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ORIGINAL COMMUNICATION

The impact of outpatient rehabilitation on quality of life in multiple sclerosis

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Abstract It is well accepted that rehabilitative treatment can be effective in reducing disability and optimizing quality of life (QoL) of people with multiple sclerosis (MS). The aim of this study was to evaluate the effects of a comprehensive outpatient rehabilitative treatment on QoL in patients suffering from MS. We selected 111 patients from a sample of 407 patients who had consecutively entered the MS Center of Catania (which is located in southern Italy) in 1998. Fifty-eight were randomly assigned to the study treatment and 53 to a waiting list (control treatment). Kurtzke's EDSS and quality of Life (QoL)were the primary endpoints. QoL was measured with the generic multi-item SF-36 scales. We also used: the Beck Depression Inventory (BDI) for depression, the Tempelaar Social Experience Check-list (SET) for social activities and the Fatigue Impact Scale (FIS).

The study treatment group was treated for 6 consecutive weeks, 6 days a week with a comprehensive rehabilitative outpatient model. The control treatment group was in a waiting list and was trained to self-exercises at home.

EDSS remained unchanged in both groups. All health related QoL domains significantly improved in the study treatment ($p < 0.001$ in physical functioning, role physical, bodily pain, general health, and social functioning; $p < 0.05$ in vitality, role emotional and mental health).

FIS, SET and BDI also improved significantly after the rehabilitative treatment in the study group ($p < 0.001$).

The results of this study confirm the effectiveness of a short comprehensive outpatient model of rehabilitative treatment in people with MS and in particular in their QoL.

Key words multiple sclerosis · rehabilitation · outpatients · quality of life

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Introduction

Multiple sclerosis is a capricious disease, difficult to understand and difficult to cope with. Usually patients do not understand what is happening to their body. Patients complain of impaired vision, difficulty in walking, incontinence, impaired sexual function, difficulty in concentrating. The impairments may last shorter or longer periods, or may become permanent [5, 6].

In July 1993, MS care entered a new era with the decision by the Food and Drug Administration to license Betaseron [22]. Since then, the aim of the pharmacological research was to consider and test new agents with differing mechanisms of action for all stages of MS. Unfortunately pharmacological therapy alone does not constitute optimal care of MS patients, regardless of the stage of the disease [30].

Physical rehabilitation is commonly administered to MS patients, often without knowing which is the best rehabilitation strategy for patients with MS [27]. The chronic progressive nature of MS makes the patients poor candidates for rehabilitation interventions. A number of publications have described comprehensive care

or neurorehabilitation in MS [16]. Recently, Petajan et al. found that exercise training improves fitness and has a positive impact on factors related to quality of life [23]. Also Freeman et al. showed that despite unchanging impairment, inpatient rehabilitation resulted in reduced disability and handicap in progressive MS [10]. Solari et al. demonstrated the efficacy of an inpatient physical rehabilitation program [28]. In more details, disability and mental components of health related QoL perceptions improved after 3 weeks of treatment.

Previously Shapiro and associates developed a "maintenance" rehabilitation program used as "extended" home outpatient rehabilitation [26]. This rehabilitation program produced substantial benefit in persons with chronic progressive MS [7].

MS has also a considerable effect an patients' health related QoL (HRQoL) [25]. HRQoL includes general well being, social and psychological functions, which are not only directly related to neurological impairment or disability [5]. The interest in MS patients HRQoL is increasing, but it is still limited, although several clinical trial organizations have introduced QoL assessment as a standard component of new trials [2].

This study aims to discuss the effects of a comprehensive outpatient rehabilitation program an QoL of MS patients. To do this we administered a generic HRQoL instrument, the SF-36 [1], together with other scales (Fatigue Impact Scale, the Social Experiences Tempelaar check-list and the Beck Depression Inventory) to MS patients in the progressive phase of the disease [3, 8, 29].

The results of outpatient rehabilitation on disability will be discussed in another study.

