Shedding Light on the Black Box of Rehabilitation: Differential Short- and Long-Term Effects of Multidisciplinary Multiple Sclerosis Rehabilitation

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ABSTRACT

BACKGROUND: The study of the effectiveness of multidisciplinary rehabilitation (MDR) and how the symptoms and needs of individuals with multiple sclerosis (MS) interplay with the diversity of MDR interventions is still a conundrum, often referred to as a black box.

METHODS: We conducted a partial crossover randomized controlled trial with follow-ups at 1 (discharge), 6, and 12 months. Based on their rehabilitation goals, each patient was categorized into 1 of 5 main focus areas (MFAs) prior to admission: Resilience, Cognitive Function, Energy, Physical Function, and Personal Needs. The Functional Assessment of Multiple Sclerosis (FAMS) instrument scores were the primary outcome.

RESULTS: MFA groups varied in age ($P = .036$), MS type ($P = .002$), Expanded Disability Status Scale score ($P < .001$), time since diagnosis ($P = .002$), and FAMS at baseline ($P < .001$), as well as in composition and quantity of MDR services. At discharge, significant FAMS improvements were found in all 5 MFA groups (FAMS change > 10.4, $P < .05$), but the affected subdimensions and persistence of improvements varied among MFA groups. At the 6-month follow-up, estimates of controlled differences in FAMS were 9.9 ($P = .001$), 5.6 ($P = .196$), 8.5 ($P = .008$), −1.4 ($P = .548$), and 17.9 ($P = .012$) for the Resilience, Cognitive Function, Energy, Physical Function, and Personal Needs groups, respectively.

CONCLUSIONS: This study demonstrated that inpatient MDR improves functioning and health-related quality of life in people with MS; the type, degree, and persistence of the benefits are associated with a patient's main focus area of rehabilitation, which signifies the importance of the goal-setting process in MDR.

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The immunopathology of multiple sclerosis (MS)—driven by immune-mediated neuroinflammation, demyelination, and neurodegeneration—causes varying degrees of disease burden, continuing disability, and impaired quality of life (QOL),[1] which all negatively affect the day-to-day functioning and behavior of individuals with MS. Rehabilitation is an essential part of long-term MS management and aims to maximize function and enhance QOL using a multidisciplinary approach.[2] The short-term effectiveness of multidisciplinary rehabilitation (MDR) on functional status and health-related quality of life (HRQOL) in MS is well documented,[3-8] and we recently reported the overall long-term effectiveness of inpatient MDR for individuals with MS.[9]

Despite the growing body of MS rehabilitation research,[10] little is known about the dynamic interplay among the complex symptoms, heterogeneous needs, and rehabilitation goals of patients with MS; the diversity of received rehabilitation services; and the expected effectiveness in MDR—a phenomenon often referred to as the *black box* of rehabilitation.[11,12] In this context, the complexity and context of personalized MDR are widely recognized as a methodological problems in the study of MDR.[12,13] Recently, methodological efforts have been made to formalize a theory-driven specification of rehabilitation treatments[12] with an analytic focus on the identification of the active treatment ingredients in MDR that help patients meet well-defined targets within diverse aims, eventually leading to the fulfillment of rehabilitation goals. Other authors[13-16] emphasize the importance of the patient-centered goal-setting process in MDR and advocate for a flexible and pragmatic approach in the study of personalized MDR. However, evidence supporting the importance of the patient-centered goal-setting process for the effectiveness of MDR is scarce.[17]

Our objective was to conduct a pragmatic study of how the effectiveness of inpatient MDR, from short to long term,

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varies in a heterogeneous MS population. We employed the concept of the main focus area of rehabilitation (MFA) defined as strata of patients sharing similar or related MS-induced challenges and rehabilitation goals identified prior to hospitalization. The 5 MFAs were Resilience, Cognitive Function, Energy, Physical Function, and Personal Needs.[18] Based on the data of Boesen et al,[9] we then investigated the differential effectiveness in functioning and HRQOL among the 5 MFA groups of patients. The identification of patient needs, the goal-setting process, and the received MDR services all functioned as an intervention complex.[19] To illuminate this complex, we provide a detailed description of MDR services within each of the 5 MFAs using the Template for Intervention Description and Replication (TIDieR)[19] approach. TIDieR has been shown to improve the reporting of complex interventions,[13,20] but has not yet been used in MS MDR research, despite the fact that the complex interacting components that constitute MDR treatment are often underreported in MDR research.[13]

