2) divided by the number of days between the first prescription data and the last prescription date. Using the commonly accepted threshold of MPR ≥ 80% [8], PwMS were considered adherent if they were above the threshold and non-adherent when they were below this threshold.

**Multiple Sclerosis Treatment Adherence Questionnaire** (MS-TAQ; [23]). The items from MS-TAQ used in this analysis assessed whether the participant did not take a prescribed dose in the last four weeks and the reported number of these doses. In cases of reported non-adherence, the percentage was calculated per regiment.

**Probabilistic Medication Adherence Scale** (ProMAS; [24]). The ProMAS is an overall estimation 18-item questionnaire assessing adherence behaviors (e.g., "I have never changed my medicine use myself", "When I am away from home, I occasionally do not take my medicines") to which respondents indicate 'yes, true' (coded as 1) or 'no, not true' (coded as 0). Higher individual's adherence scores represent better adherence rates. Adherence categories are low (sum score 0-4), medium low (sum score 5-9), medium-high (sum score 10-14) and high (sum score 15-18). Internal reliabilities of the ProMas were baseline=0.83, Time 1=0.82 and Time 2=0.83.

An adherence score was constructed so that good adherence was defined as *either* => 80% medication claims per regiment (medication possession ratio (MPR)) or => 80% self-reported medication use by MS-TAQ or being at the medium-high and high categories of ProMAS. Full details are described in a methodological report [25]. Low adherence was defined as the complement to good adherence. Persistence was defined as staying with the same medication from baseline to Time 2.

**Habit***. Self Report Habit Index* (SRHI; [26]) is a 12-item PRO assessing habit strength, specifically repetition, automaticity of medication taking behavior and the sense of identity the medication behavior reflects (in either administration route).  The items were measured on a seven-point bipolar scale, ranging from ‘I completely agree’ (1) to ‘I completely disagree’ (7). An overall index for habit strength was constructed whereby higher values denoted more habit. Cronbach's internal reliabilities were α=0.86, α=0.88 and α=0.86 for baseline and Time 1, respectively. Cronbach's internal reliabilities were also calculated for the three different dimensions separately. For repetition the reliabilities were α=0.78, α=0.69 and α=0.68, for baseline, Time 1 and Time 2, respectively. Reliabilities for lack of awareness were α=0.84, α=0.87 and α=0.81, for baseline, Time 1 and Time 2, respectively. Reliabilities for lack of control were α=0.77, α=0.77 and α=0.78, for baseline, Time 1 and Time 2, respectively. Sub-scales scores were constructed whereby higher values denoted more repetition, lack of awareness and lack of control.

*Belief about Medicine Questionnaire* (BMQ; [27] is used to assess the cognitive representations of medicines. The 18-item scale contains two five-item subscales measuring Necessity and Concerns about medication and two four-item subscales measuring Harm and Overuse. Scores on this measure were constructed so that higher scores indicate stronger beliefs in the concepts represented by the scale. Internal reliabilities were α=0.81 for both baseline and Time 1; internal reliabilities of the subscales ranged from α=0.71 to α=0.83.

Background and clinical variables examined for this study included age, gender, marital status, educational attainment and subjective social economic status, ethnicity, comorbidity, MS duration, time on current DMT and type of DMT. *Physical disability* was assessed by a neurologist using a widely used scale of disease progression and neurological impairment (Kurtzke Expanded Disability StatusScale, EDSS;[28]).

**Statistical Analysis**

Descriptive analyses for background and clinical characteristics were conducted and reported for all participants. For categorical variables, counts and percentages are provided whereas means and standard deviations (SDs) are presented for continuous variables. Habit dimension (repetition, lack of awareness and lack of control) scores and index were calculated for baseline, Time 1 and Time 2 and descriptive statistics were presented for those PwMS with scores on all time points (n=90). Then, each dimension was tested by three different repeated measures MANOVA, where time was the within participant variable and mode of DMT route administration (oral or injectable) was the between participant variable. Dimensions at each time point (repetition, lack of control, lack of awareness) were also compared using repeated measures MANOVA, where dimension type was the within participant variable. Finally, associations between the habit dimensions, adherence and persistence in medication taking, beliefs about medications and clinical characteristics were assessed. For adherence and persistence, measured as categorical variables, the Mann-Whitney U test was used, comparing the adherent to non-adherent on the habit dimensions. For beliefs about medication and adherence assessed only by the patient-reported outcome (PRO) of ProMas, Pearson correlation were computed. Statistical significance was set for p<0.05. All statistical analyses were conducted with SPSS version 25.