Methods

Patients

All consecutive patients diagnosed with primary or secondary progressive MS [17], admitted to the Centro Sclerosi Multipla of the Policlinico of the University of Catania, Italy, between January 1998 and December 1998 were included in the study. Selection criteria were clinically definite or laboratory-supported MS [24]; Expanded Disability Status Scale (EDSS) score [15] at inclusion ranged between 4.0 and 8.0, and age between 18 and 65 years. Exclusion criteria were as follows: one or more exacerbations in the preceding 3 months; cognitive impairment likely to interfere with adherence to the study, as determined by a Mini-Mental State Examination (MMSE) score of ≤ 24 [18]; history of cardiovascular, respiratory, orthopedic, psychiatric, or other medical condition precluding participation; pregnancy; treatment with immunosuppressives, interferons, copolymer, 4-amminopyridine, or experimental drugs in the six months before enrollment, rehabilitation therapy in the three months before admission; non Italian speaking patients.

All eligible patients were blindly randomized and divided into two groups: immediate comprehensive outpatient rehabilitation (treatment group) and self exercise-treatment at home (control group). The first group was treated for 6 weeks with a comprehensive outpatient rehabilitation program and further 6 weeks with self exercises at home, the second for 12 weeks with self exercise-treatment at home.

Randomization of patients was performed in accordance with a computer-generated randomization sequence by using consecutively numbered, opaque, sealed envelopes. The two groups of patients underwent a complete neurological, and neuropsychological examination, comprehensive of all self-questionnaires, within 24 hours of entering the rehabilitation programs and then again at weeks 6 and 12. The evaluating physician had no further access to any of the initial scores before the second and the successive assessments.

All eligible patients signed informed consent forms. Patients assigned to the control group were offered the outpatient rehabilitation program at the end of the rehabilitation treatment period (12 weeks).

Three physicians were the assessors during the study: the referring physician recorded patients' general information, clinical data and follow-up history. The treating physician was responsible for the rehabilitation program. The evaluating physician, who was blinded to treatment assignment, administered the evaluation scales, which consisted of Kurtzke's EDSS. In addition SF-36, FIS questionnaire, an Italian version of the Social Experiences check-list of Tempelaar (SET), and of the Beck Depression Inventory (BDI) were given to each patient every visit. Each patient completed the questionnaires on the same day before the neurological examination. Any bias that may be introduced by discussing the patients' health and emotions before neurological examination was therefore avoided.

Quality of life assessment

All patients assessed their quality of life using the SF-36. It is a generic questionnaire that measures two major health concepts (Physical and Mental Health) with 36 questions and eight multi-item scales: Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Functioning Emotional (RE) and Mental Health (MH). SF-36 was adopted in the Italian version of 1990 [1]. An additional one-item measure of self-evaluated change in health status is also available. SF-36 scores were assembled using the Likert methods for summed ratings; the raw scores were then linearly transformed to 0–100 scales, with 0 and 100 assigned to the lowest and highest possible values respectively. Higher transformed scores indicated better health, while higher scores on symptom scales meant more intensive symptoms. There is good evidence to support the reliability and validity of the SF-36 [1].

Beck Depression Inventory

Each patient was asked to read several groups of statements and then pick up one statement in each group which best described the way he/she had been feeling during the "past week, up today". This scale is widely used also in neurological diseases and measures either depression or distress in disable people. Suggested cut-off values are the following: 0–10 = no depression; 11–17 = mild depression; 18–23 = moderate depression; 24–39 = severe depression [3].

Fatigue Impact Scale (FIS)

The FIS patients asked to rate how much fatigue influenced 40 different statements during the past month, including the day of testing. The patient was asked to circle the appropriate response for each: 0 = no problem; 1 = small problem; 2 = moderate problem; 3 = big problem; 4 = extreme problem [8].

Social Experience Check-list of Tempelaar (SET)

The SET patients asked to rate how much social function influenced 16 different statements during the past two weeks, including the day of testing. The patient was asked to circle the appropriate response for each: 0 = no problem; 1 = small problem; 2 = moderate problem; 3 = severe problem; 4 = extreme problem [29].

All of these three last self-questionnaires were given to each patient to obtain further information on QoL of MS patients.

