Movement Disorders
CLINICAL PRACTICE
RESEARCH ARTICLE

Activities of Daily Living Are Improved by Inpatient Multimodal Complex Treatment for PD—a Real-World Cohort Study

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Abstract: Background: The multimodal complex treatment for Parkinson's disease (MCT) provides inpatient care by a multi-disciplinary team for people with Parkinson's disease (PwP) in Germany.
Objectives: We conducted a 5-year real-world mono-center cohort study to describe the effectiveness of MCT in the full cohort and various subgroups and outcome predictors.
Methods: We collected an anonymized dataset between Jan 2015 and Dec 2019, involving $N = 1773$. The self-reported MDS-UPDRS part II was used as primary outcome, and clinical routine data for explanatory variables. PwP were categorized as responders or non-responders according to a response of at least 3 points 4 weeks after discharge.
Results: N = 591 complete data records were available for statistical analyses. The full group improved by −2.4 points on the MDS-UPDRS II ($P = <0.0001$). 47.7% (n = 282) and 52.3% (n = 309) were coded as responders and non-responders, respectively. A clinically meaningful response was positively associated to age ($\chi^2 = 11.07$, $P = 0.018$), as well as baseline-severity of the MDS-UPDRS II ($\chi^2 = 6.05$, $P = 0.048$) and negatively associated to the presence of psychiatric disorder ($\chi^2 = 3.9$, $P = 0.048$) and cognitive dysfunction ($\chi^2 = 7.29$, $P = 0.007$). Logistic regression showed that baseline severity of the MDS-UPDRS II predicted therapy success. PwP with moderate baseline-severity had an about 2fold chance (OR 2.08; 95% CI 1.20–3.61; $P = 0.009$) and with severe an about 6fold chance (OR 5.92; 95% CI 2.76–12.68; $P < 0.0001$) to benefit clinically meaningful.
Discussion: In a naturalistic setting of a specialized Parkinson's center, MCT improved ADL disability of PwP at least 4 weeks after discharge. Moderately and severely impaired patients were more likely to achieve clinically meaningful responses.

Parkinson's disease (PD) is a complex disorder producing motor and non-motor symptoms over a long span of time.[1] PD impacts the life of affected people in numerous ways on various levels of functioning.[2] Meanwhile, abundant treatment options have evolved that encompass pharmaco-therapeutical approaches, and numerous functional therapies to improve e.g. speech or gait.[3,4] The provision of an individually tailored therapy to people with PD is recognized as an important clinical challenge. A practical approach in the last years was the development and implementations of multidisciplinary therapy programs that can span up to several weeks, and can be set in an outpatient or inpatient environment. It is noteworthy that all those programs adopt highly practical approaches as they are implemented in the health systems of the respective countries and have to be aligned with local regulations and standards of care.[5]

By now, several such inpatient programs have been published with promising effects on relevant outcome parameters.[6–10] Some of the initial projects were developed in Italy where a 4-week Italian multidisciplinary intensive rehabilitation treatment with three to four daily sessions of physical, occupational and speech therapy five times per week demonstrated noticeable

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effects on motor symptoms, Activities of daily living (ADL) and quality of life (QoL).[6–8] Another Italian inpatient 2-month multidisciplinary program of task-oriented exercises provided by physiotherapists, cognitive-behavioral training conducted by neuropsychologist, and occupational therapy improved motor impairment, ADLs and QoL in subjects with long-duration PD.[9] A 6-week American self-management group rehabilitation program included physical and speech exercises, functional training by occupational therapists and a discussion of self-management strategies two or three times per week. Increased rehabilitation hours showed a beneficial effect on QoL.[10]

In Germany the *multimodal complex treatment* (MCT) was established as an inpatient multidisciplinary concept.[11] MCT is formally indicated when PwP require both optimization of medical treatment and enhanced multi-disciplinary therapy, such as physical-, occupational- or speech-therapy.[12] The introduction of MCT was triggered by the observation of unsatisfactory therapy responses from the limited hospital stay durations within the framework of the diagnosis-related groups (DRG) system.[13,14] For a German hospital to become eligible to offer MCT, it must demonstrate certified medical expertise, daily adjustment of PD medication, and weekly interdisciplinary team meetings. MCT has to provide at least 7.5 hours per week of multi-disciplinary therapy, including 5 hours of individual therapy per week, and at least three health professional disciplines, including physical and occupational therapy.[13]

In 2015, 2% of German PwP received MCT.[15] From 2010 to 2019 the number of MCTs administered increased from 4635 to 16,881, a 3.64-fold increase.[11,16] In 2016, 207 hospitals provided MCT with a yearly case load varying from few patients to more than 500.[11] Three smaller studies had already evaluated MCT.[17–19] One trial including 126 PwP administered 3 weeks of MCT and reported improved motor and non-motor scales before and after MCT.[17] Another trial with 43 PwP who received 2 weeks of MCT stated increases in mobility, quality of life and reductions of depressive symptoms.[18] A 6-week follow-up evaluation with 38 patients showed sustained motor symptom improvements, and positive self-reported state of health. Interestingly, lower motor symptom severity and normal cognitive abilities in the MoCA score both were negatively associated with motor improvement in the part III of the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS).[20] A recent study analyzed the short and medium-range effects of MCT in 134 PwP. On discharge from hospital, balance and motor symptoms were stated as improved. Motor improvement was reported to be positively correlated with the MDS-UPDRS III at admission and negatively with depression. The 4 week follow-up revealed that subjective well-being was related to motor improvement, younger age and absence of depression.[19]

Here, we aimed to identify a robust dataset by including a large real-world sample of all PwP who received MCT over the time span of 5 years for statistical evaluation. We analyze the effectiveness of MCT and determine the predictors for a positive outcome of MCT concerning activities of daily living (ADL) as defined by the achievement of a minimal clinically relevant change.[21,22] Particularly we looked at basic parameters such as age and gender, the degree of baseline ADL-impairment and baseline motor disability as measured by the MDS-UPDRS motor score, the neuropsychiatric comorbidity, and at the type and the intensity of the therapy provided in MCT.

