

# Rehabilitation improves dyskinesias in Parkinsonian patients: A pilot study comparing two different rehabilitative treatments

Giuseppe Frazzitta<sup>a,\*</sup>, Gabriella Bertotti<sup>a</sup>, Micaela Morelli<sup>c,i</sup>, Giulio Riboldazzi<sup>d</sup>, Elisa Pelosin<sup>e</sup>, Pietro Balbi<sup>a</sup>, Natalia Boveri<sup>a</sup>, Cristoforo Comi<sup>f</sup>, Marinella Turla<sup>g</sup>, Serena Leva<sup>h</sup>, Guido Felicetti<sup>a</sup> and Roberto Maestri<sup>b</sup>

<sup>a</sup>Department of Neurorehabilitation, Scientific Institute of Montescano, S. Maugeri Foundation IRCCS, Montescano, Italy

<sup>b</sup>Department of Biomedical Engineering, Scientific Institute of Montescano, S. Maugeri Foundation IRCCS, Montescano, Italy

<sup>c</sup>Department of Toxicology and Centre of Excellence for Neurobiology of Dependence, University of Cagliari, Cagliari, Italy

<sup>d</sup>Center for Parkinson's Disease, Macchi Foundation, Varese and Department of Rehabilitation, "Le Terrazze" Hospital, Cunardo, Italy

<sup>e</sup>Department of Neurosciences, University of Genoa, Genoa, Italy

<sup>f</sup>Department of Neurology, University of the Eastern Piedmont, Novara, Italy

<sup>g</sup>Department of Neurology, Valle Camonica Hospital, Esine, Italy

<sup>h</sup>Department of Neurology, University of Insubria, Varese, Italy

<sup>i</sup>CNR Institute for Neuroscience, Section of Cagliari, Italy

**Abstract.** *Goal and objectives:* The present study was devised: (a) to test whether an intensive (60 hours in 4 weeks) multidisciplinary rehabilitation treatment (involving physiotherapy, exercises to improve gait and balance using treadmill and stabilometric platform, occupational therapy) for Parkinsonian patients is effective in improving dyskinesia and motor performance compared to a control group undergoing a non-intensive non multidisciplinary rehabilitation treatment (30 hours in 4 weeks involving physiotherapy only); and (b) to verify whether rehabilitation may lead to a reduction in levodopa dosage.

*Material and Methods:* Forty Parkinsonian patients suffering from dyskinesias were admitted to study: 20 for an intensive multidisciplinary (Group1) and 20 for a non-intensive non multidisciplinary rehabilitation treatment (Group2). The rating scales used for the clinical evaluation were: Unified Parkinson's Disease Rating Scales (UPDRS) II, III, IV, Parkinson's disease disability scale (PDDS), Abnormal Involuntary Movement Scale (AIMS).

*Results:* All outcome measurements improved in both groups of patients, but patients Group1 presented better results: UPDRS II was reduced by 33% in Group1 and by 22% in Group2, UPDRS III 29% vs. 22%, UPDRS IV 74% vs. 10%, PDDS 18% vs. 12%, and AIMS 71% vs. 8%. A different behaviour was observed for levodopa dosage at baseline and after treatment: dosage decreased by an average value of 210 mg ( $p < 0.0001$ ) in Group1 and was virtually unchanged (30 mg reduction,  $p = 0.08$ ) in Group2.

*Conclusion:* Our findings suggest that a rehabilitation protocol should be considered as a valid non-invasive therapeutic support for patients who show dyskinesias and that there are better results when the treatment is intensive.

**Keywords:** Parkinson's disease, intensive rehabilitation, dyskinesias

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\*Corresponding author: Giuseppe Frazzitta, Department of Neurorehabilitation, Scientific Institute of Montescano, S. Maugeri Foundation IRCCS, Via per Montescano, 27040 Montescano (PV), Italy.

