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Impact of an electronic monitoring device and behavioral feedback on adherence to multiple sclerosis therapies in youth: results of a randomized trial

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Availability of data and supporting materials Supporting documentation for our findings is provided in manuscript data and figures and tables. Scientists wishing to gain access to our data may contact the first author (EAY), who will consider such requests on a case-by-case basis, subject to the scientific rigor of the proposed research question.

Compliance with ethical standards

Conflict of interest The authors (SG, VEP, GA, KE, MG, TEM, JM, LM, JN, MO, RS, EW and CES) have no relevant conflicts of interest to disclose. EAY and CES wrote the first draft of the manuscript and neither received an honorarium, grant, or other form of payment to do so. BLB serves as a consultant to Novartis for the purposes of a clinical trial and as an unpaid advisor to Biogen, Teva neuroscience and Sanofi. She is also a chief editor for Multiple Sclerosis and Related Disorders and is on the editorial board for Neurology. JG has received grant funding from the Race to Erase MS, Biogen and Genentech. AW has received grant funding from the National Institutes of Health (USA) and Biogen Idec. EAY receives research funding from NMSS, CMSC, OIRM, SCN, CBMH Chase an Idea, SickKids Foundation, Rare Diseases Foundation, MS Scientific Foundation (Canada), McLaughlin Centre, Mario Batalli Foundation. She performs relapse adjudication for ACI, has received unrestricted funding for a symposium from the Guthy Jackson Charitable Foundation and Teva and has served on a Scientific Advisory Board for Neurotoxicity with Juno Pharmaceuticals.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants and their parent or legal guardian included in this study.

Study Sites We are also grateful for the hard work and dedication of the investigators and study teams at each site (Table 7).

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Abstract

Purpose—To report the results of a randomized controlled trial using an electronic monitoring device (EM) plus a motivational interviewing (MI) intervention to enhance adherence to disease-modifying therapies (DMT) in pediatric MS.

Methods—Fifty-two youth with MS (16.03 ± 2.2 years) were randomized to receive either MI ($n = 25$) (target intervention) or a MS medication video ($n = 27$) (attention control). Primary endpoint was change in adherence. Secondary outcomes included changes in quality of life, well-being and self-efficacy. Random effects modeling and Cohen's effect size computation evaluated intervention impact.

Results—Longitudinal random effect models revealed that the MI group decreased their EM adherence (Group $\times$ Time interaction = -0.19), while increasing frequency of parental DMT reminder (26.01)/administration (11.69). We found decreased EM use in the MI group at 6 months (Cohen's $d = -0.61$), but increased pharmacy refill adherence ($d = 0.23$). Parental reminders about medication increased in MI subjects vs controls ($d = 0.59$ at 3 months; $d = 0.70$ at 6 months). We found increases in self-reported adherence ($d = 0.21$) at 3 but not 6 months, fewer barriers to adherence at three ($d = -0.58$) and six months ($d = -0.31$), better physical ($d = 0.23$ at 3 months; $d = 0.45$ at 6 months), emotional ($d = 0.25$ at 3 months) and self-efficacy function ($d = 0.55$ at 3 months; 0.48 at 6 months), but worse well-being, including self-acceptance ($d = -0.53$ at 6 months) and environmental mastery ($d = -0.42$ at 3 and 6 months) in intervention as compared to control patients.

Conclusions—Participants receiving MI + EM experienced worsening on objective measures of adherence and increased parental involvement, but improved on some self- and parent-reported measures. MI participants reported improvements in quality of life and self-efficacy, but worsened well-being.

Keywords

Multiple sclerosis; Pediatric; Quality of life; Well-being; Behavioral intervention

Introduction

Disease-modifying therapies (DMTs) are being used widely for children and adolescents with MS [1]. Literature regarding medication adherence in pediatric MS is limited, but two studies have suggested poor medication adherence in up to 70% of this population [1–3]. Adolescence poses specific challenges with regard to medication adherence due to an increase in risk-taking behaviors, greater reliance on peers and growing independence.

Interventions for medication adherence that have been studied may be grouped into (1) patient education; (2) changes in medication administration, i.e., improving dosing schedules; (3) improving physician/patient communication; (4) improving access to care; and (5) behavioral/family interventions. Of these, behavioral and multi-component interventions are most effective, with one meta-analysis of psychological approaches to promoting adherence in pediatric chronic conditions showing a medium effect size for behavioral, but only a small effect size for educational interventions [4]. A subsequent meta-analysis using a different methodology found similar effect sizes for multifaceted and behavioral interventions and negligible effect sizes for purely technological interventions, such as multimedia computer programs or video games [5, 6]. All of these studies have been small and have shown only small to medium effects.

Effective, multi-component interventions that include cognitive-behavioral approaches are costly and time-consuming to administer, as they involve individual visits with a therapist on a weekly basis. They may not suit patients who must travel long distances for care. Conversely, behavioral approaches, which focus on behavioral change using specific interview techniques, are simple to administer, and their efficacy is straightforward to evaluate. Among these techniques, motivational interviewing (MI) has been widely used to encourage self-directed motivation for behavioral change. MI uses interview techniques focused on open-ended questions, collaboration and reflective questioning. It has been shown to be effective in promoting lifestyle change [7]. The effectiveness of this approach may be augmented by the use of an electronic monitoring (EM) device, such that information from the electronic device is combined with MI-based feedback administered by a behavioral therapist. Feedback with EM devices has enhanced adherence to medication use in adult HIV, [8] adult hypertension [9] and pediatric asthma [10–12].