METHODS

Study Design

The study was designed as a pragmatic partial crossover randomized controlled trial with follow-up at 6 months (6-MFU) and 12 months (12-MFU).[9,18] Patients were randomly assigned to 1 of 2 groups that received different treatment sequences: group A or group B, as illustrated in **FIGURE S1** (which can be found online at IJMSC.org in **APPENDIX S1**). Following a baseline assessment at study entry, group A patients were immediately admitted for 4 weeks of MDR with follow-up at discharge as well as at 6 and 12 months after study entry. Group B patients consisted of wait-list controls (6 months), followed by 4 weeks of inpatient MDR with treatment follow-up at discharge and 6 months after admission. Group B patients were assessed at study entry (baseline for control period) and reassessed immediately before admission (6-MFU for the control period and baseline for the treatment period). The MDR treatments are reported in accordance with TIDieR guidelines.[20]

Written informed consent was obtained from all patients. This study met the standards of the World Medical Association Declaration of Helsinki and was approved by the Danish Research Ethics Committee of the Region of Zealand (reference number 1-01-83-0002-07) and the Danish Health Data Authority (reference number 2011-41-6751). It was also registered at www.isrctn.com (BMC/Springer Nature; ISRCTN05245917).

Study Participants

Recruitment of study participants took place among all referred individuals with MS aged 18 to 65 years with an Expanded Disability Status Scale (EDSS) score of less than 7.5. Individuals were excluded if they were within 3 months of their most recent relapse, were less than 6 months from initial diagnosis, had inpatient MDR within the past 6 months, had cognition subscale scores of EDSS larger than 2, had cognitive limitations, or had any other illness that could impede study participation. All patients underwent full neurological examinations prior to enrollment in the study, with the examining neurologists making the final decision on participant enrollment.

Randomization and Masking

Patients were placed randomly into immediate treatment (group A) or wait-list control (group B) using a computer-generated minimization sequence to ensure balance in hypothesized prognostic factors.[18] Strict blinding of patients and MS hospital practitioners was not possible. However, only the case managers and patients were directly informed about their enrollment status, and they were urged not to disclose enrollment status.

Outcome Measures

The Functional Assessment of Multiple Sclerosis[21] (FAMS) scale was used as primary outcome. FAMS is an MS-specific instrument that encompasses a broad range of HRQOL-related functioning and other MS-related aspects. It consists of 44 items within 6 subdimensions: Mobility (7 items), Symptoms (7 items), Emotional Wellbeing (7 items), General Contentment (7 items), Thinking/Fatigue (9 items), and Family/Social Wellbeing (7 items). Each item is rated on a 5-point Likert scale (0-4), yielding a total FAMS score range of 0 to 176. Higher scores reflect higher functioning and HRQOL. A change of 5 points in FAMS total score was considered clinically important.[18]

Patient Challenges, Goal Setting, and MFA Assignment

All enrolled patients participated in a 1-on-1 goal-setting session with their case manager 1 week before admission, at most. All case managers were certified coaches. Prior to the session, the case manager obtained information from the patient's referrals, medical records, and notes from the evaluating neurologist, as well as patient-reported information that included a personal information form (**APPENDIX S2**), FAMS, and the Measure Yourself Concerns and Wellbeing questionnaire (MYCaW). The MYCaW questionnaire quantifies 2 self-perceived problems related to a patient's concerns and challenges.[22] In accordance with the conceptual framework of the International Classification of Functioning, Disability, and Health (ICF)[23] and following a detailed instruction form (Appendix S2), a shared decision was made on the intended rehabilitation goals. Based on this, each patient was assigned to 1 of the 5 MFAs: (1) Resilience (psychological well-being), including strengthening coping, confidence, self-care, cognition, and adjustment skills; (2) Cognitive Function, including memory, concentration, and insight; (3) Energy, including fatigue, scheduling, breaks, and structure; (4) Physical Function, including walking, balance, endurance, strength, and mobility; and (5) Personal Needs, including transferring, toileting, bathing, and medication administration.[18] MFA categorization occurred independently of random assignment to group A or B. For 15 patients, the case manager