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Tel.: +39 03852471; Fax: +39 038561386; E-mail: giuseppe.frazzitta@fsm.it.

## 1. Introduction

Pharmacological treatment has changed the natural history of Parkinson's disease (PD), improving survival [19,40,11]. A major limiting factor in levodopa therapy is the development of motor complications, in particular dyskinesia, which affects 30–40% of chronically treated PD patients [18,21]. In the early stages of PD, levodopa is stored in surviving presynaptic dopaminergic terminals in the striatum and gradually released. When those terminals are lost, the duration of the levodopa effect becomes shorter and simply reflects its plasma half-life. The exposure of the denervated basal ganglia to the pulsatile plasma levodopa levels may lead to dyskinesia induction [26].

Dyskinesias are usually choreiform and peak-dose, worsen the quality of life of patients, and constitute a very difficult-to-treat, important adverse side effect of levodopa treatment.

Even though dyskinesias can improve by reducing the dopaminergic therapy, it is usually cumbersome to decrease the levodopa dosage since this reduction elicits a worsening of motor symptoms in Parkinsonian patients: an increased bradykinesia, an increased "off time", a reduction of motor performances and of autonomy in daily activities.

Moreover, dyskinesias generally respond poorly to drugs [6,8,24], and other effective strategies, such as deep brain stimulation of the subthalamic nuclei, can be applied only in selected patients [12,41].

Recently published studies on animals [28,30] allow hypothesizing a direct action of physical activity on the mechanisms responsible for dyskinesias.

The present study was devised: (a) to test whether an intensive multidisciplinary rehabilitation treatment (IRT) for Parkinsonian patients is effective in improving dyskinesia, motor performance, and autonomy in daily living activities and whether there are differences compared to a control group undergoing a non-intensive non-multidisciplinary rehabilitation treatment (NIRT); and (b) to verify whether rehabilitation allows a reduction in levodopa dosage.

## 2. Methods

### 2.1. Study population

Patients were screened from among those consecutively admitted to the movement disorder ambulatories of the Rehabilitation Institute of Montescano and

the Rehabilitation Institute of Cunardo. Eligibility criteria for patients were (a) diagnosis of "clinically probable" idiopathic Parkinson's disease according to Gelb et al. [15], (b) development of dyskinesias in the last 3 years and a history of several failed attempts to improve dyskinesia by reducing or modifying drug dosage, (c) ability to walk without any physical assistance, (d) no cognitive impairment (mini-mental state examination score  $\geq 26$ ), (e) no comorbidity unrelated to Parkinson's disease, (f) no vestibular/visual dysfunction limiting locomotion or balance, and (h) antiparkinsonian medications stable for  $> 4$  weeks.

Twenty eligible patients were invited to be admitted to the Rehabilitation Institute of Montescano for a 4-week IRT (Group 1), and twenty eligible patients were invited to be admitted to the Rehabilitation Institute of Cunardo for a 4-week NIRT (Group 2).

Patients were examined by a neurologist who was blinded to the study design.

The study was approved by the local Ethics Committee, and all subjects gave their informed written consent before participation.

### 2.2. Assessment of outcome

The primary outcome measure was the Unified Parkinson's Disease Rating Scale Sections 2, 3, and 4 (UPDRS II, III, IV) [10] and the self-assessment Parkinson's Disease Disability Scale (PDDS) [2]. To assess the severity of dyskinesia, we used the Abnormal Involuntary Movement Scale (AIMS) [35]. The neurologist examined the patients in the morning, one hour after they had taken the first dose of levodopa, both at baseline and at the end of the rehabilitation treatment (stage "on").

The secondary outcome measure was the dosage of levodopa equivalent.