There have been no studies to date of adolescents or children with MS using EM with MI-based feedback as an interventional tool despite the critical benefit to be gained by maximizing adherence to DMT to prevent disability progression. Here, we report the results of a randomized controlled trial of EM plus MI feedback to enhance medication adherence in pediatric MS.

Methods

This study was approved by the institutional review boards of all participating centers (Table 1). We recruited subjects from nine pediatric MS clinics from North America from October 2013 to January 2016 (Fig. 1). All patients were screened by local study personnel for eligibility and enrolled in the study if eligible and in agreement. Eligibility criteria included age 10–18, MS diagnosis using revised McDonald diagnostic criteria and International Pediatric MS Study Group criteria, [13, 14] and exposure to MS DMT for 6 months. Exclusion criteria were (1) use of IV DMT (e.g., natalizumab) or (2) being non-English speaking as our intervention was only available in English. Parent or guardian completed questionnaires complementary to the patient self-reports. Participants were randomized into either the behavioral feedback or attention control intervention. The randomization was stratified by: (1) oral versus injectable DMT; (2) whether the DMT injection is administered by the child's parent/guardian. Randomization took place after the baseline questionnaire was completed. A random number list for each of the strata was created (i.e., four columns of randomly assigned group listings) and assigned people in the order listed by strata. The study schema is shown in Fig. 2.

Interventions

The behavioral feedback + electronic monitoring device (MEMS cap) intervention was implemented from the Hospital for Sick Children by a group of behavioral interventionists who received certified MI training. Subjects received a supplemental device which downloaded their adherence data from the MEMS cap for use by the behavioral interventionist during a telephone feedback session. The behavioral interventionist scheduled three monthly telephone calls with participants at 1, 2 and 3 months post-enrollment and, during each call, used a standard MI script which focused on goals related to DMT adherence and problem-solving around barriers to adherence. Parents were not involved in phone calls.

MI fidelity—Fidelity of the MI interviews was analyzed following established methods by a MI-trained psychologist blinded to subject status (adherence status) and interviewer. Transcribed interviews were coded according to the Motivational Interviewing Integrity (MITI) Code two times on two separate occasions. Fidelity scores were calculated using the following formulas: *Global Spirit Score* = (Evocation + Collaboration + Autonomy/Support)/3; *Proportion Complex Reflection* = Complex Reflection/(Complex Reflection + Simple Reflection); *Proportion Open-ended Questions* = Open-ended questions/(Open-ended questions + closed-ended questions); *Proportion MI Adherent* = Proportion of MI adherent counts/(Counts of MI Adherence + Counts of MI non-adherence); *Ratio of Reflections to Questions* = (Simple Reflections + Complex Reflections)/(Open-ended Questions + Closed-Ended Questions). *Global ratings* are rated on a scale of 1–5. Behavior counts are indicative of the number of times the outcome was used in the middle 20 min of the interview. Means were computed for each component on the MITI Coding Sheet as well as the composite scores recommended by the MITI [15]. *Fidelity cutoffs* recommended by the MITI were the following for beginning competency and competency, respectively:

Global Spirit Score (3.5, 4); Proportion Complex Reflection (0.4, 0.5), Proportion Open Questions (0.5, 0.7), Proportion MI adherent (0.9, 1.0), Reflection:Question ratio (1, 2).

The attention control intervention consisted of a video related to DMT in pediatric MS. Use of this as the attention control intervention follows work that points to small to negligible effect sizes of purely educational approaches (mean $d = 0.16$, 95% CI = 0.10–0.22) and technological interventions (mean $d = 0.08$, 95% CI = 0.09–0.25) on adherence [4, 16]. The participants were asked to complete a satisfaction questionnaire after the video to ensure completion of the task. The video was sent to the participants three times at 1, 2 and 3 months post-enrollment by email as a link to the SurveyGizmo Web site.

Measures

Primary outcome—Adherence was measured using five objective and self-report methods focusing on different time frames and behaviors (Table 2). Objective sources of information included: (A) *pharmacy refill data* provided by site coordinators for 12 months prior to study entry and for 6 months post-study entry and (B) the *MEMS cap*, an EM device (MEMS, AARDEX) that captures each time the patient discards a needle from their injection or opens their pill bottle. Adherence information from MEMS caps is downloaded and stored on a secured web-platform (medAmigo™). These data were used to compile drug-dosing history data and to calculate medication adherence during the course of the study for baseline to one month; months 1–3; and months 3–6. Self-reported adherence from patients and parents included: (A) the *Morisky Adherence Measure*, a widely used 8-item patient-/parent-reported measure with documented reliability and validity [17]. The following scoring algorithm was used: 8 = high adherence, 6–7 = medium adherence, and <6=low adherence. (B) The *Multiple Sclerosis Treatment Adherence Questionnaire (MSTAQ)*, which assesses missed doses, side effects and barriers of taking DMTs, and behavioral coping strategies used (e.g., icing the injection site, taking pain medication) over the past four weeks [18]. We adapted the MSTAQ to include both oral and injectable medications. We used a standardized scoring algorithm, where higher scores reflected numbers of missed doses, side effects, barriers, or behavioral coping strategies. Subjects completed only the barriers items, and the parent completed all items. (C) *Parental involvement in DMT administration* was tracked with the proportion of time (labeled as 0-25-50-75-100%) the parent reported (1) *reminding* the child to take her/his DMT; (2) *being present* when the child took her/his DMT; and (3) *administering* the child's DMT.

Adherence definition—Whereas for most analyses we kept adherence variables continuous, for those analyses where we sought to characterize a non-adherent subgroup, we used the widely accepted cutoff for characterizing non-adherence as missing 20% of doses, either from pharmacy refill or from parent-reported data [19]. Because each adherence variable addressed a different time frame and they did not factor-analyze into one score, we analyzed the variables separately.