TABLE 1. Patient Characteristics of the 5 MFA Groups

	Resilience	Cognitive function	Energy	Physical function	Personal needs	*P*
n (n of those with 2 MFAs)	69 (7)	62 (7)	135 (10)	142 (5)	12 (1)	
A/B ratio	43/26	31/31	65/70	70/72	6/62	
Female, %	70	71	73	66	75	.816
A/B ratio	70/69	71/71	72/73	64/68	83/67	
Age (years)	49 (42-55)	50 (42-59)	51 (44-56)	54 (48-58)	52 (47-57)	.036
A/B ratio	49/49	50/50	51/51	54/54	51/55	
Employment status						
Full- or part-time, %	23	23	27	20	9	.186
A/B-ratio	29/12	32/16	28/27	22/17	2/15	
Retired/early retirement, %	< 1/66	6/53	1/54	4/67	< 1/74	
A/B-ratio, early retirement	58/80	42/65	55/53	67/69	80/67	
Disease history						
Relapsing-remitting MS, %	45	52	50	28	8	.002
A/B ratio	47/42	42/61	54/47	33/25	17/< 1	
Secondary progressive MS, %	39	35	36	54	83	
A/B ratio	35/46	45/26	32/39	49/58	83/83	
Primary progressive MS, %	16	13	14	18	8	
A/B ratio	19/12	13/13	14/14	19/17	< 1/17	
EDSS	4.0 (3.5-6.5)	4.0 (3.5-4.5)	4.0 (3.0-6.0)	6.0 (4.0-6.5)	6.5 (6.5-7.0)	< .001
A/B median ratio	4.0/4.0	4.0/4.0	4.5/4.0	6.0/6.0	6.5/7.0	
Immunotherapy, %	49	61	62	46	50	.084
A/B median ratio	51/46	65/58	65/63	44/49	33/67	
Years since diagnosis	6 (2-12)	6 (3-11)	7 (2-14)	11 (5-16)	12 (9-19)	.002
A/B median ratio	6/6	7/5	7/8	11/11	15/11	
	Resilience	**Cognitive function**	**Energy**	**Physical function**	**Personal needs**	***P***
Functioning and health-related quality of life						
FAMS total score	98 (82-117)	112 (93-126)	113 (96-130)	124 (106-139)	110 (101-124)	< .001
A/B median ratio	96/103	115/109	119/110	125/122	116/99	
Mobility	14 (11-18)	17(11-21)	14 (12-20)	14 (10-17)	9 (8-12)	.008
Symptoms	19 (15-23)	22 (16-25)	20 (15-25)	23 (19-26)	23 (21-26)	.006
Emotional wellbeing	19 (12-22)	22 (17-25)	22 (19-25)	23 (19-26)	20 (14-23)	.001
General contentment	15 (10-19)	18 (14-21)	18 (14-22)	19 (16-23)	16 (10-19)	.001
Thinking/fatigue	18 (13-24)	15 (10-22)	18 (12-23)	24 (18-29)	26 (18-29)	< .001
Family/social wellbeing	18 (15-21)	21 (17-23)	22 (18-26)	23 (19-26)	21 (17-26)	< .001
Inpatient hospitalization						
Length of stay, days	20 (18, 20)	20 (18, 20)	20 (18, 20)	20 (19, 20)	19 (18, 20)	.289
High-intensity MDR,[a] hours/day	3.4 (2.7, 4.1)	3.2 (2.8, 3.8)	3.4 (2.8, 4.0)	3.1 (2.6, 3.7)	3.1 (2.6, 3.2)	.267
Received services						
Supervision, sessions	5 (4, 6)	6 (5, 7)	5 (5, 6)	5 (5, 6)	5 (4, 6)	.026
1-on-1 conversations, PoP %	79	66	78	55	64	< .001
Interdisciplinary classes, sessions	4 (1, 6)	11 (8, 14)	5 (2, 8)	4 (2, 6)	2 (1, 6)	< .001
Psychologist consultation, PoP %	87	82	47	26	27	< .001