**Results.**

**Characterization of participants**

The study cohort consisted of 140 PwMS meeting the inclusion criteria and having follow-up data. Their demographic and clinical characteristics at baseline are depicted in Table 1. PwMS were predominantly married women. The majority attainted post-secondary or tertiary education and assessed their economic status as average or above. Comorbidity was reported by 20.4% of PwMS and their average physical disability was relatively low (M=2.62, SD=2.0). Respondents have had MS for a mean duration of 7.48 and were taking the medication under study for a mean duration of 27.6 months. Most respondent were on oral DMT (72) and the minority were on injectable (n=18).

**Habit dimensions: across time and by administration route**

The means of the habit’s sub-dimensions as well as the index are presented in Figure 2. Means presented in Figure 2 are based on reports of PwRMS who had data on all time points (n=86 to 90, depending on the variable). As can be seen, the dimension of repetition is higher than the dimensions of lack of awareness and lack of control and all dimensions increased over time; the index falls in between. A one-way within repeated measures ANOVA was conducted to compare the habit dimensions – repetition, lack of awareness and lack of control – at each time point. Mauchly’s test indicated that the assumption of sphericity had been violated at all time points, χ2(2)=9.98, p=.007, χ2(2)=0.52, p=.770, χ2(2)=.80, p=.670, respectively at baseline, Time 1 and Time 2. The dimensions were significantly different from one another at baseline, Wilks’ Lambda = 0.55, *F* (1,88) = 40.09, *p* <.000, ηp2= 0.313; at time 1 Wilks’ Lambda = 0.55, *F* (1,86) = 35.49, *p* <.000, ηp2= 0.292 and also at time 2: Wilks’ Lambda = 0.66, *F* (1,85) = 35.88, *p* <.000, ηp2= 0.297.

A one-way within repeated measures ANOVA was conducted to compare the effect of time and administration route on habit dimensions – repetition, lack of awareness and lack of control. Means are presented in Figure 3. Mauchly’s test indicated that the assumption of sphericity had not been violated, χ2(2)=4.01, p=.134, χ2(2)=0.52, p=.770, χ2(2)=.80, p=.670, in all three habit dimensions respectively. In the repetition dimension, there was a significant effect of the time, Wilks’ Lambda = 0.89, *F* (2,81) = 4.55, *p* =.013, ηp2= .010 so that repetition increased over time. There was no significant effect of administration route, *F* (1,82) = 1.14, *p* =.290, ηp2= .014 and no interaction between time and administration route *F* (2,82) = 0.34, *p* =.565.

In the lack of awareness dimension (n=85), there was also a significant effect of the time, Wilks’ Lambda = 0.90, *F* (2,82) = 4.55, *p* =.013, ηp2= .010, but contrary to our hypothesis, there was no significant effect of administration route, *F* (1,119) = 1.68, *p* =.198, ηp2= .020, and no interaction *F* (2,83) = 0.47, *p* =.627, ηp2 = .006. In the lack of control dimension, however, there was no significant effect of time, Wilks’ Lambda = 0.93, *F* (2,82) = 2.17, *p* =.144, ηp2= .068, no significant effect of administration route, *F* (1,83) = 0.79, *p* =.377, ηp2= .009 and no significant interaction *F* (2,83) = 1.79, *p* =.184, ηp2 = .021.

Lastly, the index of habit yielded a significant effect of the time, Wilks’ Lambda = 0.89, *F* (2, 84) = 5.19, *p* =.008, ηp2= .110, but contrary to our hypothesis, there was no significant effect of administration route, *F* (1,85) = 0.81, *p* =.453, ηp2= .007, and no interaction *F* (2, 84) = 0.82, *p* =.444, ηp2 = .019.