Methods

Study Design, Setting and Participants

The research project was a pragmatic observational retrospective cohort study with data collected in the clinical routine from one certified movement disorder center, the Schön Klinik München Schwabing, Germany.[23] In German hospitals, all inpatient cases are routinely classified by senior medical staff according to the international classification of diseases, 10th version, German modification (ICD-10-GM) diagnosis codes[24] and related operating and procedure keys (OPS-301 codes).[13] Accordingly, MCT is listed in the index of operating and procedure keys (OPS-301 codes) within the German diagnosis-related groups (DRG) systems issued by the German Federal Institute for Drugs and Medical Devices (BfArM, 2008).

Included in the data set were anonymized data of patients with primary Parkinson's disease (ICD-10 G20.0, G20.1, G20.2, G20.9) who received MCT (OPS 8-97d.0, OPS 8-97d.1, OPS 8-97d.2) between January 1, 2015 and December 31, 2019. A further inclusion criterion was the availability of a completed MDS-UPDRS-II at admission (i.e. baseline) and at about 4 weeks after discharge (i.e. follow-up). Up to three missing item records were accepted for datasets to be considered completed. These missing data were imputed by means of the single nearest neighbor method (1NN). Data from patients with secondary or atypical Parkinson's syndromes (ICD-10-GM G21.−/ G21.4, G23.1, G23.2, G23.3) as main diagnosis were excluded.

Ethical Statement and Data Security

The research protocol was approved by the interdisciplinary ethics committee for research of the Katholische Stiftungshochschule München (date: 20210319; registry number: 2021/N14). Written and informed consent was obtained from all patients whose data sets were included as part of the hospital treatment contract signed upon admission. The data were anonymized before statistical computations were performed, in accordance with the relevant guidelines and regulations.

Outcome Parameter

The MDS-UPDRS-II was assessed on hospital admission and 4 weeks after discharge from the hospital.[21] The sum score can

be instrumented to classify PwP in levels of disability, with the ranges of 0–12, 13–29, and values >30 points to constitute mild, moderate, and severe disability, respectively.[25] A reduction by 3.05 points was considered a minimal clinically relevant improvement.[22] Its use was requested from the Movement Disorder Society and authorized.

The paper based survey was driven by a standardized process. The questionnaire was explained at admission. PwP completed the questionnaire by themselves or with the help of a caregiver, before their first medical consultation. They returned the filled-out questionnaire to the admitting physicians, and the data were transferred to an excel sheet. One week after discharge, the administration team sent out a follow-up questionnaire by mail with a free shipping return envelope. In case of no response within 2 weeks, a telephone reminder was placed to the patient.

Database

An pseudonymized initial data set was generated by the quality management team through data linkage from internal Microsoft Excel files based on hospital case numbers (also see Fig. 1). Next, case numbers were deleted and substituted by anonymous identifiers. The anonymized data set was transferred to the research team for data evaluation. The dataset contained baseline and follow-up MDS-UPDRS-II data with both item and sum scores for all PwP who received MCT and were admitted to the hospital from January 1, 2015 to December 31, 2019. Further data included age and gender. The baseline MDS-UPDRS motor score (MDS-UPDRS-III) and the non-motor symptom score (MDS-UPDRS-I), both assessed by the admitting physician, were available for further evaluation. Therapy minutes of individual and group therapy from physiotherapy, occupational