TABLE 1. Patient Characteristics of the 5 MFA Groups (continued)

	Resilience	Cognitive function	Energy	Physical function	Personal needs	*P*
Occupational therapy, sessions	3 (2, 5)	3 (2, 4)	3 (2, 4)	3 (2, 4)	6 (4, 7)	.068
Group occ therapy, PoP %	65	48	87	68	45	< .001
Physiotherapy, sessions	13 (11, 15)	12 (9, 14)	11 (9, 15)	14 (12, 18)	16 (12, 18)	< .001
Group physiotherapy, PoP %	90	100	100	97	100	.001
Supervised self-training, PoP %	91	100	97	99	82	.014
Coaching, PoP %	16	3	12	8	0	.074
Nursing care, sessions	13 (6, 27)	8 (5, 16)	10 (5, 21)	10 (5, 22)	28 (16, 38)	.079

A/B, group A and group B (intervention vs wait-list control); EDSS, Expanded Disability Status Scale; FAMS, Functional Assessment of Multiple Sclerosis; MDR, multidisciplinary rehabilitation; MFA, main focus area; MS, multiple sclerosis; occ, occupational; PoP: proportion of patients who received the service.
[a]High-intensity MDR is the sum of received services excluding neurologist consultations.
Note: Continuous data are presented as median (Q1-Q3). *P* values indicate test probabilities of no between-MFA difference. Homogeneity between study groups A and B is shown as ratios. Only MDR services that differed among MFA groups at a 10% significance level are listed. For a full tabulation of all baseline patient characteristics and received MDR services, see Appendix S1.

identified 2 MFA groups of equal importance. The case manager organized the MDR team and remained the main contact for the patient throughout the admission period.

The MDR Treatment

All patients received personalized MDR to meet their individual goals using a patient-centered, collaborative, and goal-oriented approach within the ICF framework. Consequently, their MDR services were not restricted by their MFA but were collaboratively and pragmatically selected to meet individual rehabilitation goals. MDR services included supervision by case manager, education, 1-on-1 conversations with professionals, interdisciplinary classes, consultation with a psychologist, occupational therapy, group occupational therapy, physiotherapy, group physiotherapy, supervised self-training, coaching, and nursing care (see **APPENDIX S3** for a detailed TIDieR description of provided MDR services within each of the MFA groups). For each patient, data on received MDR services in terms of number of sessions and weekly time spent on services were extracted from a patient's realized weekly rehabilitation plan. In addition, patients were not reviewed during the follow-up period and were not precluded from visiting local MS clinics or from participating in community-based monodisciplinary interventions or services.

Statistical Analyses

Data analyses followed Boesen et al[9] (see Appendix S1 for a detailed description). In short, we remapped baseline characteristics using a contextual multivariate technique to achieve a confounder-controlled comparison of treatment versus wait-list control within each MFA while respecting MFA differences in terms of their baseline covariate characteristics. We then used linear mixed-effects models to model FAMS and FAMS subscale changes at 1 (discharge), 6-MFU, and 12-MFU as a function of the interaction between treatment and MFA after controlling for the remapped contextual baseline characteristics. To evaluate long- and longer-term effects on HRQOL, estimated treatment group 6-MFU and 12-MFU changes from baseline were tested against estimated 6-MFU changes in the control group. Data were analyzed using the intention-to-treat principle, except for EDSS score and use of immunotherapy. To quantify the degree of subscale specificity, the Gini coefficient (ranging from 0-1) was calculated across subscale contributions to the total FAMS score, with a greater Gini coefficient indicating a higher degree of subscale dominance.

RESULTS

The Participants

This study included 405 patients, with 62 patients exclusively categorized into Resilience, 55 to Cognitive Function, 125 to Energy, 137 to Physical Function, 11 to Personal Needs, and 15 to a combination of 2 MFAs (**TABLE 1**). The 5 MFA groups differed significantly at baseline in terms of age ($P = .036$), MS type ($P = .002$), EDSS score ($P < .001$), time since diagnosis ($P = .002$), and HRQOL ($P < .001$). Patients in the neuropsychological groups of Resilience, Cognitive Function, and Energy were, on average, younger with a shorter disease duration and lower EDSS, and more of them had a diagnosis of relapsing-remitting MS than patients in the Physical Function and Personal Needs groups. Patients in the Physical Function group reported a relatively higher HRQOL at baseline (median FAMS = 124), whereas patients in the Resilience and Personal Needs groups displayed significantly lower baseline HRQOL levels than the remaining groups. Baseline statistics and unadjusted FAMS values are presented in Table 1 and in more detail in Appendix S1.