**Association between habit to medication beliefs, medication adherence and persistence**

**Habit (repetition) and medication beliefs** .The associations between the repetition dimension of habit at the three time points and beliefs about medication were examined. Concerns about medication at Time 1 were significantly negatively associated with repetition at Time 1, Time 2, and Time 3, *r*= -0.17, *p*=.057, *r*= -0.18, *p*=.027, *r*= -0.15, *p*=.045, respectively; belief on overtreatment at Time 1 was also prospectively predicted repetition in Time 2, *r*= -0.18, *p*=.042. Perceptions at Time 2 were associated with repetition both cross sectionally and prospectively. Specifically, overtreatment perceptions were associated negatively with repetition at Time 2 and Time 3, *r*= -0.18, *p*=.016, *r*= -0.22, *p*=.017, respectively. Likewise, harm perceptions were associated negatively with repetition at Time 2 and Time 3, *r*= -0.16, *p*=.035, *r*= -0.19, *p*=.017, respectively. All medication perceptions examined at Time 3 were negatively associated cross-sectionally with repetition at Time 3: *r*= -0.20, *p*=.013, *r*= -0.21, *p*=.009, *r*= -0.16, *p*=.036, for concern, over-treatment, and harm, respectively. From Time 1 to Time 3, more beliefs on medication were associated with reported repetition.

**Habit (repetition) with adherence and persistence.** The association between repetition and medication taking was examined both on the responses to a PRO (ProMas), a continuous variable, and on the dichotomous measures of adherence and persistence comprised of being identified as non-adherent *either* by a PRO (i.e., ProMas or MS-TAQ) or MPR. These analyses were carried on all PwRMS in the sample (n=140).

The dimension of repetition, hypothesized to be positively associated with adherence, was examined both cross-sectionally and prospectively with the next time point. Repetition at Time 1 was associated with adherence as measured by the PRO ProMas at Time 1 (*r*=0.25, *p*=.027) but not with Time 2 nor Time 3 (P’s >0.05). Repetition at Time 2 and Time 3 were insignificantly associated with ProMas at these time points. Mann-Whitney U test, comparing PwRRMS who were adherent at Time 1 and Time 2 to non-adherent PwRRMS, found no significant difference between the two groups on repetition (*p*’s>0.05). Conversely, PwRRMS who were persistent in their medication were significantly different from those not persistent both in the baseline repetition dimension (Mean=5.43, SD = 1.70 vs. Mean=4.85, SD = 1.70), *U* =630.50, *p*= 0.012 and in the baseline habit index (Mean=5.43, SD = 1.70 vs. Mean=4.85, SD = 1.70), *U* =683.50, *p*= 0.030 but not in repetition at other time points.

**Association between habit dimensions and clinical characteristics**

Association between habit dimensions and the clinical characteristics of MS duration and physical disability was computed. Baseline habit index was significantly associated with physical disability (*r*=0.23, *p*=.031) and not with MS duration (*p* > 0.05).

**Discussion**

Habitual behavior in medication-taking behavior is highly relevant to every person with a chronic condition or with dependence on medication treatment. However, though many studies examined adherence and persistence among PwMS, they tended to focus on demographic variables, which are not amenable to change, or on side effects or the complexity of the medication adherence, which are also not easily modified. No studies focused on PwRRMS’ medication-taking habits over time.

This study is first in examining habits in medication-taking among PwRRMS across time and habit dimensions and has unraveled several important findings. First, the repetition dimension was found different than lack of control and lack of awareness, thus supporting Hypothesis 1. Specifically, the latter two were low, compared to repetition, indicating that the habit is not well-ingrained and has not become automatic. The second finding was that repetition and lack of awareness increased over time during the first year of medication-taking while there was no time effect in lack of control. This only partially supported Hypothesis 1. Third, the habit dimensions – repetition, lack of control and lack of awareness – were not different across the administration routes of oral and injectable DMTs. Fourth, the repetition dimension was significantly positively associated with persistence so that those who persisted had a higher repetition score at baseline than non-persisters. Repetition was also significantly associated with adherence as assessed by a continuous variable than when assessed by a binary variable. Lastly, the repetition dimension was significantly negatively associated with beliefs about medication, so that people who had concerns about their medication and believed medications to be harmful and overused repeated the behavior less often. These associations were evident in more sub-scales of the medication beliefs as time progressed from baseline to Time 2.