Changes in Levodopa dosage were made by the neurologist of the rehabilitation group according to the following guidelines: the dosage was not changed during the first week of treatment. Starting from the second week the dosage was slowly decreased by initially suspending I-COMT drugs (when used) and then, if the clinical status of the patient allowed it, progressively reducing the levodopa dosage. Usually in the last week the dosage was left unchanged. We used this strategy because we knew that the exposure of the denervated basal ganglia to the pulsatile plasma levodopa levels leads to dyskinesia induction [26]. Reducing the exposure to drugs, a reduction of duration and intensity of dyskinesia was obtained.

### 2.3. Sample size computation

From published studies we found that the standard error of measurement (SEM) is 1.4 and 4 for UPDRS II and UPDRS III respectively. We expected an effect size around 2 and 5.2 (moderate clinically important difference according to Shulman and colleagues) [33] for UPDRS II and UPDRS III respectively. Hence, to detect a change with a two-tailed type I error of 0.05 and a power of 80%, the estimated sample size (the largest between the two estimates) was 20 patients for each treatment group (Student approximation).

### 2.4. Intervention

Patients assigned to Group 1 were admitted to the Rehabilitation Institute of Montescano (Pavia), Italy, where they underwent IRT. IRT consisted of a 4-week cycle of physiotherapy that entailed three daily sessions (two in the morning and one in the afternoon), 5 days a week. The global duration of each session, including recovery periods, was about one hour. The first session comprised cardiovascular warm-up activities, relaxation exercises, muscle-stretching exercises (scapular muscle group, hip flexor, hamstring and gastrocnemius muscles), exercises to improve the range of motion of spinal, pelvic and scapular joints, exercises to improve the functionality of the abdominal muscles, and postural changes in the supine position.

The second session comprised exercises to improve balance and gait using a stabilometric platform with a visual cue (the patients were asked to follow a circular pathway on the screen by using a cursor sensitive to their feet movements on the platform) and treadmill plus (treadmill training with both a visual and an auditory cue) [14]. The last session was a session of occupational therapy aimed to improve autonomy in daily living activities: transferring from sitting position to standing position, rolling from supine position to sitting position and from sitting to supine, dressing, use of tools, and exercises to improve hand functionality and skills (for example, using screws and bolts).

Inpatients assigned to Group 2 were admitted to the Rehabilitation Institute of Cunardo (Varese) where they underwent a NIRT: a 4-week cycle of physiotherapy with one session, 5 days a week. The session, about 90 minutes, comprised cardiovascular warm-up activities, relaxation exercises, muscle-stretching exercises (scapular muscle group, hip flexor, hamstring and gastrocnemius muscles), exercises to improve the range of motion of spinal, pelvic and scapular joints, exercis-

es to improve the functionality of the abdominal muscles, postural changes in the supine position, and gait training performed in the gymnasium.

### 2.5. Statistical analysis

Descriptive statistics are given as mean  $\pm$  SD. The Shapiro–Wilk statistic was used to test the normality of the distribution of all variables.

The effect of the different rehabilitation treatments on each variable considered was assessed by a two-factor analysis of variance: the first factor was the type of treatment (IRT versus NIRT) and the second factor was time (admission versus discharge), with repeated measurements in the time factor. Within-group comparisons were carried out by paired *t*-tests or by a Wilcoxon's matched pairs test in case of violation of the normality assumption. Between-group comparisons were carried out by unpaired *t*-tests or by the Mann–Whitney U-test if appropriate.

A *p*-value  $< 0.05$  was considered statistically significant. All analyses were carried out using the SAS/STAT statistical package, release 9.2 (SAS Institute Inc., Cary, NC, USA).

## 3. Results

Demographic, clinical, and functional characteristics at baseline and after the rehabilitation program are reported in Table 1 for both groups of patients, those who underwent IRT ( $N = 20$ ) and those who performed a NIRT ( $N = 20$ ).