The MDR Treatment

The 5 MFA groups did not differ in terms of length of stay ($P = .289$, Table 1) nor in terms of the total number of active MDR services received during admission ($P = .267$). In all MFA groups, patients received, on average, over 3 hours of MDR per day during their stay. However, the MDR content substantially differed among MFA groups (Table 1), with the Resilience and the Cognitive Function groups characterized by a high proportion of patients receiving psychologist consultations (87% and 82%, respectively), and the Resilience

TABLE 2. Changes in Functioning and HRQOL Subdimensions

	Main focus area				
	Resilience	**Cognitive function**	**Energy**	**Physical function**	**Personal needs**
Number of patients at baseline					
Wait-list control	26	31	70	72	6
Treated[a]	69	62	135	142	12
Baseline	**FAMS total score,[b] mean (95% CI)**				
Wait-list control	105.4 (97.5-113.2)	111.9 (105.4-118.3)	113.8 (109.5-118.1)	121.1 (117.4-124.9)	118.0 (102.5-133.6)
Treated[a]	101.7 (94.9-108.5)	112.0 (107.2-116.7)	111.9 (108.0-115.9)	121.2 (118.1-124.3)	110.6 (96.5-124.6)
Discharge	**Adjusted FAMS change from baseline, mean (95% CI)**				
Treated[a]	16.6 (12.4-21.2)	11.9 (7.2-17.2)	13.9 (10.8-16.8)	10.4 (7.5-13.4)	11.0 (0.4-22.0)
	FAMS subscale contributions to change, %				
Mobility	12.7%	17.6%	12.4%	21.4%	22.7%
Symptoms	15.7%	14.3%	16.1%	20.4%	9.1%
Emotional wellbeing	19.9%	17.6%	16.8%	18.4%	29.1%
General contentment	19.9%	15.1%	21.9%	17.5%	27.3%
Thinking/fatigue	25.3%	33.6%	28.5%	14.6%	−3.6%
Family/social wellbeing	6.6%	1.7%	4.4%	7.8%	15.5%
Gini coefficient[c]	0.20	0.29	0.25	0.14	0.33
6-MFU	**Adjusted FAMS change from baseline, mean (95% CI)**				
Wait-list control	−5.2 (−11.3 to 0.8)	−1.6 (−8.1 to 5.1)	−4.5 (−8.7 to 0.5)	−0.9 (−5.0 to 3.0)	−13.1 (−21.0 to −3.0)
Treated[a]	4.7 (0.8-8.7)	4.0 (−1.4 to 8.8)	4.0 (1.2-6.8)	−2.3 (−4.8 to 0.1)	4.8 (−1.4 to 11.0)
DID[d]	9.9 (2.3-17.5)	5.6 (−3.1 to 13.2)	8.5 (2.5-14.0)	−1.4 (−5.8 to 3.6)	17.9 (4.6-27.4)
P value	.001	.196	.008	.548	.012

	Main focus area				
	Resilience	**Cognitive function**	**Energy**	**Physical function**	**Personal needs**
	FAMS subscale contributions to DID[d], %				
Mobility	1.0%	23.6%	12.0%	-[e]	14.0%
Symptoms	19.4%	−3.6%	21.7%	-	14.6%
Emotional wellbeing	38.8%	29.1%	24.1%	-	21.3%
General contentment	14.3%	9.1%	20.5%	-	16.3%
Thinking/fatigue	21.4%	32.7%	20.5%	-	24.7%
Family/social wellbeing	5.1%	9.1%	1.2%	-	9.0%
Gini coefficient[c]	0.40	0.38	0.24	-	0.17
12-MFU	**Adjusted FAMS change from baseline, mean (95% CI)**				
Treated[a]	7.5 (1.5-13.8)	7.9 (1.6-13.9)	6.8 (2.7-11.2)	−0.6 (−4.7 to 3.7)	4.7 (−9.1 to 19.1)
DID[f]	12.7 (4.2-22.5)	9.5 (−0.1 to 18.4)	11.3 (3.5-17.7)	0.3 (−5.8 to 7.5)	17.8 (0.9-34.6)
P value	.001	.056	.004	.944	.036