DAY 1	Physiotherapy (50 min.) 1 physiotherapist		
DAY 2	Occupational therapy (30 min.) 1 therapist	or speech therapy (30 min.) 1 therapist	Physiotherapy (30 min.) 1 physiotherapist
DAY 3	Physiotherapy (50 min) 1 physiotherapist		
DAY 4	Occupational therapy (30 min.) 1 therapist	or speech therapy (30 min.) 1 therapist	Physiotherapy (30 min.) 1 physiotherapist
DAY 5	Group physiotherapy (40 min) 2 physiotherapists	Video music (20 min.) 1 nurse	
DAY 6	Take care of symptoms (30 min.) 1 neurologist.	holistic approach, patients desires (30 min.) 1 psychologist	

Fig. 1 Flow chart of the daily rehabilitation treatment

Rehabilitation program

The outpatient rehabilitation program lasted for 6 consecutive weeks, 6 days a week and consisted of daily exercise session, each 50/60 minutes long. At the end of the period, the patients were instructed in a self executed exercise program to perform at home as previously suggested [21]. The outpatient rehabilitation program lasted for 6 consecutive weeks, 6 days a week and consisted of individualised, goal oriented therapy plan (Fig. 1); physiotherapy (five days a week, each session up to 50/60 minutes); occupational therapy (twice a week, each session 30 minutes long); speech therapy (if necessary, twice a week, each session 30 minutes long); consideration of patients' desires, a holistic approach, taking care of symptoms (on a weekly basis, each session 50 minutes long); many complementary and supportive alternatives, music, mirror/video (once a week, each session 50 minutes long); group physiotherapy (once a week, each session 50 minutes long).

The control group was instructed in a self exercise program [21] to perform at home for 12 weeks. The treatment group was also trained in this self exercise program for a further 6 weeks.

Statistical analysis

Clinical and demographic variables of the sample were described using descriptive statistics such as mean, standard deviation (sd) and proportion which are reported in Table 1. There were two primary outcome measures. The first was the effect of the rehabilitation program on QoL as measured by the SF-36 multi-items scales. The second main outcome measure was the change in neurological impairment as assessed by EDSS. Changes in the FIS, SET and Beck scores were considered as secondary efficacy endpoints. Repeated ANOVA measures were performed in both treatment and control groups to evaluate the changes of HRQoL (SF-36 and the other instruments) at weeks 6 and 12. SF-36, FIS, SET and the Beck scores in the two study groups were compared by means of the Mann-Whitney U test. All statistical tests were two sided. Probability values of less than 5% were considered significant. Kazis [12] effect size was also provided.

Results

Between January and December 1998, 407 patients were screened and 111 were included in the study, with 58 assigned to study treatment and 53 to control treatment (Fig. 2). The treatment and control groups were well matched for sex, age, disease duration, EDSS score (Table 1). Four patients withdrew from the rehabilitation program and only 1 from the control treatment. One treatment-group patient had an exacerbation 4 weeks after entry, 5 of the control group and 3 of the treatment group worsened quickly and were treated for 7 days with i. v. methylprednisolone between the 6^{th} and the 10^{th} week. All these patients were included in the analysis of results.

Impairment

The changes in EDSS scores clustered nearly around 0 in both groups at week 6 and at week 12.

Quality of life

The baseline means for each SF-36 health dimension of both control and treatment groups were compared with the age and the sex adjusted scores in an Italian general population. These adjusted scores were calculated by finding out the score for each patient in the general population of the same sex and age group in 5-years age classes [1]. As expected both control and treatment MS patients scored considerably lower than the general population in both sexes in physical domains (PF, RP).