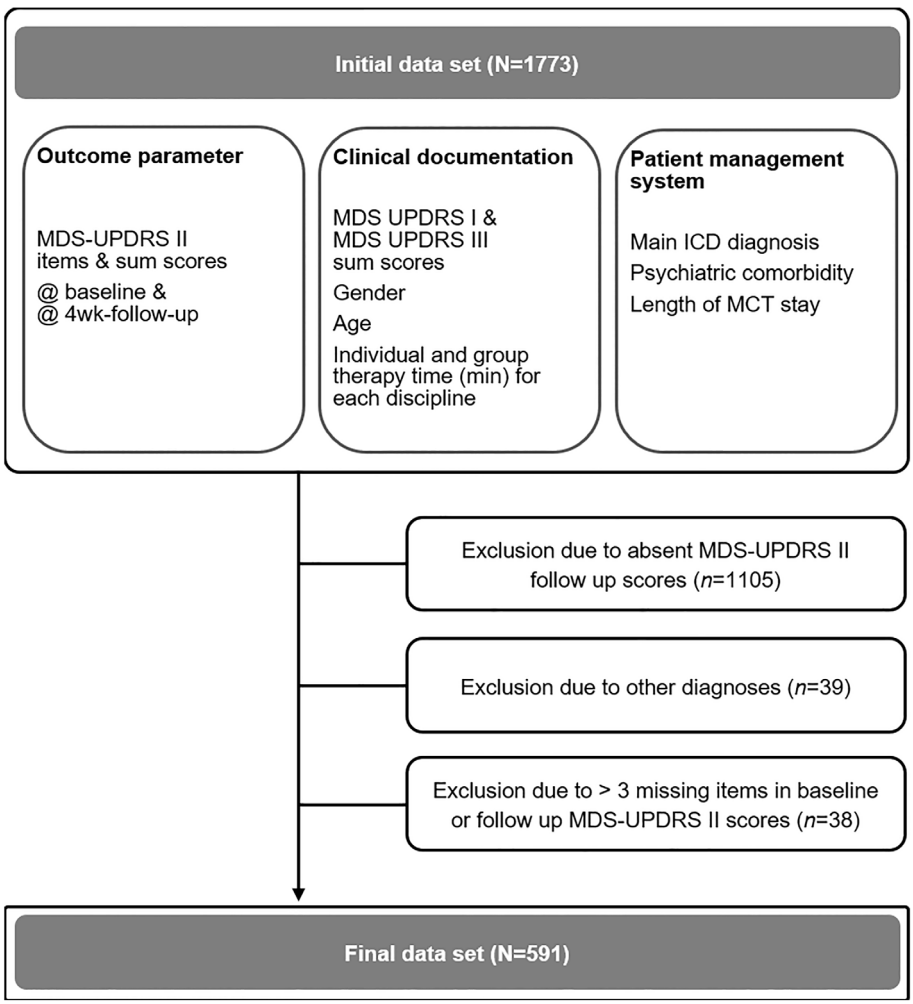

FIG. 1. Database with initial and final data set. MDS-UPDRS I, II, III: Movement disorders society unified Parkinson's disease rating scale part one, two, three.

therapy, speech therapy and neuropsychology were documented for every day of MCT. The diagnoses related group (DRG), the main diagnosis, and secondary mental diagnoses completed the dataset. Hallucination (F06.0) and cognitive dysfunction (F02.3) were coded from ICD-10 diagnoses, and statistically treated as separate entities.

PwP with missing MDS-UPDRS-II questionnaires (baseline or follow-up) were removed from the dataset and documented. The difference of the MDS-UPDRS II baseline to follow-up was calculated (Δ MDS-UPDRS II) and used to code PwP into responders (Δ ≥ 3 points) or non-responders (Δ < 3 points)[22] (also see Table 1).

Statistical Analysis

Qualitative variables values are described as absolute (*n*) and relative (*%*) frequencies. Normal distribution was established for quantitative data using the Shapiro–Wilk test and presented with median (Mdn) and interquartile ranges (IQR). To compare the initial and the final full cohort group comparisons were calculated using t-test and χ^2 statistics. Group differences between responders and non-responders in the full cohort were calculated using the chi-squared test (χ^2) and Mann–Whitney *U*-test (*U*). Improvement of ADL impairment was evaluated using the signed-rank Wilcoxon test. To identify predictors for clinically relevant responders odds ratios with 95% confidence intervals (95% CI) were calculated by logistic regression (LR) with the initial model including all factors. Age and baseline MDS-UPDRS data were introduced in the LR models as ordinal variables. The measure for statistical significance were *P*-values of <0.05. Statistical analyses were performed using the XL-Stat tool (Addinsoft, Paris, France, version 18.04) for MS Excel (Microsoft, Redmont, WA).

Results

Cohort Characteristics

Initial and Final Dataset

The initial data set contained records from 1773 PwP. For 668 patients, baseline and follow-up scores were available, and 1105 patients were excluded for missing follow-up assessments. Reevaluation of diagnosis criteria led to exclusion of 39 non-PD patients. Further 38 PwP were removed because of incomplete data (>three items missing). The final dataset included 591 PwP (33.3%), referred to as the full cohort in the text below (also see Fig. 1). These 591 records were provided by the patients with a median of 28 days (IQR 19.00–52.5) after discharge.

When compared to the initial dataset we detected significant differences for ADL disability (initial cohort: 23.0 ± 9.9 vs full cohort: 22.0 ± 10.0 points, $P = 0.040$), and motor impairment severity (41.5 ± 14.4 vs 39.9 ± 13.8; $P = 0.023$). No differences were found concerning age, gender, treatment days, psychiatric comorbidity, cognitive dysfunction as well as hours of individual therapy and resistive exercise training (see Appendix S1).

Description of the Full Cohort

In the full cohort MCT lasted between 14 and 20 days for 91.7% ($n = 542$) and 21 days or more for 8.3% ($n = 49$) with a mean duration of 16.2 ± 2.34 days (mean ± SD) (min 14 days; max 34 days). The majority of patients, i.e. 542 PwP (92%) were classified as ICD-10 G20.1 (moderate to severe disease), 42 PwP (7.1%) were severely affected and classified as G20.2, and 5 PwP (0.9%) received a G20.9 diagnosis. 348 PwP were men (58.9%) and 243 women (41.1%). 9 PwP(1.5%) were younger than 44 years, 20 (3.4%) were 45–54 years, 100 (16.9%) were 55–64 years, 228 (38.6%) were 65–74 years, 206 (34.9%) were 75–84 years and 28 (4.7%) were above 85 years old (see Table 1).