TABLE 2. Changes in Functioning and HRQOL Subdimensions (continued)

	Main focus area				
	Resilience	Cognitive function	Energy	Physical function	Personal needs
	FAMS subscale contributions to DID, %				
Mobility	4.8%	19.4.6%	13.8%	-[e]	15.3%
Symptoms	15.2%	11.8%	22.0%	-	20.5%
Emotional wellbeing	39.2%	29.0%	26.6%	-	24.4%
General contentment	16.8%	14.0%	17.4%	-	7.4%
Thinking/fatigue	14.4%	29.0%	22.0%	-	30.7%
Family/social wellbeing	9.6%	−3.2%	−1.8%	-	1.7%
Gini coefficient[c]	0.32	0.33	0.27	-	0.34

DID, difference-in-difference; FAMS, Functional Assessment in Multiple Sclerosis; HRQOL, health-related quality of life; MDR, multidisciplinary rehabilitation; MFA, main focus area; MFU, months follow-up.
[a]Combined treatment group (group A and group B) from partial crossover design.
[b]FAMS total score ranges from 0 to 176: the higher the score, the better the HRQOL.
[c]The Gini coefficient measures inequality, with 0 corresponding to perfect equality in contribution and 1 corresponding to perfect inequality with only 1 contributing component.
[d]DID: The difference-in-difference estimator is the treated vs control difference in the respective changes from baseline.
[e]FAMS subscale contributions are only shown for MFA groups with significant or marginally significant FAMS changes.
[f]Treatment group at 12-MFU against wait-list control group at 6-MFU.

and Energy groups characterized by a high proportion of patients receiving 1-on-1 conversations with professionals (79% and 78%, respectively). In terms of duration, the Cognitive Function group received a high number of interdisciplinary classes (median of 525 min), while a high occurrence of physiotherapy was found for the Physical Function and Personal Needs groups (median of 510 min and 570 min, respectively). The Personal Needs group received more than twice as many nursing care sessions than any other group (median of 28 sessions). Details are provided in Appendix S1.

Dropout Rate

Three hundred sixty patients completed 6-MFU, an attrition rate of 11.1%; 179 patients completed 12-MFU (group A only), an attrition rate of 14.4%. **FIGURE S2** presents the trial flowchart (Appendix S1). Dropouts did not differ significantly among the 5 MFA groups ($P = .930$) (Appendix S1).

The Outcomes

Personalized MDR resulted in clinically relevant improvements in functioning and HRQOL at discharge in all 5 MFA groups when compared with baseline ($P < .05$), with adjusted mean FAMS changes of 16.6 (95% CI, 12.4-21.2) for the Resilience group, 11.9 (95% CI, 7.2-17.2) for the Cognitive Function group, 13.9 (95% CI, 10.8-16.8) for the Energy group, 10.4 (95% CI, 7.5-13.4) for the Physical Function group, and 11.0 (95% CI, 0.4-22.0) for the Personal Needs group. However, the protraction of FAMS improvements throughout follow-up time as well as the relative contributions of HRQOL subdimensions to the found improvements differed among MFA groups (**TABLE 2**). The Physical Function group revealed short-lived improvements, with the Mobility and Symptoms subscales comprising the largest contributions to the improvement at discharge (21.4% and 20.4%, respectively), with decline to baseline levels and nonsignificance at 6-MFU. In the remaining MFA groups, clinically important as well as persistent MDR effects on FAMS were found throughout follow-up, except for nonsignificance in the Cognitive Function group. In the Resilience group, improvements were mainly found in Emotional Wellbeing (38.8% at 6-MFU and 39.2% at 12-MFU), whereas improvements in the Cognitive Function and Energy groups were in the Thinking/Fatigue subscale (33.6% at discharge and 20.5% at 6-MFU, respectively). The Energy group also had lower subscale specificity as indicated by a smaller Gini coefficient and higher contributions from the Symptoms and General Contentment subscales. At discharge, the Personal Needs group had improvements to Emotional Wellbeing (29.1%), General Contentment (27.3), and Mobility (22.7%), whereas at 12-MFU, Thinking/Fatigue (30.7%) and Emotional Wellbeing (24.4%) dominated. All patients had unchanged EDSS and immunotherapy status during the study period (Appendix S1).