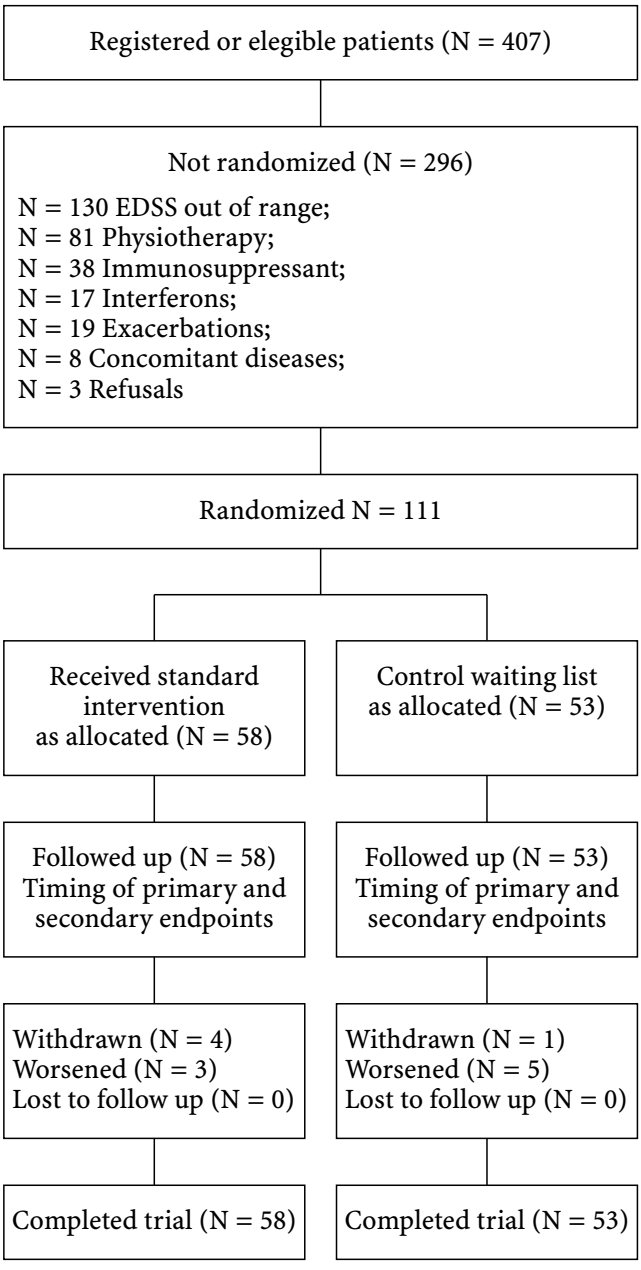

Fig. 2 Flow chart of the randomized controlled trial

Table 1 General and clinical findings of patients

	Treatment group	Control group
N.	58	53
Age, mean ± sd (min–max)	45.2±12.0 (25–60)	46.1±6.0 (30–57)
Men	24 (41.4%)	23 (43.4%)
Women	34 (58.6%)	30 (56.6%)
Duration, mean ± sd (min–max)	17.2±8.1 (5–30)	17.2±4.8 (9–26)
EDSS, mean ± sd (min–max)	6.2±1.2 (4–8)	6.1±1.2 (4–8)

Differences were especially high also for GH, VT, MH, RE, SF and BP (Fig. 3).

There were no significant differences between the two patient groups in any health scale at baseline including PF and RE ($p < 0.05$).

SF-36

Overall, the treatment group SF-36 profile improved in all scales. This improvement was unchanged 6 weeks after the end of the treatment period. The difference between treatment and control groups was significant for PF, RP, GH, VT, BP, SF and MH ($p < 0.001$) and RE ($p < 0.005$) at 6 and 12 weeks. The Kazis effect value ranged from 0.29 to 0.70 (Table 2).

FIS-SET-BDI

At week 12 rehabilitation significantly reduced fatigability, improved social functioning and depression ($p < 0.001$) of the treatment group MS patients, with Kazis effect values of –0.77, –0.46 and –0.50 (Table 3).

Discussion

Multiple sclerosis patients with moderate to not very severe disability (EDSS around 6.0 which means ambulatory patients with permanent unilateral aid), admitted to a rehabilitation unit of a neurological ward, have a low HRQoL as measured by the SF36 (Fig. 2). Similar to other MS samples the dimensions most affected were physical functioning and role limitations [4, 9]. In both control and treatment groups the physical and mental components behave differently. This is predictable because the components were designed to measure different concepts [1].

In this study we found that the rehabilitation program does not influence the impairment, as measured by the EDSS. The SF-36 profile improved for those patients who underwent rehabilitation; the difference was statistically significant for all SF-36 health domains at 6 and 12 weeks.