All outcome measurements improved by the end of treatment in both groups of patients. However, the changes over time of UPDRS II and IV scores were different in IRT and in NIRT patients, as assessed by a significant time-treatment interaction ( $p = 0.036$  and  $p < 0.0001$ , respectively) in the analysis of variance. In the IRT group UPDRS II was reduced by 33% ( $p < 0.0001$ ) and UPDRS IV was reduced by 74% ( $p < 0.0001$ ) while in the NIRT group UPDRS II was reduced by 22% ( $p < 0.0001$ ) and UPDRS IV was reduced by 10% ( $p < 0.0001$ ).

The time course of UPDRS III did not differ in the two groups ( $p = 0.064$  for time-treatment interaction), with an average 26% reduction ( $p < 0.0001$ ).

The changes over time of PDDS were different in the two groups of patients ( $p < 0.0001$  for time-treatment interaction), with a 18% reduction in IRT and a 12% reduction in NIRT patients ( $p < 0.0001$  for both).

Table 1  
Demographic, clinical, and functional characteristics at baseline and after the rehabilitation program for patients who underwent intensive rehabilitation treatment (IRT) and non-intensive rehabilitation treatment (NIRT)

	IRT (N = 20)		NIRT (N = 20)	
	Baseline	After rehabilitation	Baseline	After rehabilitation
Age (years)	71 ± 8		70 ± 7	
Duration of the disease (years)	12.8 ± 6.6		13.0 ± 3.6	
Duration of dyskinesias (years)	5.3 ± 3.3		5.7 ± 3.5	
Male/female	8/12		9/11	
Levodopa (mg/die)	907 ± 416	697 ± 363 <sup>†</sup>	808 ± 189	793 ± 188
UPDRS II score	16.6 ± 5.5	11.2 ± 4.7 <sup>†</sup>	17.4 ± 4.2	13.7 ± 3.8 <sup>†</sup>
UPDRS III score	21.8 ± 5.6	15.4 ± 4.4 <sup>†</sup>	24.6 ± 7.9	19.5 ± 7.1 <sup>†</sup>
UPDRS IV score	6.3 ± 3.2	1.6 ± 1.4 <sup>†</sup>	7.0 ± 2.0	6.4 ± 2.1 <sup>†</sup>
PDDS score	68.0 ± 20.7	50.3 ± 13.7 <sup>†</sup>	56.0 ± 21.4	49.7 ± 19.8 <sup>†</sup>
AIMS score	13.2 ± 6.8	3.5 ± 2.7 <sup>†</sup>	13.3 ± 7.4	12.4 ± 7.4 <sup>‡</sup>

<sup>†</sup>:  $p < 0.0001$  compared to Baseline.

<sup>‡</sup>:  $p < 0.05$  compared to Baseline.