**\*\*\*\*\*\*\*\*\*\*\*\*newly written \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\***

The division of the SRHI into three subscales uncovered that repetition was higher than lack of control and lack of awareness and increased over time. The association of repetition with adherence and persistence echoes the dictum “past behavior is the best predictor of future behavior” [29, p. 1120], and the many findings on such an association [e.g., 30]. However, the relatively weak associations with adherence measures attests that one variable is not a model that can explain substantial part of the variance and thus that habit may need to be examined within a more comprehensive model [31, 32], possibly including cues to action [33], suggested in a qualitative study among PwMS [11]. These weak associations between habit dimensions and adherence found in the present study were similar to the values found in other studies on medication adherence [31] and lower than in other studies [33].

The association of repetition with adherence was higher when a continuous variable was used to measure adherence and less when a dichotomous variable was employed. This may reflect a methodological feature, whereby higher association is found between continuous variables than dichotomous variables [22]. The association of habit with beliefs about medication is consistent with previous findings, though in a different health condition [33]. **\*\*\*NEW SECTION ENDS**

The low levels of automaticity in medication-taking habit (i.e., lack of control, lack of awareness) identified the dimensions of habit requiring intervention and exemplify the usefulness of focusing on malleable constructs. Interventions, whether integrated into patient support programs of pharmaceutical companies, in medication Apps or in interpersonal dialogue with a healthcare provider (physician, nurse or psychologist), should focus on strategies a person can devise to make the medication habit more automatic and responsive to cues. Moreover, the prospective associations between medication beliefs and repetition point at specific perceptions that need to be discussed with the PwMS. Relatedly, the weak association of the habit index with adherence recorded in this sample [21] may be due to the low values of the control and awareness dimensions.

If habits in medication-taking repeatedly fail to develop, physicians and PwMS encountering issues in medication adherence or persistence may re-consider administration regimen. Such instances may call for considering DMTs which are independent of personal agency, such as periodic regimen administration (e.g. one-e-month or once every six months infusion).

A main strength of the current study is the division of the habit index into its three components: repetition, lack of awareness, and lack of control. This afforded identification of hindrances in the development of habits in medication-taking among PwMS. The low levels of lack of awareness and lack of control also afforded an interpretation for the weak, though significant, association between repetition and adherence, namely that the habit was not well-developed. Another strength is that our data was collected over a year, in three separate time points, on a medium-sized sample. The duration of this study is relatively long, compared with other studies on habit in medication-taking. Thirdly, only a handful of studies in MS directly compared between oral and injectable routes of administration in adherence [34] .

This study also has several limitations. First, some of the latest studies among PwMS assessed medication-taking daily with an objective measure (Sauri-Suárez, et al., 2020; Vališ, et al., 2020). In our study two of the three measurement tools used were based on self-report and were collected on a half-yearly basis. Still, past studies with a similar self-report assessment among PwMS have shown a high level of validity (e.g., Wicks, et al., 2011) and this study also utilized a more objective measurement method (i.e., retrieved data from the pharmacy withdrawals). Second, this study followed participants for only one year and a longer time-period and daily assessment would be an advancement. Third, the examination of association between habit and other variables involved many comparisons and some of the findings could have resulted by chance. Finally, the data was collected at a single centre. This may have attenuated findings, reflecting the unique organizational culture of the specific centre, but it could also be an advantage, allowing for continuity of care in the context of devising and reinforcing habits in medication-taking.

Future studies could thus examine habits using daily ecological monetary assessments, incorporating patient-reported outcomes with objective measures, and testing means of developing and maintaining habits – different cues to action, reinforcements, feedbacks, reminders, and optimal scheduling of all these. Habits may be a useful tool in shaping and maintaining other health behaviours pertinent for PwMS such as diet and physical activity [35, 36]. Lastly, work on habit formation in medication-taking, physical activity and other target behaviors could become part of a therapeutic toolbox focused on the quality of life of the person with chronic disease, tailored to specific person.