105 PwP (17.8%) rated their ADL impairment before MCT as mild, 339 PwP (57.4%) as moderate, and 147 (24.9%) considered it to be severe. Data from the MDS-UPDRS-I (non-motor symptom severity) showed that at baseline 110 PwP (18.6%) had mild, 261 PwP (44.2%) moderate, and 220 PwP (37.2%) severe non-motor symptoms. Motor symptom severity according baseline MDS-UPDRS-III rating scores revealed that 148 PwP (29.3%) were mildly, 321 PwP (63.4%) moderately, and 37 PwP (7.3%) severely disabled.

Psychiatric disorders were present in 435 PwP (73.6%), cognitive dysfunction was present in 198 PwP (33.5%), and hallucinations were experienced by 152 PwP (25.7%).

The full cohort received individual therapy with a median of 12.25 hours (IQR 11–14). Group therapy was provided to the full cohort with a median of 8.5 hours (IQR 7.0–10.5). PwP were involved with median 4.0 (IQR 3.0–4.0) allied health care professions, Resistive exercise training was performed with a median of 0.0 hours (IQR 0.0–1.0) in the full cohort.

Differentiation of Responders Vs. Non-responders

In the full cohort a meaningful response was detected in 282 PwP (47.7%). 309 PwP (52.3%) did not attain such an outcome and were considered non-responders (see Fig. 2).

Among women more non-responders were seen; among men responder and non-responder were evenly distributed (see Table 1). We saw higher percentages of responders in the relatively younger age groups <44, 45–54, and 55–64. In the non-responder subgroup, mild and moderate baseline ADL impairment levels were more frequently reported compared to the responder subgroup. On the contrary, severe ADL limitations were reported more frequently by responders. The non-motor disease burden was equally distributed between responders and non-responders, while the motor symptom burden was equally distributed for levels of mild and moderate motor severity, only. PwP with severe motor severity were less often responding meaningfully to MCT. PwP with psychiatric comorbidity were more often non-responders (54.7% vs.45.3%). Similarly, PwP with cognitive dysfunction were seen more often in the non-responder group (60.1% vs. 39.9%), and PwP with hallucinations also were more likely non-responders (55.3% vs. 44.7%). Responders and non-responders received similar amounts of individual therapy with median of 12.5 hours (IQR 11.25–

TABLE 1 *Characteristics of all patients and of the subgroups "responder" and "non-responder"*

	Total group ($N = 591$)		Subgroup: Responder ($n = 282$; 47.7%)		Subgroup: Non-responder ($n = 309$;52.3%)		Responder vs. non-responder		
	n	%	n	%	n	%	χ^2	df	*P*-value
Age in years							11.07	5	**0.018**
<44	9	1.5	5	55.6	4	44.4			
45–54	20	3.4	16	80.0	4	20.0			
55–64	100	16.9	54	54.0	46	46.0			
65–74	228	38.6	109	47.8	119	52.2			
75–84	206	34.9	85	41.3	121	58.7			
>85	28	4.7	13	46.4	15	53.6			
Gender							1.77	1	0.183
Men	348	58.9	174	50.0	174	50.0			
Women	243	41.1	108	44.4	135	55.6			
Baseline severity level									
MDS-UPDRS I							0.77	2	0.679
Mild (0–10)	110	18.6	55	50.0	55	50.0			
Moderate (11–21)	261	44.2	127	48.7	134	51.3			
Severe (>22)	220	37.2	100	45.4	120	54.6			
MDS-UPDRS II							6.05	2	**0.048**
Mild (0–12)	105	17.8	40	38.1	65	61.9			
Moderate (13–29)	339	57.4	163	48.1	176	51.9			
Severe (>30)	147	24.9	79	53.7	68	46.3			
MDS-UPDRS III ($n = 506$)							1.29	2	0.525
Mild (0–32)	148	29.3	71	48.0	77	52.0			
Moderate (33–58)	321	63.4	161	50.2	160	49.8			
Severe (>59)	37	7.3	15	40.5	22	59.5			
Disease severity (ICD-10-GM)							0.31	2	0.854
Moderate (G20.1)	542	92.0	257	47.4	285	52.6			
Severe (G20.2)	42	7.1	20	47.6	22	52.4			
Unclassifiable (G20.9)	5	0.9	3	60.0	2	40.0			
Fluctuations							0.09	1	0.765
No	203	34.8	98	48.3	105	51.7			
Yes	381	65.2	179	47.0	202	53.0			
Psychiatric disorder (any F-diagnosis)							3.9	1	**0.048**
No	156	26.4	85	54.5	71	45.5			
Yes	435	73.6	197	45.3	238	54.7			
Cognitive disorder (F02.3)							7.29	1	**0.007**
No	393	66.5	203	51.7	190	48.3			
Yes	198	33.5	79	39.9	119	60.1			

(Continues)