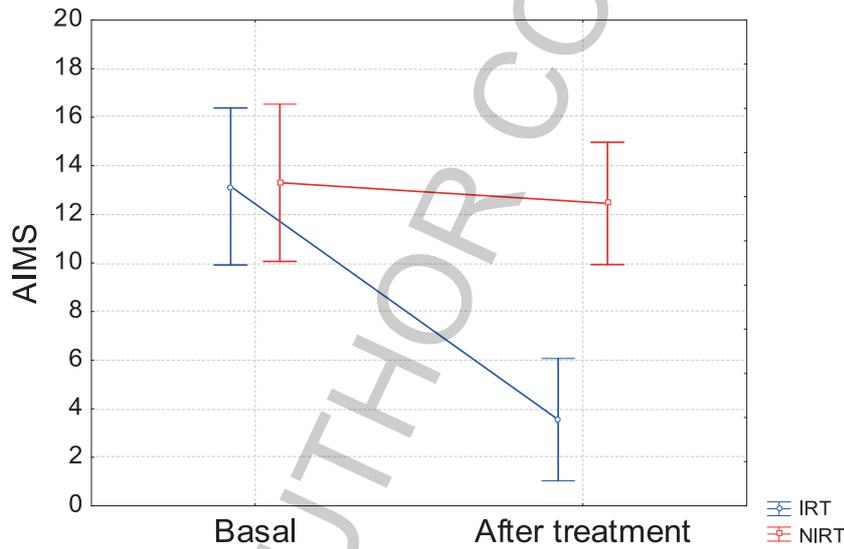


Fig. 1. Graphical representation of time-treatment interaction for the variable AIMS. Differences in treatment effect are reflected by differences in the slope of the lines joining the mean value AIMS at baseline and after rehabilitation in the two groups. Data are plotted as mean ± 95% confidence interval, solid line for patients who underwent intensive rehabilitation treatment (IRT) and dashed line for patients who underwent non-intensive rehabilitation treatment (NIRT).

As far as the severity of dyskinesia is concerned, an impressive difference was observed in the two groups ( $p < 0.0001$  for time-treatment interaction): while AIMS was dramatically reduced in IRT patients ( $-71\%$ ,  $p < 0.0001$ ); in patients who underwent NIRT, this index was only reduced by 8% ( $p = 0.006$ ).

Finally, concerning drugs, a different behaviour was observed for levodopa dosage at baseline and after treatment in the two groups of patients ( $p < 0.0001$  for time-treatment interaction). Levodopa was decreased by an average value of 210 mg (23%,  $p < 0.0001$ ) in pa-

tients who underwent IRT and was virtually unchanged (30 mg reduction,  $p = 0.08$ ) in the NIRT patients.

Figures 1 and 2 give a graphical representation of obtained results for AIMS and for levodopa.

#### 4. Discussion

In our study we found that after 4 weeks of IRT dyskinesias were reduced in all of the patients, in parallel with significant levodopa dosage reduction. Usually, a relevant reduction of levodopa dosage leads to a wors-

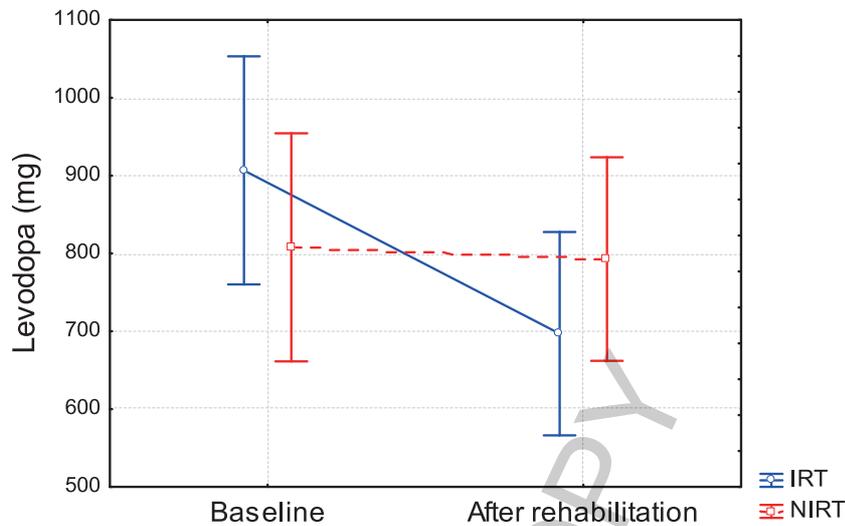


Fig. 2. Graphical representation of time-treatment interaction for the Levodopa dosage. Differences in treatment effect are reflected by differences in the slope of the lines joining the mean Levodopa dosage at baseline and after rehabilitation in the two groups. Data are plotted as mean  $\pm$  95% confidence interval, solid line for patients who underwent intensive rehabilitation treatment (IRT) and dashed line for patients who underwent non-intensive rehabilitation treatment (NIRT).

ening of symptoms and personal autonomy. On the contrary, our patients significantly improved their motor performance and autonomy in daily life activities.

The patients assigned to the NIRT group also improved motor performance and autonomy, but in this group only 3 patients reduced levodopa dosage. Nevertheless, at the end of the treatment the dyskinesias were also reduced in this group, even if by a much lesser extent.