Secondary outcomes: quality of life and psychosocial outcomes—Secondary outcomes focused on patient-reported outcomes reflecting quality of life (QOL) and psychosocial well-being. Questionnaires were completed at baseline, 3 and 6 months. *QOL*

was measured by: (1) the 23-item Pediatric QOL Inventory (PedsQL) measure of physical, social, emotional, and school functioning (Child/Teen report). The PedsQL has documented reliability and validity [20]. (2) *Cognitive Functioning* was assessed using the informant-report version of the MS Neuropsychological Screening Assessment Questionnaire (MSNQ) [21]. This tool has documented high test–retest stability and predictive and construct validity. Informant reports correlate with cognitive dysfunction and are less biased by patient depression [22].

Psychosocial outcomes—(a) the *MS Self-Efficacy Scale* (MSSE) is a reliable and valid 18-item measure of confidence in one's ability to manage disease symptoms (MSSE Function subscale); and reactions to disease-related limitations and the impact of the disease on life activities (MSSE Control subscale); [23] (b) *Ryff Scales of Psychological Well-Being* (autonomy, environmental mastery and self-acceptance subscales), [24] a reliable and valid measure of well-being that has been used successfully with adolescents [25].

Covariates included demographics and the *Patient-Determined Disease Steps* (PDDS) [26] a measure that correlates highly with the Expanded Disability Status Scale (EDSS) [27]. It characterizes disability level into one of nine steps (0 = normal, 1 = mild disability, 2 = moderate disability, 3 = gait disability, 4 = early cane, 5 = late cane, 6 = bilateral support, 7 = wheelchair or scooter, 8 = bedridden). An informant-reported version of the tool was administered to parent/guardians (the Flesch–Kincaid Grade Level estimate for the PDDS is grade 8.3, suggesting a level appropriate for participants >13 years).

Statistical analysis

Descriptive statistics on the above measures were used to summarize the sample. We examined correlations among the measures of adherence. T tests were used to compare outcomes and demographic characteristics across groups (Table 1). We began by using longitudinal random effects models. Models were computed separately for objective adherence variables as well as parent- and patient-report using each of the above measures as dependent variables. Independent variables were group (behavioral intervention vs. control), time (baseline, 3, 6 months) and the interaction of group and time. We focused on the interaction term to examine whether the intervention had a differential effect over time.

Effect size and sample size calculations—Our sample size was sufficient to yield a large effect size (0.8), 80% power, $\alpha = 0.05$ [28]. In order to evaluate whether the intervention yielded small to medium effect sizes, we characterized mean changes in terms of Cohen's effect sizes (small = 0.20–0.49; medium = 0.5–0.79; and large = 0.80 or larger) [28].

Post hoc analyses sought to test whether the intervention had an impact on patient self-management and to examine differences between those participating the full trial ($n = 52$) in comparison with those who dropped out ($n = 14$) for possible bias. Self-management analyses began by using factor analysis to create a self-management score for patients and parents. Random effects models and effect size computations were then used to examine whether there were differences over time on the self-management scores. Selection bias analyses were performed by computing effect sizes comparing mean baseline results from

participants/parents who provided baseline data only as compared to those provided data for two or all three time points.

All analyses were performed using Stata 14 [29].

Results

Sample characteristics

The demographic characteristics of the two randomization groups were not significantly different (Table 1). Two-thirds of the sample was on an injectable DMT and one-third on an oral DMT. The sample had a low level of disability at baseline. Table 3 shows the descriptive statistics over time for the patient- and parent-reported outcomes.

MI fidelity metrics

Overall, the behavioral interventionists (MI facilitators) used for this study were at or above competency level in Global Spirit Score (4.12 ± 0.3), Proportion Complex Reflection (0.57 ± 0.13), Proportion Open Questions (0.57 ± 0.11) and lower than beginning competency in Proportion MI Adherent (0.87 ± 0.16), and Reflection: Question ratio (0.69 ± 0.4).

Estimates of adherence and inter-correlations

Depending on the adherence measure used, 1–41% of the sample was non-adherent at baseline. Those who were poor adherers using MEMS cap data at baseline tended to drop out. Among those with good adherence, those with lower adherence scores had lower adherence scores at 3- and 6-month follow-up (Fisher's exact $p = 0.003$, <0.0001 , respectively). Table 4 shows a correlation matrix with the adherence measures used in this study included.

Impact of the intervention over time

Primary outcomes—Results of the random effects models revealed significant or trend group-by-time interactions on MEMS cap adherence (6 months, $p < 0.10$), parent-reported reminding (6 months, $p < 0.05$), and administering (3 months, $p < 0.10$) the DMT (Table 5). Table 2 shows group means at each time point as well as effect sizes. The intervention group decreased their MEMS cap adherence, while increasing how often their parents reminded and administered their DMT. The intervention group exhibited lower MEMS cap adherence (both at 3 and at 6 months) but better pharmacy refill adherence (at 6 months) compared to the control group, and no difference on parent-reported proportion missed doses over time (Fig. 3). Parents of youth receiving the behavioral intervention reported increasing reminding (3–6 months, $d = 0.59, 0.70$), being present (6 months, $d = 0.35$), and administering the DMT (3 and 6 months, $d = 0.33, 0.29$) over time, better Morisky adherence (3 months, $d = 0.21$), more MSTAQ Barriers ($d = 0.45$) and MSTAQ Side Effects ($d = 0.44$), and fewer MSTAQ Behavioral Coping Strategies (3 months, $d = -0.39$, 6 months $d = -0.68$), compared to the control group. While the behavioral intervention patients also reported better Morisky adherence (3 months, $d = 0.21$), they reported fewer MSTAQ Barriers (3 months, $d = -0.58$, 6 months, $d = -0.31$) over time compared to the control group (Table 2).