TABLE 1 *Continued*

	Total group ($N = 591$)		Subgroup: Responder ($n = 282$; 47.7%)		Subgroup: Non-responder ($n = 309$;52.3%)		Responder vs. non-responder		
	n	%	n	%	n	%	χ^2	df	*P*-value
Hallucination (F06.0)							0.73	1	0.394
No	439	74.3	214	48.8	225	51.2			
Yes	152	25.7	68	44.7	84	55.3			
Days of treatment							1.9	1	0.168
14–20	542	91.7	254	46.9	288	53.1			
≥21	49	8.3	28	57.1	21	42.9			
	Mdn	**IQR**	**Mdn**	**IQR**	**Mdn**	**IQR**	***U* (standardized)**		***P*-value**
Individual therapy in hours	12.25	11.0–14.0	12.50	11.25–14.25	12.00	11.00–13.75	−2.22		**0.026**
Group therapy in hours	8.50	7.0–10.5	9.00	7.00–10.88	8.50	7.00–10.00	−1.55		0.120
Number allied health care profession	4.00	3.0–4.0	4.00	3.00–4.00	4.00	3.00–4.00	−0.53		0.593
Resistance exercise in hours	0.0	0.0–1.0	0.00	0.00–1.75	0.00	0.00–1.00	−2.18		**0.029**

The "mild–moderate–severe" baseline severity levels used for the MDS-UPDRS parts I to III are based on the categories published by Martinez-Martin et al.[25] MDS-UPDRS I, II, III: Movement Disorders Society Unified Parkinson Disease Rating Scale part one, two, three; ICD-10-GM: International Statistical Classification of Diseases and Related Health Problems, 10. Revision, German Modification.

14.25) for responders vs. median 12.0 hours (IQR 11.00–13.75) for non-responders. Similar data were seen with group therapy that was given to responders with a median of 9.0 hours (IQR 7.0–10.88), and to non-responders with a median of 8.5 (IQR 7.0–10.0). Resistive exercise training was provided with a median of 0.0 hours (IQR 0.0–1.75) to responders and with 0.0 hours (IQR 0.0–1.0) to non-responders.

Effects of MCT on the Motor Aspects of Experiences of Daily Living

In the full cohort, the self-reported motor aspects of experiences of daily living improved from 22.3 ± 10.2 (mean ± SD) at baseline to 19.9 ± 11.2 at follow-up by −2.4 points ($P < 0.0001$) (see Fig. 2 and Table 2).

Slightly better responses were detected in the subgroups of younger age (45–54 y, n = 20: −3.2; $P = 0.019$ from 16.6 ± 8.3 to 13.4 ± 10.0 and 55–64 y, n = 100: −3.8; $P = <0.0001$ from 18.7 ± 9.2 to 14.8 ± 9.2). Also the subgroup of PwP without psychiatric comorbidity (n = 156) enhanced by −3.2 points ($P = <0.0001$) from 18.1 ± 8.5 to 14.9 ± 8.9. The subgroup of PwP without a diagnosis of cognitive decline ($n = 393$) improved by −3.0 ($P = <0.0001$) from 19.3 ± 9.1 to 16.4 ± 9.5. More than four points of ADL improvement were reached by the subgroup of severe baseline ADL impairments

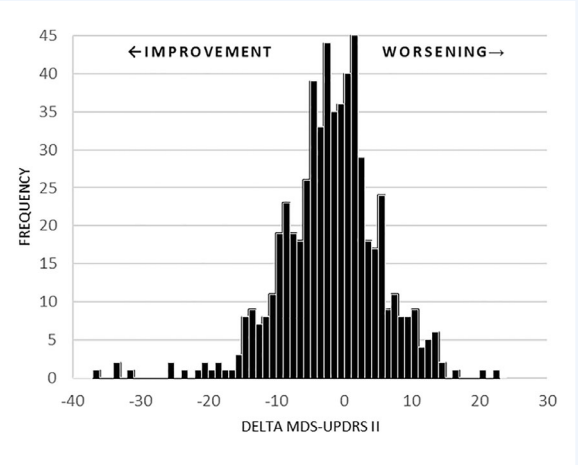

FIG. 2. The histogram shows the frequencies of observed differences between baseline (BL) an follow-up (FU) assessments of the MDS-UPDRS II scores.

(n = 147): −4.6; $P = <0.0001$; from 36.3 ± 4.9 to 31.7 ± 9.8, the subgroup of severe disease severity (n = 42): −4.7; $P = <0.0001$; from 36.7 ± 8.9 to 32.1 ± 12.2, and the subgroup of a longer treatment duration with more than 20 days (n = 49): −4.3; $P = <0.0001$; from 25.5 ± 10.3 to 21.1 ± 10.7 (see Table 2).

We detected statistically significant associations of the outcome to MCT with age (χ^2 (5, $N = 591$) = 11.07, $P = 0.018$), with the

TABLE 2 *Effectiveness of multimodal complex treatment for the whole group and subgroups*