DISCUSSION

The current study found that people with MS who completed 4 weeks of inpatient MDR had clinically relevant HRQOL improvements. However, the degree and protraction of improvement at 6-MFU and 12-MFU differed among the 5 MFA groups, with HRQOL subdimension improvements largely matching the needs and challenges characteristic of the MFA group. Thus, our study provides novel evidence for the important role of the patient-centered goal-setting process in MDR, as discussed by Ørtenblad et al.[15] According to Wade's general theory of rehabilitation,[24] MDR seeks to match rehabilitation goals to patient needs (Wade's diagnostic function of rehabilitation) and rehabilitation ingredients to rehabilitation goals (Wade's assistive and catalytic function of rehabilitation) to facilitate improvement and homeostatic recalibration. Our study provides evidence for this matching process to be used in the pragmatic MDR setting

PRACTICE POINTS

The patient-centered goal-setting process is key for successful multidisciplinary rehabilitation (MDR) in people with multiple sclerosis (MS).

Neuropsychological challenges and rehabilitation goals of improved resilience, cognitive function, and energy are likely to show considerable long-term MDR benefits in health-related quality of life (HRQOL) for individuals with MS, particularly in emotional well-being and perceived thinking/fatigue. We recommend an increased clinical focus on the timeliness of MDR for patients with low levels of emotional well-being and general contentment regardless of their disease progression state.

Individuals with MS with physical function challenges are likely to experience barriers to a successful long-term carryover of gained HRQOL improvements following MDR. We recommend supervised outpatient or telehealth sessions to maintain the benefits. ■

of Danish MS hospitals. By employing the concept of MFA as strata of patients sharing similar or related needs, our study demonstrated (1) how patient-centered goal-setting and MFA assignment prior to hospitalization were significantly related to disease progression state and HRQOL impairments at baseline (Table 1); (2) how MFA groups significantly differed in terms of the MDR services they received—for example, with more psychological support in the neuropsychological MFA groups and more physiotherapeutic support in the Physical Function and Personal Needs groups (Table 1); and, finally, (3) how MFA groups significantly differed in terms of their degree and timing of HRQOL improvements with subdimension improvements largely matching the MFA-related needs and goals (Table 2). Therefore, our study provides valuable insight into the black box of rehabilitation. Although we believe that the intervention system in our clinical setting actively drives the observed between-MFA outcome differences, we recognize that our study cannot address the equally important question of active ingredients in MDR as formulated by Hart et al.[12] Complex interventions typically involve a number of separate but synergistically interacting or compensating components, possibly with multiple equally valid adaptive pathways of interconnected ingredients leading to goal fulfillment[19]; hence, no single ingredient can be highlighted based on our study.

Our findings are in line with previous studies that reveal that the effectiveness of MDR depends on the initial state of a patient—for example, MS type or level of disability.[25-27] The short-term findings of our study are also consistent with previously published studies.[4,5,7,28] However, the magnitude of long-term benefits in the neuropsychological MFA groups and the Personal Needs group superseded the results from the few long-term studies conducted to date.[5,6] Long-term improvements were primarily concentrated around the FAMS subdimensions Emotional Wellbeing, General Contentment, and Thinking/Fatigue (Table 2), all of which were related to emotional and mental health, thereby highlighting the importance of the clinician's attention to hidden neuropsychological symptoms in MS.[29] The neuropsychological MFA groups generally had a high proportion of patients with relapsing-remitting MS, a shorter disease duration, and relatively lower mean EDSS scores. It has been suggested[25,26] that the likelihood of a beneficial outcome from rehabilitation is associated with relapsing-remitting MS, short disease duration, and low EDSS, all of which were also confirmed by our findings. The importance of mental health is also emphasized by HRQOL improvements in the Personal Needs group, but its members are characterized by high EDSS scores. This group resembled the Physical Function group in terms of the disease progression state, but echoed the Resilience group in terms of low Emotional Wellbeing and General Contentment scores at baseline (Table 1). Apparently, patients in these 2 groups tended to be in a personal crisis, which is also indicated by the significant 6-MFU HRQOL declines found in their respective control groups (Table 2). This may indicate that timely MDR treatment can be critical for these groups and should warrant increased attention from a clinical perspective.