Secondary outcomes—Results of the random effect models revealed significant or trend group-by-time interactions on patient-reported PedsQL physical functioning (6 months, $p < 0.10$) and MSSE Control (3 months, $p < 0.05$; Table 5). An examination of mean changes shows that intervention patients reported better MSSE Functioning ($d = 0.64$) and MSSE control ($d = 0.43$) compared to the control group (Table 2). The effect size comparisons revealed that intervention patients had worse parent-reported MSNQ cognitive and PedsQL school functioning over time (6 months, $d = -0.22$, and 3 months, $d = -0.35$, respectively), but improved PedsQL Physical Functioning (3 months, $d = 0.36$ and 6 months, $d = 0.21$) compared to the control group. Intervention patients reported better MSSE Function and control (3 months, $d = 0.55, 0.54$, and 6 months, $d = 0.48, 0.21$ respectively), and better PedsQL Physical (3 months, $d = 0.23$ and 6 months, $d = 0.45$), Emotional (3 months, $d = 0.25$) and Social (3 months, $d = 0.25$) Functioning. Conversely, they reported worse well-being outcomes, i.e., lower Ryff Self-Acceptance (6 months, $d = -0.53$) and Ryff Environmental Mastery (3 months, $d = -0.42$ and 6 months, $d = -0.42$), compared to control patients (Table 2).

Changes in self-management—Rotated factor analyses created two parent- and two patient-reported self-management scores. The first parent-reported self-management factor score—*Behavioral Involvement*—summarized the Present, Administer, and MSTAQ Behavioral Coping scores, and the second factor score—*Cognitive Involvement*—summarized the Remind and MSNQ Cognitive Function scores (eigenvalues = 2.18 and 1.24). The first patient-reported self-management factor score—*Self-Efficacy*—summarized the MSSE Function and control scores, and the second factor score—*Well-Being*—summarized the Ryff Autonomy, Self-Acceptance, and Environmental Mastery scores (eigenvalues = 1.89 and 1.52). Results of the random effect models revealed significant or trend group-by-time interactions on Cognitive Involvement (6 months, $p < 0.05$) and Self-efficacy (3 months, $p < 0.10$). Effect size comparisons revealed that the intervention group had more Cognitive Involvement at 6 months, better Self-efficacy at 3 and 6 months, but worse Well-Being at 3 and 6 months, compared to the control group (Table 2).

Selection biases—While an intention-to-treat analysis is ideal, it was not possible to implement such in the present study because 14 (21%) of the 66 randomized participants provided only baseline data. A next best alternative is to examine potential selection biases in the study sample. Table 6 shows results of effect size comparisons of the sample lost to follow-up with the analytic sample. It revealed that patients who opted out of the study after randomization were younger and had parents with less-than-college education. They were more likely to speak English as a primary language and less likely to have an Individualized Education Program. On the primary adherence outcomes, they had lower adherence on “pharmacy refills” and on “proportion missed doses,” higher utilization of behavioral coping, worse side effects, worse barriers (parent and patient), and worse patient-reported Morisky adherence scores. Those lost to follow-up also had worse parent-reported PedsQL Physical, Emotional, Social, and School Functioning. They had worse patient-reported MSSE Control, Ryff Autonomy, Self-Acceptance and Environmental Mastery, and worse PedsQL Physical, Emotional, and School Functioning (Table 6).

Discussion

While youth participating in our trial started with and maintained high levels of medication adherence using most adherence measures, several interesting and potentially contradictory findings emerged. We found improvements which were sustained at 3 and 6 months in self-efficacy (MSSE function and control) and patient- and parent-reported physical function, but found sustained decreases in patient-reported environmental mastery in those receiving the intervention versus controls. Small deterioration in parent-reported school function and small improvements in patient-reported emotional and social function were seen at 3 months but not sustained at 6 months.

Adherence rates in most measures showed small effect size changes. We found a modest effect on rates of pharmacy refills and parent-reported adherence (Morisky) at three months, which was not sustained at six months, in the intervention group compared to the control group. However, surprisingly there was a *marked* drop in use of the EM device in the last three months of the study in the intervention group but not the control group. Reasons for the discrepancy in MEMS cap data versus self-report and refill data are unknown, but may include less attention to day-to-day study procedures following the completion of the behavioral intervention cycle of interviews, or a true decrease in medication adherence due to the lack of the behavioral interventionist reminding the patient to use the study materials. Remarkably, we saw *increased* parental reminders at the 6-month mark in comparison with the 3-month mark, with concomitant increasing drop-off in MEMS cap use in subjects. The directionality of this association is unknown: Did parents remind more frequently due to noticed drop-off in medication use OR did children decrease their medication use as parents increased their reminders? Differences between the behavior of the intervention versus control groups suggest the need for further, more granular analysis about what may have led to the behavioral change in the intervention group. This question will be addressed in a phenomenological assessment of interview data from this cohort.

Development of self-management skills constitutes one of the key elements to successful transition to adulthood and is especially important in youth with chronic illness [30]. While the primary goal of the trial was to change adherence, methods used in our intervention were aimed at providing tools for increasing self-management. We found some important secondary effects of the intervention including increased skills that may improve self-management, as reflected in increased self-efficacy scores. Concomitantly and perhaps reflecting increased parental involvement in adherence, parents of the intervention group reported decreases in cognitive and school functioning over time, and the children reported decreased self-acceptance and environmental mastery. This phenomenon was not seen in the control group.