Our data are in agreement with the recently published waiting-list randomized study of Freeman et al. on progressive MS patients. That study is different from ours because it was based on an inpatient population. Despite this difference, both studies showed a positive effect an QoL and a negligible effect on impairment. Freeman et al. also showed a positive effect of rehabilitation on both disability and handicap [10]. These authors showed that the benefits gained from rehabilitation were partly maintained after one year despite worsening of neurological status [11]. Petajan et al. also found that ambulatory MS patients benefited from aerobic fitness in terms of fitness, reduced fatigability, and

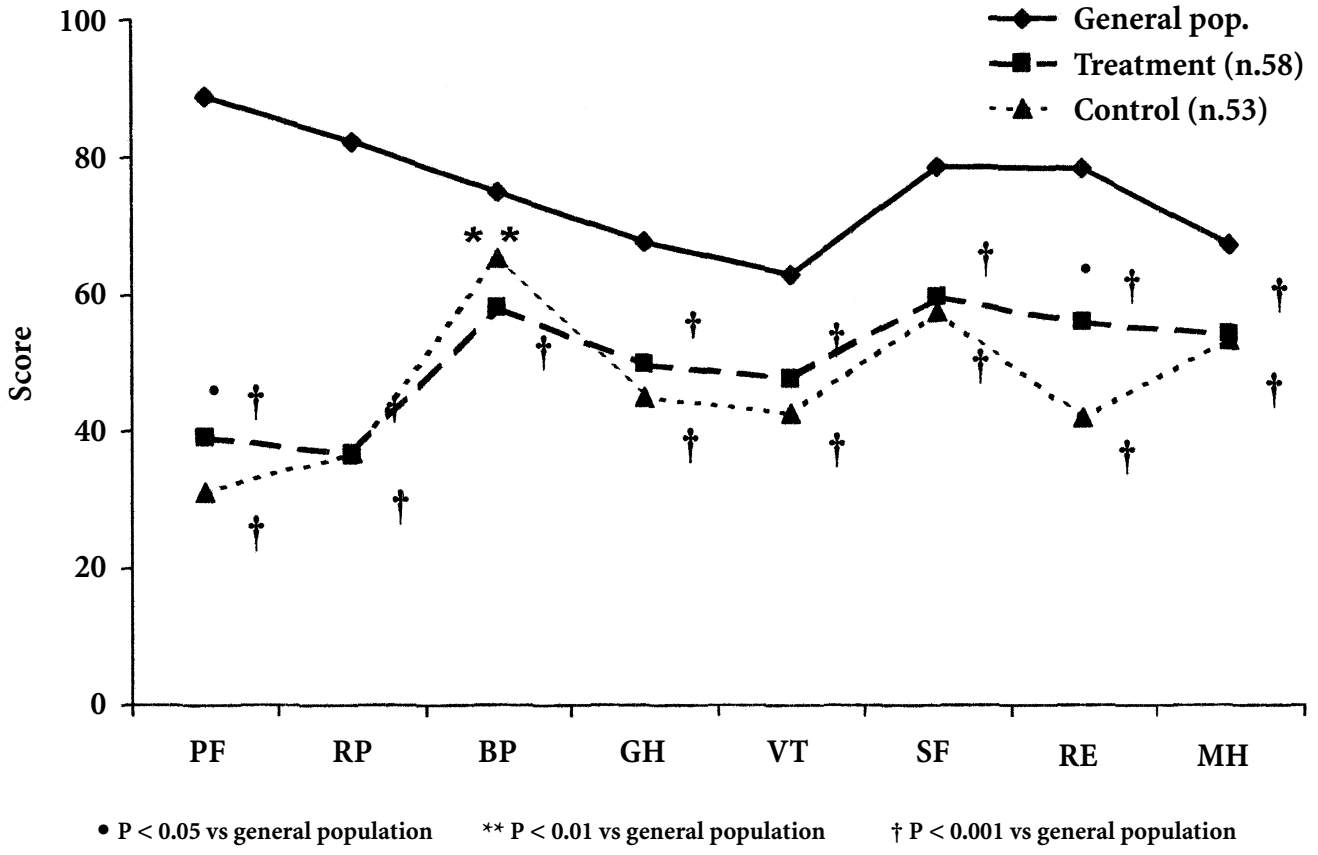

Fig. 3 Mean 36 – item Short Form Health Survey Questionnaire at baseline in comparison with Italian normative data. Value on the y axis are scores.
PF Physical Functioning; *RP* Role Physical; *BP* Bodily Pain; *GH* General Health; *VT* Vitality; *SF* Social Functioning; *RE* Role-Functioning Emotional; *MH* Mental Health