An unexpected finding of our study is that the participants in the neuropsychological MFA groups experienced additional improvements in HRQOL between 6-MFU and 12-MFU. Although we cannot preclude other reasons, an explanation for a delayed improvement might be that behavioral changes following newly learned self-management skills and health education, which entail improving mastery and coping strategies, require time to unfold within the home environment.

In the Physical Function group, we found signs of "the disability paradox,"[30] where high levels of HRQOL were reported at baseline despite relatively high levels of disability, indicating that patients generally had come to terms with their health status. However, the Physical Function group still had significant and clinically relevant improvements at discharge, even though these were lost in the long term. This may indicate that patients with physical function challenges are prone to obstacles in

implementing learned skills into their regular regimen in their home environments.[16] For example, regular exercise may be difficult to carry over into a daily life constrained by limited physical capabilities and a sedentary lifestyle. It has been suggested that structured, internet-based physical activity aftercare promotion programs can preserve benefits obtained from inpatient physical exercise rehabilitation.[31] Thus, supervised maintenance sessions in an outpatient or telehealth setting may be recommended to enhance the carryover of the functioning and HRQOL improvements into the home environment.

Our study has several limitations.[8,9] First, the nonrandom allocation of patients to MDR treatment regimens does not allow a thorough evaluation of the relative roles of the specific treatments received and the characteristics of the specific patient population within each MFA group. However, the clinically relevant treatment differences found between wait-list control and MDR intervention groups within each of the MFA groups signifies that the received MDR content indeed was part of the mechanism of action that drove the reported differences in outcomes. Future MDR research should focus on the relative roles of symptoms, needs, MDR goals, and MDR regimens. Second, the a priori discretization of patient-centered needs and rehabilitation goals into the 5 MFAs—although guided by a screening study[18]—should be viewed as a methodological choice to address the differential effectiveness of MDR. A different categorization would likely have resulted in different numerical estimates, although probably similar qualitative findings. Furthermore, it should be noted that patients categorized into the same MFA—although sharing similar or related goals—do indeed have distinct personal needs and goals. We emphasize that, despite the significant differences between MFA groups, all of them had a considerable overlap in their characteristics at baseline (intraclass correlation coefficient of 0.13; Appendix S1). Third, we cannot rule out that at least some of the between-MFA differences found in effectiveness are attributable to differences in baseline characteristics among the 5 MFA groups according to the regression-to-the-mean phenomenon[32] or differences in FAMS subscale sensitivity to detect HRQOL changes. However, the large within- vs between-MFA variance ratio of the baseline characteristics indicates that the regression-to-the-mean phenomenon is unlikely to explain most of the MFA differences. Lack of FAMS subscale sensitivity is unlikely to explain our findings, as large treatment effects were detected at discharge in all MFA groups. However, we cannot eliminate undetected HRQOL dimensions. Fourth, due to ethical reasons, the current study used a pragmatic partial crossover design to provide an attractive research program for patients, thereby potentially yielding biased controlled 12-MFU estimates. However, due to the progressive nature of MS, it is unlikely that patients would experience significant HRQOL improvements in the wait-list control group, thereby rendering the bias, if it exists, to be conservative.

CONCLUSIONS

This pragmatic study on the effectiveness of MDR in a heterogeneous patient population in terms of disease progression state, patient needs, and rehabilitation goals demonstrated that individualized MDR improves functioning and HRQOL for individuals with MS. The type, degree, and persistence of these benefits depended on the MFA of rehabilitation, thereby signifying the importance of the patient-centered goal-setting process in MDR. Further research is required to improve our understanding of the effective elements and their causal relationships in individualized MDR. ■

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