Furthermore, parent reports from intervention participants described more barriers, side effects and fewer behavioral coping strategies. It is possible that even if parents were not involved in behavioral feedback calls, use of MI led to greater parental involvement and changes in awareness of cognitive challenges that the youth were facing. Whether this increase in parental involvement was beneficial or detrimental to self-management remains to be seen, but decreases in MEMS cap use by intervention participants suggest the need to

explore the effect of increasing parental involvement on medication adherence. Design of future interventions involving adolescents with MS should consider this striking observation.

Importantly, we found inconsistency between parents and patients on several outcomes, including barriers to adherence, PedsQL Emotional, Social, and School Function, which suggests that parents and children interpret their experiences differently and/or attend to different factors when evaluating the same variables/items. This phenomenon has been widely reported [31, 32] and emphasizes the need to seek both parent and child perspectives in research on evaluative constructs such as quality of life.

One of the most striking findings from our study was that youth who may have benefited most from the intervention dropped out from the study after consent. Youth in the group lost to follow-up represented 21% of the consented population. They were more likely to be non-adherent, had lower parental education, lower parent-reported and self-reported quality of life scores, and lower self-reported self-efficacy (MSSE control) and autonomy, self-acceptance, and environmental mastery scores (Ryff). The study was explicitly set up to address concerns of attrition and participation by offering a flexible, telephone-based intervention, perhaps mitigating a higher attrition rate. Nonetheless, based on these findings, it is clear that barriers unique to documented characteristics of those lost to follow-up must be addressed in future studies.

This study has limitations. The relatively few statistically significant differences comparing intervention and control groups are likely due to low power to detect the medium to small effect sizes generally found in behavioral intervention studies [33, 34]. In quality-of-life studies, a moderate effect size is generally considered to be a clinically relevant [35]. Our analysis focus on characterizing effect sizes yields valuable information on the impact of the intervention on change, some of which are clinically important and others of which are small effect sizes that are relevant nonetheless [35].

In addition, blinded fidelity assessment of the MI interviews suggested greater adherence to MI principles in some domains of fidelity than others: The intervention therefore could have had a greater effect if there had been a higher level of overall fidelity to these principles. Duration of follow-up was limited to 6 months. Finally, the high rates of baseline adherence in our cohort not only restricted our ability to improve adherence levels, but also make regression to the mean a possible explanation for any putative worsening in adherence outcomes.

In summary, in this cohort of youth with MS, increased pharmacy refills, increases in self-reported adherence, increases in quality of life and self-efficacy but decreases in well-being and use of an EM device were documented after the use of an intervention combining an EM device and MI-based feedback. This may have long-term implications for youth with MS, as these factors play strongly into future independence and disease management. Strategies for engaging youth and maintaining their engagement are important and necessary in future trials.

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Abbreviations

DMT	Disease-modifying therapy
EM	Electronic monitoring
MI	Motivational interviewing
MS	Multiple sclerosis
MSSE	MS Self-Efficacy Scale
MSTAQ	Multiple Sclerosis Treatment Adherence Questionnaire
PedsQL	Pediatric Quality of Life Inventory
SD	Standard deviation

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Pediatric MS Adherence Study Group

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Fig. 1.
Recruitment flow chart

Fig. 2.
Study schema

Fig. 3.
Bar chart showing adherence results

Table 1

Sample demographics by randomization group

Variable	Whole sample (n = 52)	Control (n = 27)	Intervention (n = 25)	p value
Mean age (sd)	16.03 (2.20)	15.76 (2.52)	16.32 (1.81)	0.37
Mean age at diagnosis (sd)	13.62 (2.27)	13.18 (2.28)	14.11 (2.21)	0.14
Mean age at menarche (sd)	11.55 (1.21)	11.50 (1.15)	11.60 (1.30)	0.82
How often did you remind your child to take his/her medications? (proportion of time, expressed in %) (mean, sd)	44.61 (38.83)	51.85 (40.98)	36.46 (35.34)	0.16
How often were you present during the administration of your child's medication? (proportion of time, expressed in %) (mean, sd)	65.20 (37.11)	66.67 (34.67)	63.54 (40.36)	0.77
How often did you administer the medication to your child? (proportion of time, expressed in %) (mean, sd)	36.27 (41.33)	37.96 (41.82)	34.38 (41.58)	0.76
Mean PDDS (sd)	0.47 (0.84)	0.60 (0.91)	0.33 (0.76)	0.27
Mean informant-reported MSNQ (sd)	17.90 (13.42)	17.81 (13.84)	18.0 (13.23)	0.96
Mean EDSS (sd)	1.23 (1.01)	1.09 (0.94)	1.38 (1.07)	0.31
Gender (% female)				
Female	65.38	59.26	72	0.34
Race (% White)				
White	44.23	40.74	48	0.60
Mother education (%)				
Less than college	50	55.56	44	0.40
College degree or more	46.15	40.74	52	
Missing	3.85	3.7	4	
Father education (%)				
Less than college	61.54	74.07	48	0.08
College degree or more	36.54	25.93	48	
Missing	1.92	0	4	
Mode of administration (%)				
Paper and pencil	21.15	25.93	16	0.34
Computer	76.92	70.37	84	
Missing	1.92	3.7	0	
Tobacco use (%)				
No	90.38	92.59	88	0.80
Yes, occasionally	3.85	3.7	4	
Prefer not to answer	5.77	3.7	8	
Primary language (%)				
English	82.69	85.19	80	0.55
Spanish	1.92	3.7	0	
Other	13.46	11.11	16	
Missing	1.92	0	4	
Individualized educational program (%)				
No	59.62	55.56	64	0.31