		BL MDS-UPDRS II		FU MDS-UPDRS II			
	N	**Mean**	**SD**	**Mean**	**SD**	**Δ**	**P**
Whole group	591	22.3	10.2	19.9	11.2	−2.4	<0.0001
Subgroup age							
<44	9	15.0	6.1	11.7	6.5	**−3.3**	0.109
45–54	20	16.6	8.3	13.4	10.0	**−3.2**	0.019
55–64	100	18.7	9.2	14.8	9.2	**−3.8**	<0.0001
65–74	228	20.5	9.9	18.0	10.8	−2.5	<0.0001
75–84	206	26.2	9.9	24.5	10.8	−1.6	0.010
>85	28	27.8	8.6	26.8	8.8	−1.0	0.386
Subgroup gender							
Men	348	23.3	10.4	20.5	11.4	−2.8	<0.0001
Women	243	20.9	9.7	19.1	10.8	−1.8	0.0001
Subgroup baseline severity level							
MDS-UPDRS I							
Mild (0–10)	110	14.4	7.7	12.2	8.3	−2.2	<0.0001
Moderate (11–21)	261	20.7	8.3	18.5	9.7	−2.2	<0.0001
Severe (>22)	220	28.2	9.9	25.5	11.2	−2.7	<0.0001
MDS-UPDRS II							
Mild (0–12)	105	8.9	2.9	8.3	5.6	−0.6	0.026
Moderate (13–29)	339	20.4	4.8	18.4	8.0	−1.9	<0.0001
Severe (>30)	147	36.3	4.9	31.7	9.8	**−4.6**	<0.0001
MDS-UPDRS III ($n = 506$)							
Mild (0–32)	148	15.6	7.4	13.5	8.9	−2.0	<0.0001
Moderate (33–58)	321	23.5	9.2	20.6	10.0	−2.9	<0.0001
Severe (>59)	37	34.5	8.1	31.6	11.1	−2.9	0.013
Subgroup							
Disease severity (ICD-10-GM)							
Moderate (G20.1)	542	21.1	9.4	19.0	10.6	−2.2	<0.0001
Severe (G20.2)	42	36.7	8.9	32.1	12.2	**−4.7**	<0.0001
Unclassificable (G20.9)	5	26.8	12.2	24.6	13.5	−2.2	0.416
Fluctuations							
No	203	22.1	9.8	19.9	10.4	−2.2	<0.0001
Yes	381	22.3	11.4	19.9	11.4	−2.4	<0.0001
Subgroup							
Psychiatric disorder (F-diagnosis)							
No	156	18.1	8.5	14.9	8.9	**−3.2**	<0.0001
Yes	435	23.8	10.3	21.7	11.4	−2.1	<0.0001

(Continues)

TABLE 2 *Continued*

		BL MDS-UPDRS II		FU MDS-UPDRS II			
	N	Mean	SD	Mean	SD	Δ	P
Subgroup							
Cognitive disorder (F02.3)							
No	393	19.3	9.1	16.4	9.5	**−3.0**	<0.0001
Yes	198	28.2	9.7	27.0	10.9	−1.2	0.080
Subgroup							
Hallucination (F06.0)							
No	439	20.3	9.4	17.7	10.1	−2.6	<0.0001
Yes	152	28.0	10.3	26.3	11.8	−1.7	0.018
Subgroup							
Days of treatment							
14–20	542	22.0	10.1	19.8	11.2	−2.2	<0.0001
≥21	49	25.5	10.3	21.1	10.7	**−4.3**	0.0006

Improvements of the MDS-UPDRS II in subgroups above the clinically meaningful response of three points are in bold.

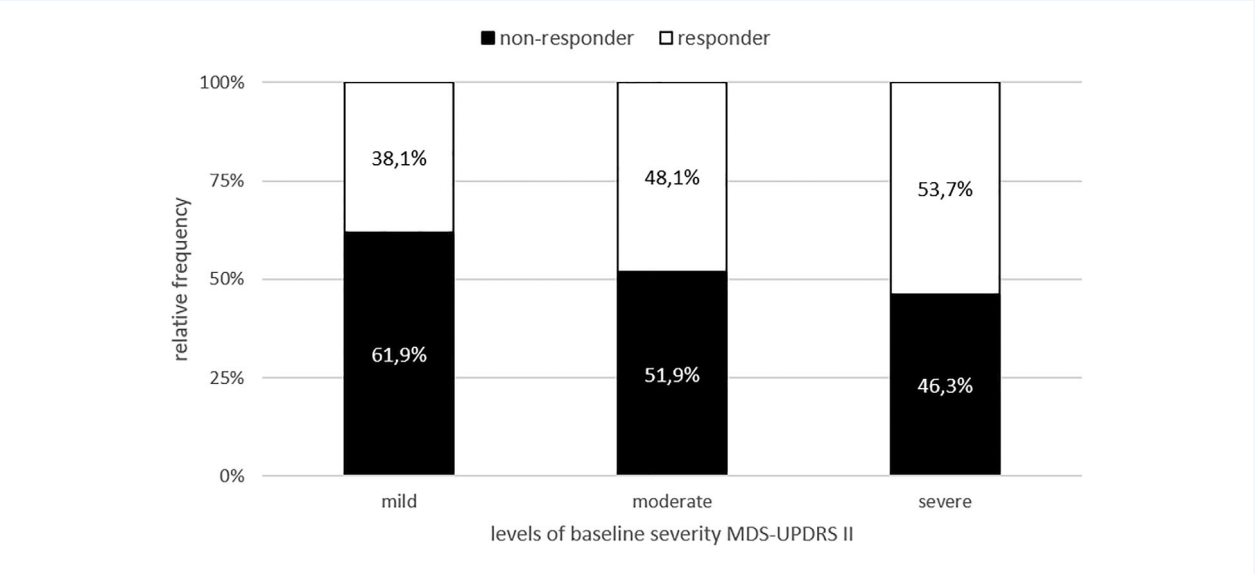

FIG. 3. There was a significant trend ($P = 0.048$) towards a more beneficial MCT response associated with higher baseline levels of ADL disability.

level of ADL impairment at baseline (χ^2 (2, $N = 591$) = 6.05, $P = 0.048$), with psychiatric comorbidity (χ^2 (1, $N = 591$) = 3.9, $P = 0.048$), and with presence of cognitive decline (χ^2 (1, $N = 591$) = 7.29, $P = 0.007$) (see Table 1).