The mechanisms underlying this phenomenon are still to be elucidated.

Several preclinical investigations performed in animal models of Parkinson's disease have demonstrated that an overload of redundant motor information is stored in the basal ganglia motor circuits of dopamine-denervated animals upon the performance of movement following the administration of dopamine agonist drugs. This phenomenon would dramatically favour the manifestation of abnormal motor responses to repetitive dopaminergic stimulation [28–30].

This view is supported by experimental evidence pointing to a major role for the caudate-putamen in the acquisition of motor habits, the execution of motor programs, and in pathological forms of motor learning [22, 25, 27, 38, 43].

The execution of movements plays a fundamental role in determining the outcome of subsequent motor responses elicited by dopamine receptor stimulation [34]. Extensive plasticity can occur in caudate-putamen and related brain areas as a consequence of

physical activity that may markedly influence the execution of movement at a later time [17, 31, 36, 39].

Exaggerated movements in response to a stimulation of dopaminergic receptors, as those which occur during dyskinesia, might consequently convey erroneous information to the motor caudate-putamen circuits. Therefore, when concomitant, competing corrected movements are performed, such as the physical activity described in the present study, the manifestation of abnormal dyskinetic movements may be attenuated. This study, therefore, suggests the possibility that the competition between a correct motor behaviour and an abnormal motor response may depend on the balance between the trace memory of the two.

Another explanation for this phenomenon may be related to a neurorestorative strategy. Since the degree of nigral denervation is the most important factor in the induction of dyskinesia, even a small improvement in nigral dopaminergic cell numbers should have a positive effect. In studies with animals treated with MPTP, the intracerebral injection of glial-cell-line-derived neurotrophic factor (GDNF) produced a small increase in the number of dopaminergic cells in the substantia nigra and reduced dyskinesia in response to levodopa [4, 20].

In recent years, many studies have demonstrated the neuroplastic and neuroprotective effect of physical activity [5, 23, 37]. Zigmond et al. showed that exercise reduces the behavioural effects of MPTP and 6-OHDA in treated animals and the loss of dopamine neurons as

demonstrated by PET imaging, and by biochemical and histochemical assessment. He suggests that the efficacy of exercise is due to an increase in the expression of neurotrophic factors, particularly GDNF [36]. A direct effect of exercise on the level of several growth factors has been revealed [1,5,7]. Studies on the effectiveness of a rehabilitation treatment in patients suffering from multiple sclerosis demonstrated that physical activity can increase the serum level of growth factors even in humans [3,16].

Moreover, we believe that the difference between the two groups in improving dyskinesia and UPDRS scores must be related to the intensity of treatment (60 vs. 30 hours between two different protocols) [9,32,42] and to the multidisciplinary approach of the experimental group with a relatively greater response to the disease symptoms.

In conclusion, our findings suggest that properly designed intensive multidisciplinary rehabilitation protocols should be considered as a valid non-invasive therapeutic support for patients who show dyskinesias, allowing a reduction in drug dosage and in related adverse side effects.

## 5. Study limitations

The first study limitation which deserves mention is the lack of a follow-up period to assess whether the acute reduction in dyskinesias persists over time. In a recent study from our group [13], we demonstrated that the beneficial effects of the IRT persist over a one-year follow-up period. This finding leads us to hypothesize that the reduction in drug dosage associated with the improvement in motor performance might be maintained over time, limiting dyskinesia symptoms.

A second study limitation is the different site where the patients assigned to the two different treatments were hospitalized. We had to follow this strategy to avoid the contemporaneous presence in the same hospital of patients undergoing treatments entailing different sessions and different durations. However, even though in principle the involvement of different teams of physiotherapists might have influenced the study outcome, we think that the close similarity of the improvement observed in UPDRS III in both groups guarantees the substantial equivalence of the different teams.

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