Table 2 Results of rehabilitation on 36 item short form Health Survey

	Treatment group (n = 58)		Control group (n = 53)				
	T_0	T_1	T_0	T_1		Treatment group	Control group
Variable	m ± sd	m ± sd	m ± sd	m ± sd	Kazis value	m ± sd	m ± sd
PF	39.3±23.0	46.2±26.7[a]	31.2±23.3	31.1±23.1	0.64	6.91±18.1	−0.1±0.3[c]
RP	36.9±36.2	50.9±41.6[a]	26.4±36.8	26.2±36.5	0.67	14±24.3	−0.2±0.5[c]
BP	58.2±26.0	73.1±23.9[a]	65.4±27.1	65.3±27.0	0.29	14.9±20.0	−0.1±0.6[c]
GH	49.9±21.1	55.7±19.3[a]	45.0±20.6	44.8±20.4	0.52	5.8±10.5	−0.2±0.5[c]
VT	47.8±17.5	55.2±15.8[a]	42.7±18.4	42.6±18.1	0.70	7.4±12.5	−0.1±0.5[b]
SF	59.8±21.5	71.2±18.7[a]	57.6±27.1	57.5±27.0	0.57	11.5±14.6	−0.1±0.3[c]
RE	56.1±40.4	62.3±36.8	42.1±43.4	42.0±43.3	0.48	6.2±23.7	−0.1±0.3[b]
MH	54.2±22.8	61.9±20.3[a]	53.4±23.7	53.2±23.5	0.38	7.7±15.8	−0.1±0.5[b]

[a] ANOVA test, $p < 0.001$ vs T_0; [b, c] MANN WHITNEY U test, [b] $p < 0.05$ vs Control Group; [c] $p < 0.001$ vs Control Group
PF Physical Functioning; *RP* Role Physical; *BP* Bodily Pain; *GH* General Health; *VT* Vitality; *SF* Social Functioning; *RE* Role-functioning Emotional; *MH* Mental Health; *m* mean; *sd* standard deviation

improved quality of life perception [23]. However, there are some differences between the two studies due to the inclusion criteria. Petajan et al. enrolled patients with relapsing remitting MS and those with a low level of disability and this allowed them to receive regular aerobic training. In our study the comprehensive outpatient rehabilitation program significantly reduced fatigability in MS with moderate to severe disability (see results of FIS, GH and VT).

Beneficial effects on QoL were also obtained by Solari et al. [28] in their ambulatory (EDSS 3.0–6.5) hospitalized patients after 3 weeks of inpatient physical rehabil-

Table 3 Results of rehabilitation on FIS, SET, BDI

	Treatment group (n = 58)		Control group (n = 53)		T_0–T_1		
	T_0	T_1	T_0	T_1		Treatment	Control
Variable	m ± sd	m ± sd	m ± sd	m ± sd	Kazis value	m ± sd	m ± sd
FIS	116.8±40.9	98.0±37.2[a]	127.0±36.0	127.6±35.7	−0.77	−18.8±14.3	0.6±0.9[b]
SET	28.9±6.0	26.3±4.8[a]	29.3±5.9	29.0±5.8	−0.46	−2.6±6.0	−0.3±0.8[b]
BDI	11.0±7.5	8.8±6.7[a]	12.5±7.6	12.7±7.6	−0.50	−2.2±3.4	0.1±1.0[b]

[a] ANOVA test, $p < 0.001$ vs T_0; [b] MANN WITHNEY U test, $p < 0.001$ vs Control Group
FIS Fatigue Impact Scale; *SET* Social Experiences Tempelaar; *BDI* Beck Depression Inventory; T_1 12 weeks

itation program. They found a mild positive effect of rehabilitation on the overall quality of life profile and MH at 3 and 9 weeks. In contrast with this latter study, we showed that rehabilitation significantly improved PF, RP and VT in physically compromised patients (Kazis effect values were 0.64, 0.67 and 0.70 respectively). The study of Solari et al. only included physical therapy in hospitalized patients, while our rehabilitation program (see methods) included: physical, occupational, and speech therapies, and psychosocial support. Furthermore, in our experiment, rehabilitation treatment was administered in a group of non-hospitalized patients. Similarly to Solari et al. [28], we found that rehabilitation significantly improved mental scales of SF-36 (MH, SF, and GH). After a six-weeks rehabilitation program also RE is significantly improved in treated patients ($p < 0.05$, Table 2). These results are supported by the evidence that rehabilitation improves social activities (as shown by SET scores and depression BDI scores).