To conclude, treatment-related behaviors are repeated through two main mechanisms: automatic processes and reflective means (Phillips, et al., 2016), the former enacted in habits. An increase in habit dimensions of repetition and lack of control was observed among PwRRMS over a one-year time period. However, the dimensions of lack of awareness and lack of control were low, possibly indicating that the automaticity of the habit was not well ingrained and needs further nurturing.

**List of abbreviations**

**DMTs:** disease-modifying therapies

**EDSS**: Expanded Disability StatusScale

**HMO**: Health Maintenance Organization

**MPR**: medication possession ration

**MS**: multiple sclerosis

**MS-TAQ**: Multiple Sclerosis Treatment Adherence Questionnaire)

**PRO**: patient-reported outcomes

**PwMS**: persons with multiple sclerosis

**PwRRMS**: persons with relapsing-remitting multiple sclerosis

**ProMAS:** Probabilistic Medication Adherence Scale

**RRMS**: relapsing-remitting multiple sclerosis

**SRHI:**Self Report Habit Index

**SD**: standard deviations

**Declarations**

1. Ethical approval - the study has been approved by Carmel Medical Center (Haifa, IL) IRB (#0061-14-CMC) and registered (clinical trials registry #NCT02488343). Participants were notified of the research purposes of data collection and consented to the collection of personally identifiable clinical data.
2. Consent for publication – not applicable (no individual data).
3. Data availability - the datasets analyzed during the current study contain identifying information and is therefore unavailable publicly.   Source documents of the research project are securely kept at the MS clinic, Carmel Medical Center, Haifa , Israel and are available from Dr. Miller on reasonable request.
4. Financial Disclosures/competing interests - Dr. Miller has served on the scientific advisory board, and has received personal compensation for consulting and/or speaking activities and/ or honoraria and/or received grant support for research from: Avanir Pharmaceuticals; Bayer-Schering Pharma; Biogen Idec; Mapi Pharma; Medison Pharma Ltd.; Merck Serono; Novartis, Sanofi-Genzyme and Teva Pharmaceutical Industries Ltd.
5. Funding/Support - This work was supported in part by Novartis Pharmaceuticals, Biogen Idec and Merck Serono.
6. Acknowledgements – The authors wish to acknowledge the work of clinic staff who did not work in this specific research project or who worked in the project for a short period in early stages (Sara Dishon, Izabella Lejbkowicz, Sharonne Ratzabi).
7. Authorship – EN contributed to study’s design, data analysis, interpretation and writing; LGM contributed to study’s design, interpretation and writing; AW contributed to data collection; IL contributed to study’s design, data collection, data analysis and interpretation; AM contributed to study’s conception, design, interpretation and writing. All authors approved submission.

1. Filippi M, Bar-Or A, Piehl F, Preziosa P, Solari A, Vukusic S, et al. Multiple sclerosis. Nat Rev Dis Prim. 2018;4:1–27. doi:10.1038/s41572-018-0041-4.

2. Tintore M, Vidal-Jordana A, Sastre-Garriga J. Treatment of multiple sclerosis — success from bench to bedside. Nat Rev Neurol. 2018;:1–3. doi:10.1038/s41582-018-0082-z.

3. Warrender-Sparkes M, Spelman T, Izquierdo G, Trojano M, Lugaresi A, Grand’Maison F, et al. The effect of oral immunomodulatory therapy on treatment uptake and persistence in multiple sclerosis. Mult Scler. 2015;22:520–32.

4. Menzin J, Caon C, Nichols C, White LA, Friedman M, Pill MW. Narrative Review of the Literature on Adherence to Disease-Modifying Therapies Among Patients with Multiple Sclerosis. J Manag Care Pharm. 2013;19 1 Supp A:S24–40.