Variable	Whole sample (<i>n</i> = 52)	Control (<i>n</i> = 27)	Intervention (<i>n</i> = 25)	<i>p</i> value
Yes	36.54	44.44	28	
Missing	3.85	0	8	
Medication type (%)				
Injectable	73	78	68	0.43
Avonex or Avonex pre-filled syringe (Interferon Beta1a-intramuscular)	18.42	24	12	
Copaxone (Glatiramer acetate)	55.26	52	59	
PLEGRIDY (peginterferon beta-1a)	7.89	0	18	
Rebif (Interferon Beta1b -subcutaneous)	18.42	24	12	
Oral	27	22	32	
Gilenya (fingolimod)	15	33	71	
Tecfidera (BG-12 or dimethyl fumarate)	69	67	29	
Terifluononide	15	0	0	
Site (%)				
Hospital for Sick Children, Toronto	40.38	37.04	44	0.41
Childrens Hospital of Philadelphia	5.77	3.7	8	
Childrens Hospital of Pittsburgh	3.85	7.41	0	
Boston Childrens Hospital	11.54	7.41	16	
University of Alabama at Birmingham	11.54	18.52	4	
University of Colorado Denver	5.77	3.7	8	
University of California at San Francisco	5.77	7.41	4	
Texas Childrens Hospital, Baylor College of Medicine	11.54	14.81	8	
Alberta Childrens Hospital	3.85	0	8	

sd standard deviation

Table 2

Effect sizes for primary and secondary outcomes by group and over time

Source Outcome	Baseline			3-month follow-up			6-month follow-up			Baseline versus 3-month ES ^b		Baseline versus 6-month ES ^b	
	Control mean	MI mean	ES ^a	Control mean	MI mean	ES ^a	Control mean	MI mean	ES ^a				
Primary outcomes: adherence													
Objective													
MEMS cap adherence	0.82	0.80	-0.09	0.85	0.79	-0.34	0.78	0.55	-0.70	-0.24			
Pharmacy refills	0.94	0.96	0.17	0.85	0.88	0.15	0.81	0.89	0.39	-0.01			0.23
Parent													
MSTAQ proportion missed doses	0.08	0.03	-0.26	0.08	0.05	-0.16	0.09	0.06	-0.18	0.10			0.08
Adherence remind	51.85	36.46	-0.40	34.00	41.30	0.19	28.00	38.54	0.30	0.59			0.70
Adherence present	66.67	63.54	-0.08	54.00	56.52	0.06	52.00	62.50	0.27	0.15			0.35
Adherence administer	37.96	34.38	-0.09	28.00	38.04	0.24	26.00	34.38	0.21	0.33			0.29
Morisky	6.35	6.20	-0.10	6.23	6.59	0.24	6.35	6.05	-0.16	0.34			-0.06
MSTAQ barriers	50.96	49.08	-0.18	47.60	49.88	0.26	50.22	48.31	-0.20	0.45			-0.02
MSTAQ side effects	49.45	50.78	0.14	47.04	52.56	0.58	48.58	49.59	0.10	0.44			-0.04
MSTAQ behavioral coping	47.15	52.97	0.61	48.46	50.29	0.22	49.66	48.92	-0.07	-0.39			-0.68
Patient													
Morisky	6.02	5.84	-0.10	5.91	6.09	0.10	6.19	5.69	-0.26	0.21			-0.16
MSTAQ barriers	48.30	49.49	0.13	52.72	48.41	-0.45	51.09	49.09	-0.18	-0.58			-0.31
Secondary outcomes: QOL and psychosocial													
Parent													
MSNQ cognitive function	17.81	18.00	0.01	17.44	17.68	0.02	21.68	18.75	-0.20	0.01			-0.22
PEDS physical function	82.41	78.13	-0.19	74.75	78.80	0.16	80.75	81.12	0.02	0.36			0.21
PEDS emotional function	75.74	70.00	-0.27	77.20	68.91	-0.44	75.40	69.06	-0.32	-0.17			-0.05
PEDS social function	82.41	82.29	-0.01	84.00	84.57	0.03	83.50	85.99	0.12	0.04			0.13
PEDS school function	67.04	69.58	0.16	69.80	66.30	-0.19	68.00	68.54	0.03	-0.35			-0.13
Patient													
MSSE function	810.00	824.80	0.09	829.17	873.33	0.64	796.00	879.58	0.57	0.55			0.48
MSSE control	712.22	709.20	-0.01	728.75	792.08	0.53	722.40	757.08	0.19	0.54			0.21
Ryff autonomy	28.56	28.64	0.02	29.71	29.46	-0.06	27.48	28.42	0.16	-0.07			0.14

Source Outcome	Baseline			3-month follow-up			6-month follow-up			Baseline versus 3-month ES ^b	Baseline versus 6-month ES ^b
	Control mean	MI mean	ES ^a	Control mean	MI mean	ES ^a	Control mean	MI mean	ES ^a		
Ryff self-acceptance	27.56	27.20	-0.10	27.96	26.75	-0.28	28.40	26.29	-0.64	-0.17	-0.53
Ryff environmental mastery	24.48	25.04	0.13	27.00	25.58	-0.29	25.56	24.04	-0.29	-0.42	-0.42
PEDS physical function	82.75	81.88	-0.05	80.08	82.94	0.18	75.13	83.46	0.40	0.23	0.45
PEDS emotional function	72.04	70.20	-0.09	67.83	71.25	0.16	65.60	67.71	0.10	0.25	0.19
PEDS social function	82.04	85.20	0.20	76.25	85.00	0.45	79.60	85.83	0.31	0.25	0.11
PEDS school function	66.11	66.80	0.04	64.17	66.46	0.14	64.00	66.88	0.15	0.10	0.11
Post hoc analyses: self-management factor scores											
Parent											
Behavioral involvement	-0.05	0.07	0.12	-0.26	-0.08	0.20	-0.36	-0.13	0.24	0.08	0.12
Cognitive involvement	0.20	-0.25	-0.44	-0.34	-0.13	0.24	-0.18	0.04	0.23	0.68	0.68
Patient											
Self-efficacy	-0.02	0.02	0.04	0.10	0.37	0.68	-0.01	0.29	0.36	0.65	0.32
Well-being	-0.01	0.02	0.03	0.41	0.08	-0.32	0.13	-0.21	-0.38	-0.35	-0.42