Fatigue is a common symptom, difficult to quantify by both clinicians and patients [14]. Measurement of this symptom is difficult and ratings of fatigue are usually not included in the routine quantitative evaluation of neurological impairment [8]. In our study, the low energy levels reported an the SF-36 and the high levels of fatigue reported on the FIS support the importance of rating the fatigue and the role of rehabilitation on this disabling symptom. The results of this study showed that patients with MS who participated in a comprehensive outpatient rehabilitation program experienced less fatigue. Similar results had been previously obtained by Di Fabio et al. [7] in a different study based on a "maintenance" rehabilitation program [26], and later referred as "extended" outpatient rehabilitation [7]. This study differs from ours because it was not randomized, the control group was located in a waiting list, the duration of treatment and the assessment methods were different.

In our experimental conditions it is possible that a comprehensive outpatient rehabilitation program could partly reduce the stress coming from the hospitalization and the beneficial effects of rehabilitation could be reinforced by the positive effects of living at his/her home (partly maintaining his/her jobs, occupational activities, hobbies, etc). Evidence is provided by few studies which implied that physical health and QoL for people with MS are influenced by family and social support [13, 20]. Most patients in the treatment group demonstrated a significant improvement of self-evaluated change in health status that remained unchanged in the following six weeks.

Pain is considered a frequent symptom in multiple sclerosis with a frequency estimated around 55% [19]. Our results suggest that higher levels of pain are present compared with the general Italian population. In our study the rehabilitative treatment significantly improved the patients' perception of bodily pain.

This controlled study investigated the effectiveness of a comprehensive outpatient rehabilitation program in patients with MS in the progressive phase of disease. The results demonstrate that rehabilitation is effective in improving QoL in people with progressive and disabling MS, despite unchanging levels of neurological impairment. We conclude that people with MS are suitable candidates for outpatient rehabilitation and can gain considerable benefit from this intervention.

This study underlines the conviction that outpatient rehabilitation should be part of a continuum of care involving rehabilitation environment and the community and social service sectors. It is important to continue evaluating rehabilitation input in order to identify the most effective rehabilitation strategy and to compare different models of rehabilitative treatment (inpatient, outpatient, home).