5. Sánchez Martínez I, Cerdán Sánchez M, López Román J, Iniesta Martínez F, Carreón-Guarnizo E, Meca Lallana JE, et al. Possible Influence of the Route of Treatment Administration on Treatment Adherence in Patients With Multiple Sclerosis. Clin Ther. 2020;:1–13.

6. Reich D, Lucchinetti C, Calabresi PA. Multiple Sclerosis. N Engl J Med. 2018;378:169–80.

7. Hugtenburg J, Timmers L, Elders P, Vervloet M, van Dijk L, Vervloet M, et al. Medication adherence: WHO cares? Mayo Clin Proc. 2011;86:304–14. doi:10.4065/mcp.2010.0575.

8. Haynes RB. A critical review of the “determinants” of patient compliance with therapeutic regimens. In: Sackett D, Haynes R, editors. Compliance with therapeutic regimens. Baltimore, Maryland: Johns Hopkins University Press; 1976. p. 26–39.

9. Conway DS, Cecilia Vieira M, Thompson NR, Parker KN, Meng X, Fox RJ. Patient-Reported Disease-Modifying Therapy Adherence in the Clinic: A Reliable Metric? Mult Scler J - Exp Transl Clin. 2018;4:205521731877789. doi:10.1177/2055217318777894.

10. World Health Organization (WHO). Adherence to long-term therapies; Evidence for action. 2003.

11. Yeh EA, Chiang N, Darshan B, Nejati N, Grover SA, Schwartz CE, et al. Adherence in Youth With Multiple Sclerosis: A Qualitative Assessment of Habit Formation, Barriers, and Facilitators. Qual Health Res. 2019;29:645–57.

12. Unni EJ, Sternbach N, Goren A. Using the Medication Adherence Reasons Scale (MAR-Scale) to identify the reasons for non-adherence across multiple disease conditions. Patient Prefer Adherence. 2019;13:993–1004.

13. Devonshire V, Lapierre Y, Macdonell R, Ramo-Tello C, Patti F, Fontoura P, et al. The Global Adherence Project (GAP): A multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis. Eur J Neurol. 2011;18:69–77.

14. Wood W, Neal DT. A New Look at Habits and the Habit-Goal Interface. Psychol Rev. 2007;114:843–63.

15. Gardner B. A review and analysis of the use of “habit” in understanding, predicting and influencing health-related behaviour. Health Psychol Rev. 2015;9:277–95. doi:10.1080/17437199.2013.876238.

16. Phillips AL, Leventhal H, Leventhal EA. Assessing theoretical predictors of long-term medication adherence: Patients’ treatment-related beliefs, experiential feedback and habit development. Psychol Heal. 2013;28:1135–51.

17. Badawy SM, Shah R, Beg U, Heneghan MaB. Habit Strength, Medication Adherence, and Habit-Based Mobile Health Interventions across Chronic Medical Conditions: Systematic Review. J Med Internet Res. 2020;22:1–15.

18. Horne R, Weinman J, Verplanken B, Orbell S, Horne R, Weinman J, et al. Patients’ beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res. 2019;47:555–67. doi:10.1016/S0022-3999(99)00057-4.

19. Gardner B, Abraham C, Lally P, de Bruijn G-J. Towards parsimony in habit measurement: Testing the convergent and predictive validity of an automaticity subscale of the Self-Report Habit Index. Int J Behav Nutr Phys Act. 2012;9:102. doi:10.1186/1479-5868-9-102.

20. Reyes Fernández B, Monge-Rojas R, Solano López AL, Cardemil E. Re-evaluating the self-report habit index: the cases of physical activity and snacking habits. Psychol Heal. 2019;34:1161–78. doi:10.1080/08870446.2019.1585852.

21. Neter E, Glass-marmor L, Wolkowitz A, Lavi I, Miller A. Beliefs about medication as predictors of medication adherence in a prospective cohort study among persons with multiple sclerosis. BMC Neurol. 2021;:1–9.

22. Cohen J. The cost of dichotomization. Appl Psychol Meas. 1983;7:249–53.

23. Wicks P, Massagli M, Kulkarni A, Dastani H. Use of an online community to develop patient-reported outcome instruments: The multiple sclerosis treatment adherence questionnaire (MS-TAQ). J Med Internet Res. 2011;13.