Bold indicates small effect size, italic indicates medium effect size, bold italic indicates large effect size

^aCompares the two randomization groups

^bCompares the two time points

ES effect size

Table 3

Descriptive statistics of outcome measures

Variable	Baseline			3-month FU			6-month FU		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
<i>Primary outcomes: measures of adherence</i>									
Objective									
Pharmacy refill adherence (past 12, 3, 6 months)	51	0.95	0.12	52	0.86	0.20	49	0.85	0.22
MEMs cap adherence (baseline, 3, 6 months)	46	0.81	0.22	47	0.82	0.18	45	0.66	0.32
Parent-Reported									
MSTAQ proportion of missed doses (past 28 days)	47	0.06	0.18	45	0.07	0.19	47	0.07	0.22
Parent remind (past 2 weeks)	51	44.61	38.83	48	37.50	37.90	49	33.16	34.76
Parent present (past 2 weeks)	51	65.20	37.11	48	55.21	39.26	49	57.14	39.53
Parent administer (past 2 weeks)	51	36.27	41.33	48	32.81	41.95	49	30.10	40.82
MSTAQ behavioral coping strategies (past 4 weeks)	35	49.64	9.58	33	49.24	8.28	34	49.33	10.76
MSTAQ side effects (past 4 weeks)	37	50.03	9.63	34	49.48	9.58	35	49.04	10.63
MSTAQ barriers (past 4 weeks)	47	50.12	10.42	41	48.66	8.60	46	49.31	9.74
Morisky (no time frame)	49	6.28	1.46	47	6.40	1.50	49	6.20	1.85
Patient-reported									
MSTAQ Barriers (past 4 weeks)	45	48.88	9.22	41	50.40	9.57	46	50.09	10.90
Morisky (no time frame)	52	5.93	1.74	48	6.00	1.82	49	5.94	1.91
<i>Secondary outcomes: quality of life and psychosocial outcomes</i>									
Parent-reported									
PedsQL physical functioning	51	80.39	22.32	48	76.69	24.60	49	80.93	21.34
PedsQL emotional functioning	51	73.04	21.61	48	73.23	19.03	49	72.30	20.09
PedsQL social functioning	51	82.35	18.56	48	84.27	17.74	49	84.72	20.06
PedsQL school functioning	51	68.24	16.27	48	68.13	18.24	49	68.27	19.75
MSNQ	49	17.90	13.42	47	17.55	12.41	49	20.24	14.60
Patient-reported									
PedsQL physical functioning	52	82.23	17.85	48	81.51	15.95	49	79.21	20.64
PedsQL emotional functioning	52	71.15	20.52	47	69.57	21.44	49	66.63	20.50
PedsQL social functioning	52	83.56	15.85	48	80.63	19.34	49	82.65	20.36

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Correlation matrix of adherence measures

Table 4

	Pharmacy refills	Proportion received/expected	Proportion missed doses (parent-report)	Parent Remind	Parent Present	Parent Administer	Morisky Adherence (parent)	Behavioral Coping (MSTAQ parent)	Side Effects (MSTAQ parent)	Barriers (MSTAQ parent)	Morisky Adherence (patient)
<i>Pharmacy proportion refills received/expected refills</i>											
Proportion missed doses (parent-report)	<i>-0.45</i>										
Parent remind	-0.29		0.27								
Parent present	0.04		0.07	<i>0.35</i>							
Parent administer	0.19		0.17	0.29	<i>0.60</i>						
Morisky adherence (parent)	<i>0.37</i>		<i>-0.46</i>	-0.23	-0.14	-0.19					
Behavioral coping (MSTAQ parent)	0.03		-0.01	0.11	<i>0.58</i>	<i>0.37</i>	0.02				
Side effects (MSTAQ parent)	0.05		0.12	0.03	0.16	0.23	-0.14	<i>0.43</i>			
Barriers (MSTAQ parent)	-0.17		0.06	0.21	0.20	0.13	-0.16	0.12	0.21		
Morisky adherence (patient)	<i>0.34</i>		-0.30	-0.12	0.00	-0.02	<i>0.59</i>	0.01	0.18	-0.07	
Barriers (MSTAQ patient)	<i>-0.31</i>		-0.04	0.12	0.19	0.29	-0.25	<i>0.34</i>	0.09	<i>0.31</i>	<i>-0.42</i>

Bold indicates small correlation, Italic indicates medium correlation, Bold italic indicates large correlation