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References

1. Apolone G, Mosconi P (1998) The Italian SF-36 Health Survey: Translation, Validation and Norming. J Clin Epidemiol 51 (11):1025–1036
2. Apolone G, Brunetti M, De Carli G, Acquadro C (1999) (for the European Regulatory Issues on QoL Assessment [ERIQA] Group). A review and evaluation of the EMEA documents with reference to quality of life (QoL) assessment Value in Health; 2 (3):157
3. Beck AT, Ward CH, Mendelson M, Mock JE, Erbaugh JK (1961) An inventory for measuring depression. Arch Gen Psychiatry 4:567–571
4. Brunet DG, Hopman WH, Singer MA, Edgar CM, MacKenzie TA (1996) Measurement of health-related quality of life in multiple sclerosis patients. Can J Neurol Sci 23:99–103
5. DeLisa JA, Hammond MC, Mikulic M, Miller RM (1985) Multiple Sclerosis: Part I. Common physical disabilities and rehabilitation. AFP 32 (4):157–163
6. DeLisa JA, Hammond MC, Mikulic M, Miller RM (1985) Multiple Sclerosis: Part II Common functional problems and rehabilitation. AFP 32 (5):127–132
7. Di Fabio RP, Soderberg J, Choi T, Hansen CR, Shapiro RT (1998) Extended outpatient rehabilitation: its influence on symptom frequency, fatigue, and functional status for persons with progressive multiple sclerosis. Arch Phys Med Rehabil 79:141–146
8. Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ (1994) The Impact of Fatigue on Patients with multiple sclerosis. Neurol Sci 21:9–14
9. Freeman JA, Langdon DW, Hobart JC, Thompson AJ (1996) Health-related quality of life in people with multiple sclerosis undergoing inpatient rehabilitation. J Neurol Rehab 3:185–194
10. Freeman JA, Langdon DW, Hobart JC, Thompson AJ (1999) Inpatient rehabilitation in multiple sclerosis. Do the benefits carry over into the community? Neurology 52:50–56
11. Freeman JA, Langdon DW, Hobart JC, Thompson AJ (1997) The impact of inpatient rehabilitation on progressive multiple sclerosis. Ann Neurol 42:136–144
12. Kazis EL, Anderson JJ, Meenan RF (1989) Effect sizes for interpreting changes in health status. Med Care 27 (suppl):S178–S189
13. Kraft GH, Freal JE, Coryell JK (1986) Disability, disease duration, and rehabilitation service needs in multiple sclerosis: patients perspectives. Arch Phys Med Rehabil
14. Krupp LB, Alvarez LA, La Rocca WG, Scheinberg LC (1988) Fatigue in multiple sclerosis. Arch Neurol 45:433–437
15. Kurtzke JF (1983) Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33:1444–1452
16. La Rocca NJ, Kalb RC (1992) Efficacy of rehabilitation in multiple sclerosis rehabilitation. J Neurol Rehabil 6:147–155
17. Lublin FD, Reingold SC (1996) Defining the clinical course of multiple sclerosis: results of an international survey. Neurology 46:907–910
18. Measso G, Cavarzeran T, Zappalà G, et al. (1993) The mini-mental state examination: normative study of an Italian random sample. Dev Neuropsychol 9:77–85
19. Moulin DE, Foley KM, Ebers GC (1988) Pain syndromes in multiple sclerosis. Neurology 38:1830–1834
20. O'Brian MT (1993) Multiple sclerosis: the role of social support and disability. Clin Nurs Res 2:67–85
21. Patti F, Sellaroli T, Reggio A (1998) Il trattamento multiintegrato della sclerosi multipla. Progetto neuroriabilitativo e terapia farmacologica sintomatica. Ed. Scientifiche Cuzzolin. Napoli
22. Paty DW, LI DKB (1993) The UBC MS/MRI Study Group and the IFN-beta Multiple Sclerosis Study Group. Interferon beta 1b is effective in relapsing-remitting multiple sclerosis. II MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 43:662–667
23. Petajain JH, Gappmaier E, White AT, Spencer MK, Mino L, Hicks RW (1996) Impact of aerobic training on fitness and quality of life in multiple sclerosis. Ann Neurol 39:432–441
24. Poser CM, Paty DW, Scheinberg L, et al. (1983) New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 13:227–231
25. Rudick RA, Miller D, Clough JD, et al. (1992) Quality of life in multiple sclerosis: comparison with inflammatory bowel disease and rheumathoid arthritis. Arch Neurol 49:1237–1242
26. Shapiro RT, Soderberg J, Hooley M, Terry G, Ruhsam S, Linroth R, et al. (1988) The Multiple Sclerosis Achievement Center: a maintenance rehabilitation approach toward a chronic progressive form of the disease. J Neuro Rehabil 2:21–23
27. Smith CR, Sheinberg LC (1990) Symptomatic treatment and rehabilitation in multiple sclerosis. In Cook SD (ed). Handbook of multiple sclerosis. NY: Marcel Dekker 327–349
28. Solari A, Filippini G, Salmaggi A, La Mantia L, Farinotti M (1999) Physical rehabilitation has a positive effect on disability in multiple sclerosis patients. Neurology 52:57–62
29. Tempelaar R, De Haes JC, De Ruiter JH, Bakker D, Van Den Heuvel WJ, Van Nieuwenhuijzen MG (1989) The social experiences of cancer patients under treatment: a comparative study. Soc Sci Med 29 (5):635–642
30. Thompson AJ (1995) Neurorehabilitation for people with multiple sclerosis. In: proceeding of the MS Forum: psychosocial factors in multiple sclerosis. Modern management Workshop, Rome, pp 9–12