24. Kleppe M, Lacroix J, Ham J, Midden C. The development of the ProMAS: a Probabilistic Medication Adherence Scale. Patient Prefer Adherence. 2015;9:355–67.

25. Neter E, Wolkowitz A, Glass-Marmor L, Lavi I, Ratzabi S, Leibkovitz I, et al. Multiple modality approach to assess adherence to medications across time in Multiple Sclerosis. Mult Scler Relat Disord. 2020;40:101951.

26. Verplanken B, Orbell S. Reflections on past behavior: A self-report index of habit strength. J Appl Soc Psychol. 2003;33:1313–30.

27. Horne R, Weinman J. Patients’ beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res. 1999;47:555–67.

28. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded\ndisability status scale (EDSS). Neurology. 1983;33:1444–52.

29. Ajzen I. The theory of planned behaviour: Reactions and reflections. Psychol Heal. 2011;26:1113–27.

30. Conner M, Armitage J. Extending the theory of planned behavior: A review and avenues for further research. J Appl Soc Psychol. 1998;28:1429–64.

31. Liddelow C, Mullan B, Boyes M. Understanding the predictors of medication adherence: applying temporal self-regulation theory. Psychol Heal. 2021;36:1–20. doi:10.1080/08870446.2020.1788715.

32. Phipps DJ, Hagger MS, Hamilton K. Evidence that habit moderates the implicit belief-behavior relationship in Health behaviors. Int J Behav Med. 2021. doi:10.1007/s12529-021-09975-z.

33. Phillips LA, Cohen J, Burns E, Abrams J, Renninger S. Self-management of chronic illness: the role of ‘habit’ versus reflective factors in exercise and medication adherence. J Behav Med. 2016;39:1076–91.

34. Munsell M, Frean M, Menzin J, Phillips AL. An evaluation of adherence in patients with multiple sclerosis newly initiating treatment with a self-injectable or an oral disease-modifying drug. Patient Prefer Adherence. 2017;11:55–62.

35. Hagger MS. Habit and physical activity: Theoretical advances, practical implications, and agenda for future research. Psychology of Sport and Exercise. 2019;:118–29.

36. Rebar AL, Rhodes RE, Gardner B. How we are misinterpreting physical activity intention - Behavior relations and what to do about it. Int J Behav Nutr Phys Act. 2019;16:71.

Excluded (n=27):

Language literacy 14

Declined to participate 2

Cognitive impairment 3

Moved to another clinic 8

Participants recruitment (n=226)

Participants screening for eligibility at baseline (n=199)

Time 1 & 2 follow-up (n=140)

Not analyzed at Time 1 or 2 follow-up:

No Time 2 data yet 10

Switched to non-study DMT (e.g., infusion) 3

Being on same medication > 12 months

at baseline 46

**Figure 1. Enrollment of Participants**

**Table 1.**

Baseline demographic and clinical characteristics (N=140)

N (%) M (SD)

Age 37.7 (12.7)

Gender, N (%)

Male 38 (27.1)

Female 102 (72.9)

Marital Status, Married 81 (59.6)

Education\*

Secondary 46 (33.1)

Post-secondary 24 (17.3)

Tertiary 69 (49.6)

Social Economic Status\*

Low 12 (8.8)

Average and above 128 (91.4)

Ethnicity

Jewish 89 (63.6%)

Arab 45 (32.1)

Other 5 (3.6%)

Comorbidity

Yes 27 (20.0)

No 103 (76.3)

Physical disability

EDSS at baseline 2.5 (1.7))

MS duration in years, Mean (SD) 5.9 (6.7)

Time on current DMT in months

Mean (SD) at baseline 1.8 (3.3)

*Note*: EDSS: Expanded Disability Status Scale

\* missing data: education - 1 cases, social economic status - 1 case, comorbidity -10 cases, ethnicity - 1.

Figure 2

Habit dimensions and index across time.

**Figure 3**. Habit dimensions across time and administration route (n=90).