Table 5

Results of random effect models

Outcome	Months	Group × Time Interaction
<i>Primary outcomes: measures of adherence</i>		
Objective		
Pharmacy refills	3	−0.02
	6	0.07
MEMs cap	3	0.02
	6	−0.19**
Parent-reported		
MSTAQ proportion missed doses	3	0.01
	6	0.01
Parent remind	3	17.65
	6	26.01*
Parent present	3	1.94
	6	12.63
Parent administer	3	11.69**
	6	12.85
MSTAQ behavioral coping strategies	3	−3.69
	6	−4.66
MSTAQ side effects	3	0.64
	6	−1.35
MSTAQ barriers	3	0.99
	6	−0.03
Morisky	3	0.34
	6	−0.26
Patient-reported		
MSTAQ barrier	3	−2.90
	6	−3.56
Morisky	3	0.20
	6	−0.35
<i>Secondary outcomes: quality of life and psychosocial outcomes</i>		
Parent-reported		
PedsQL physical function	3	1.63
	6	3.93
PedsQL emotional function	3	−0.92
	6	−0.44
PedsQL social function	3	1.03
	6	2.19
PedsQL school function	3	−4.51
	6	−2.90
MSNQ	3	−1.85

Outcome	Months	Group $\times$ Time Interaction
	6	-3.27
Patient-reported		
PedsQL physical function	3	4.93
	6	9.13**
PedsQL emotional function	3	4.21
	6	3.11
PedsQL social function	3	1.11
	6	1.42
PedsQL school function	<i>Model did not converge</i>	
MSSE function	3	56.21
	6	68.53
MSSE control	3	80.80*
	6	33.25
Ryff autonomy	3	1.33
	6	0.80
Ryff self-acceptance	3	-0.89
	6	-1.74
Ryff environmental mastery	3	-0.04
	6	-2.09
<i>Post hoc analyses: self-management factor scores</i>		
Informant		
Behavioral involvement	3	-0.01
	6	0.26
Cognitive involvement	3	0.31
	6	0.75*
Patient		
Self-efficacy	3	0.35**
	6	0.26
Well-being	3	-0.02
	6	-0.36

* $p < 0.05$;

** $p < 0.10$

Table 6

Effect sizes comparing of characteristics of attrition versus retention samples

Variable	Dropped from Analysis (baseline data only)		Analytic sample (had two or three timepoints)	
	n	Mean or proportion	n	Mean or proportion
<i>Demographic characteristic</i>				
Proportion randomization to control group ^b	10 ^a	0.50	52	0.52
Age	14	15.27	52	16.03
Age at diagnosis	7	11.86	31	11.55
Age at menarche	7	6.86	31	6.55
Race not white ^b	6	0.50	23	0.44
Mother's education less than college ^b	10	0.91	26	0.52
Father's education less than college ^b	9	0.82	32	0.63
No tobacco use ^b	12	0.92	47	0.96
Primary language English ^b	11	1.00	43	0.84
No individualized educational program ^b	8	0.80	31	0.62
PDDS	12	0.58	49	0.47
<i>Adherence characteristics at baseline</i>				
Objective				
Pharmacy refills	5	0.90	51	0.95
Parent				
Proportion of missed doses	11	0.15	47	0.06
Adherence remind	12	52.08	51	44.61
Adherence present	12	62.50	51	65.20
Adherence administer	12	31.25	51	36.27
MSTAQ coping	6	60.05	35	49.64
MSTAQ side effects	6	58.40	37	50.03
MSTAQ barriers	10	56.89	47	50.12
Morisky	11	6.34	49	6.28
Patient				
MSTAQ barriers	13	52.30	45	48.88
				0.37

Variable	Dropped from Analysis (baseline data only)		Analytic sample (had two or three timepoints)	
	n	Mean or proportion	n	Mean or proportion
Morisky	14	5.23	52	5.93
<i>QOL and psychosocial scores at baseline</i>				
Parent				
MSNQ	12	21.92	49	17.90
PedsQL physical functioning	12	74.22	51	80.39
PedsQL emotional functioning	12	68.75	51	73.04
PedsQL social functioning	12	78.33	51	82.35
PedsQL school functioning	12	61.25	51	68.24
Patient				
MSSE function	14	790.00	52	817.12
MSSE control	14	613.57	52	710.77
Ryff autonomy	14	25.14	52	28.60
Ryff self-acceptance	13	25.85	52	27.38
Ryff environmental mastery	14	23.43	52	24.75
PedsQL physical functioning	14	72.54	52	82.23
PedsQL emotional functioning	14	56.43	52	71.15
PedsQL social functioning	14	81.79	52	83.56
PedsQL school functioning	14	52.86	52	66.44

Bold indicates small ES, *Italic* indicates medium ES, Bold *italic* indicates large ES

^aFour of the 14 did not get randomized, so this computation is based on the remaining 10 versus 52

^bComputed ES for proportions as per Cohen's formula

Table 7

Site investigators and study coordinators

Site	Site Investigator	Site Coordinator(s)
Alberta Children's Hospital, Calgary, AB	Dr. Jean K. Mah	Tiffany Haig/Karla Sanchez
Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA	Dr. Tim Lotze	Rubi Mendoza/Marija Stosic/Mariam Pontifes/Rory Mahabir
Boston Children's Hospital, Boston, MA, USA	Drs. Mark Gorman and Lauren Mednick	Susana Camposano
Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA	Drs. Brenda Banwell and Amy Waldman	Geraldine Liu/Amy Lavery/Maleka Smith
Hospital for Sick Children, Toronto, Ontario, Canada	Dr. E. Ann Yeh	Stephanie Grover/Austin Noguera/Carolynn Darrell/Dr. Ruth Slater
University of Alabama Birmingham, Birmingham, AL, USA	Dr. Jayne Ness	Sarah Dowdy
University of California San Francisco, San Francisco, CA, USA	Drs. Emmanuelle Waubant and Jennifer Graves	Janace Hart/Hardeep Chohan
University of Colorado Denver, Denver, CO, USA	Dr. Teri Schreiner	Alexander Stein/Kawonas Jenkins
University of Pittsburgh, Pittsburgh, PA, USA	Dr. Gulay Alper	–