PwP who had a clinically meaningful response to MCT received more individual therapy compared to non-responders (12.5 vs.12.0, $U = -2.22$, $P = 0.026$). In addition, we saw that responder PwP spent more hours with resistive exercise training (0 vs. 0, $U = -2.18$, $P = 0.029$) (see Table 1).

Predictors of Treatment Response to MCT

LR revealed that the MDS-UPDRS-II baseline severity level predicted the outcome to MCT in terms of attaining a meaningful response (see Fig. 3). PwP with moderate severity had an about 2fold chance (OR 2.08; 95% CI 1.20–3.61; $P = 0.009$) and PwP with severe severity had an about 6fold chance (OR 5.92; 95% CI 2.76–12.68; $P < 0.0001$) to become a

TABLE 3 *Regression results of the random effects model to examine the predictors for a clinically meaningful MCT-response*

		95% CI		
	Odds ratio (adjusted)	**Lower bound**	**Upper bound**	***P*-value**
Age in years				
<44				
45–54	3.57	0.56	22.64	0.178
55–64	1.06	0.23	4.84	0.943
65–74	0.85	0.19	3.80	0.831
75–84	0.60	0.13	2.75	0.513
>85	0.85	0.15	4.93	0.857
Gender				
Men				
Women	0.75	0.50	1.13	0.173
Baseline severity level				
MDS-UPDRS I				
Mild (0–10)				
Moderate (11–21)	0.82	0.48	1.39	0.454
Severe (>22)	0.69	0.37	1.28	0.240
MDS-UPDRS II				
Mild (0–12)				
Moderate (13–29)	**2.08**	1.20	3.61	**0.009**
Severe (>30)	**5.92**	2.76	12.68	**<0.0001**
MDS-UPDRS III				
Mild (0–32)				
Moderate (33–58)	1.15	0.73	1.81	0.542
Severe (>59)	0.58	0.24	1.44	0.241
Disease severity (ICD-10-GM)				
Moderate (G20.1)				
Severe (G20.2)	0.69	0.31	1.57	0.382
Fluctuations				
No				
Yes	1.10	0.73	1.65	0.650
Psychiatric disorder (any F-diagnosis)				
No	0.78	0.48	1.27	0.318
Yes				
Cognitive disorder (F02.3)				
No				
Yes	0.67	0.40	1.12	0.128
Hallucination (F06.0)				
No				
Yes	1.18	0.72	1.96	0.512

(Continues)

TABLE 3 *Continued*

	Odds ratio (adjusted)	95% CI		*P*-value
		Lower bound	Upper bound	
Days of treatment				
14–20				
≥21	1.37	0.64	2.92	0.416
Individual therapy in hours	1.03	0.93	1.13	0.556
Group therapy in hours	0.98	0.91	1.06	0.644
Number allied health care profession	1.13	0.86	1.47	0.388
Resistance exercise in hours	1.12	0.95	1.33	0.187

MDS-UPDRS I, II, III, Movement Disorders Society Unified Parkinson's Disease Rating Scale part one, two, three; CI, confidence interval.

responder compared to mildly impaired patients. The logistic regression model was statistically significant (χ^2 (22) = 40.68, $P = 0.009$, Nagelkerke's $R^2 = 0.12$).

No other variables significantly affected the response to MCT (see Table 3).

Discussion

Inpatient multi-disciplinary care has internationally evolved as an important contribution to meet the various individual clinical needs of PwP. In the German health care system, MCT is provided to tens of thousands of PwP every year.[11]

We describe the patient-reported outcomes on daily life motor experiences in a large cohort of 591 PwP collected over a period of 5 years from a specialized Parkinson's hospital. According to the PRECIS-2 tool, the study can be considered to follow a pragmatic approach[26] (see Appendix S2 for details). The data collection was motivated to improve the delivery of health care by systematic measurements of condition-specific outcome variables,[27] and the public reporting of quality indicators of health services.[28,29] The Schön Klinik München Schwabing had implemented such a standardized acquisition of patient-reported MDS-UPDRS II data to routinely evaluate the quality of clinical outcome.[28,30] We demonstrated that the sample chosen for statistical analyses was representative of the initial dataset.

The study revealed two main novel insights. First, it convincingly showed that MCT improved the perceived ADL disability of PwP up to 4 weeks after discharge from the hospital. This is an important finding, as 80% of PwP were moderately or severely affected in terms of their ADL disability. Thus, the study underpins the results of smaller studies concerning the effectiveness of the intervention.[17–20] It is noteworthy that the improvement of 2.4 points in the MDS-UPDRS II is comparable to the reports of two other studies that both found a similar reduction after MCT using the same outcome scale.[17,20] Moreover, ADL improvements of this scale are in line with multidisciplinary therapy programs in other countries, such as the above mentioned Italian program that enhanced ADL by 2.9 points after the first intervention, and by 2.0 points after a second intervention 1 year later.[8]

It should be pointed out that the full cohort failed to attain the meaningful response of 3.0, which again points to the important need to delineate predictors of response. Here, such a favorable group response was detected among the subgroup of PwP with severe baseline ADL impairments (−4.6) and the subgroup with severe motor impairment (−4.7). Those findings also be supported from a previous multidisciplinary program that showed that more concerns with mobility and ADL at baseline were related to increased benefit from rehabilitation.[10] Another study reported that motor symptom improvement was positively associated to the motor impairment at admission.[19]

Another subgroup that attained a meaningful response were those who received a longer treatment duration of more than 20 days. That more training hours could result in a better outcome has been shown previously, too.[10]

Cognitive abilities are an important factor for a patient's ability to make clinical progress from a rehabilitation program.[31] Here, PwP without neuropsychiatric comorbidity, and similarly PwP without cognitive impairment, improved more than their counterparts who experienced these issues. However, this data should not be used as an argument against the provision of MCT as reports from others had shown that specific, intensive rehabilitative approaches were able to gain comparable benefits in PwP with and without cognitive impairment.[32]

The second major finding of this study was that baseline ADL impairment predicted the clinically meaningful outcome of MCT. PwP with moderate impairment had a two-fold, PwP with severe impairment a 6-fold chance to attain a meaningful response.[22] Hartelt et al. had formally defined responders by a minimum of one point improvement. By this definition they described shorter disease duration and lower levodopa equivalent doses to predict an improvement in ADL impairment. In contrast to our findings baseline ADL impairment did not predict the positive MCT response.[20]

Further statistically significant predictors for a positive response to MCT were published with respect to gains in QoL, the improvement of motor impairment,[18,20] and the subjective well-being.[19] Improvements in QoL were reported to occur more frequently in PwP with mild motor symptom severity, while PwP with moderate to severe motor impairment had reduced chances for gains in QoL. PwP without cognitive impairment were found to have lower chances to improve motor symptom severity after MCT.[17,19] An absence of depression predicted a better chance to attain subjective well-being after MCT.[19] As we did not explore these outcomes we cannot compare our data against these reports, but we caution some restraint to the interpretation of such results from small cohorts.

There were other observations that merit further exploration.

We saw that the provision of extended therapy time was more often observed in those PwP positively responding to MCT. The mean individual therapy time varied significantly between responders and non-responders by 0.5 hours. This is in line with work of others suggesting greater effects on motor function, mobility, and quality of life in higher-intensity physical exercise.[33,34] Rafferty and colleagues found that a 30 min increase of exercise time was associated with slower decline in quality of life, especially for more severely impaired PwP.[34] However in our LR model, individual therapy time would not predict treatment outcome. A possible explanation might be the minimum required individual therapy of 5 hours per week that could have diminished the contrast needed to demonstrate a significant effect.[13]

Our study showed a significant difference in the amount of resistive exercise training between responders and non-responders. Such a finding was to be expected, given that regular progressive resistance training over an extended period of time was demonstrated to improve motor symptoms.[35] A similar study had shown that daily, 1-hour strength training in combination with physical and occupational therapy over a course of 4 weeks improved motor symptoms and self-rated ADL performance in PwP in moderate disease stages.[6]

There are several limitations to this mono-centre observational cohort study. First, the lack of control group makes the effects not precisely attributable to MCT. Furthermore, we did not assess the change in dopaminergic therapy so we cannot exclude that pharmacotherapy might co-explain the effects reported in this study. The data included in this retrospective analysis were routinely collected as clinical documentation for reimbursement purposes within the framework of the DRG system. Thus, coded diagnoses, secondary diagnoses, and ratings of motor and non-motor symptoms could have been affected by observer bias due to varying personnel over the long course of data acquisition.[36] Recommended measures to reduce selection bias from patient reported outcomes include careful selection of survey instruments, a survey mode that favors objectivity through postal surveys, and information and motivation of participants to ensure sufficient response.[37] All those measures were implemented here. Still a selection bias caused by missing follow-up evaluations cannot be fully ruled out.[38]

The comparison between the initial and the final cohort showed slightly less ADL disability and motor impairment within the latter group, but the ADL and motor state for both groups can be assigned as moderately impaired.[25] This marginally greater disability may have influenced the ability or motivation to return the follow-up questionnaire. Lastly, we were not able to supervise how the patients filled out the follow-up forms, with or without caregivers, which might have influenced the results as well.[39]

In summary, the study shows that MCT improves self-reported ADL impairment in a relatively short period of time of about 2 weeks that is sustained for at least 4 weeks. PwP of moderate to severe ADL impairment have a higher chance to achieve a clinically meaningful response. In-patient multi-disciplinary rehabilitation therapy in specialized units—such as MCT—could prove to be a successful model to provide individually tailored therapy for PwP.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution. (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

KZ: 1A, 1B, 1C, 2A, 2B, 3A.
MM: 1B, 1C, 3B.
MP: 1B, 1C, 3B.
KS: 1B, 1C, 3B.
BR: 1A, 2C, 3B.
UF: 1A, 1B, 1C, 2A, 2B, 3B.
AC-B: 1A, 1B, 2C, 3B.

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Ethical Compliance Statement: The research protocol was approved by the interdisciplinary ethics committee for research of the Katholische Stiftungshochschule München (date: 2021-03-19; registry number: 2021/N14). Written and informed consent was obtained from all patients whose data sets were included as part of the hospital treatment contract. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. ■

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Supporting Information

Supporting information may be found in the online version of this article.

Appendix S1. Table A1. Comparison of parameters of initial and final data set

Appendix S2. The table shows the scoring of the trial according to the PRECIS-2 tool's criteria, the spider diagram provides a visualization.