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Observational multicentric study on chronic sciatic pain: clinical data from 44 Italian centers

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Abstract. – OBJECTIVE: To provide information on the clinical presentation of sciatic neuropathy and its management in a real-world setting, and to analyze the effects of a multimodal approach based on the association of physical and pharmacological therapy.

PATIENTS AND METHODS: A multicentric observational prospective study was conducted in 44 Italian tertiary centers specialized in Physical Medicine and Rehabilitation, Orthopedics, Neurology, Neurosurgery, and Rheumatology. To develop a shared management of LPB with sciatica, a dedicated clinical record was proposed to collect data about diagnosis, treatment, and outcomes. Pain, disability, and quality of life were recorded trough validated questionnaires at baseline and after a two-month follow-up.

RESULTS: 394 patients (age, mean ± SD 55.7 ± 14.1 years, 57.1% females) with chronic LBP and sciatica were enrolled in the study. The characteristics of the selected group showed a certain variability in the clinical presentation. At baseline, patients received several different therapeutic options among physical, pharmacological and neurotrophic treatments. A subgroup of 312 patients was treated with a combination of neurotrophic agents containing alpha-lipoic acid (ALA). After a two-month follow-up, a general improvement in both perceived pain and functional disabilities was observed. A significant improvement ($p < 0.001$) in the Pain Numeric Rating Scale (NRS), Roland e Morris Disability Questionnaire (RMDQ) and Brief Pain Inventory (BPI) Italian short version was observed.

CONCLUSIONS: Sciatic neuropathy is a multifaceted condition managed by means of a wide spectrum of therapeutic options. The results of this study suggest that a multimodal approach based on the association of ALA with physical and pharmacological therapies can be beneficial in the treatment of LBP with sciatica.

Key Words:
Mesh terms) low back pain, Sciatic neuropathy, Complementary therapies, Pain management, Alpha-lipoic acid.

Introduction

Chronic low back pain (LBP) with sciatica is defined as pain and discomfort, localized below the costal margin and above the inferior gluteal folds, with referred leg pain persisting for at least 12 weeks[1-5].

Sciatic neuropathy is among the most common peripheral neuropathies, since it is estimated to affect 5 in every 10000 Western adults[6]. Thus, it represents a social problem both in terms of patients' suffering and health costs for treating the progression of the disease. More generally speaking, LBP of at least moderate intensity and duration has an annual incidence in the adult population of 10-15% and a prevalence of 15-30%. It becomes increasingly frequent in patients older than 65 years. Therefore, a relevant number of elderly people, approximately one out of every three to four, suffers from low back pain[3].

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Chronic LBP with sciatica shows a broad range of clinical manifestations and consequences on patients' lives, from a preserved functionality in spite of pain to a severe disability or an interference with sleep by persistent back pain and radicular pain and paresthesia[1-5]. Chronic LBP with sciatica is a quite common cause of long-term disability in middle-aged people and, due to its resistance to pharmacological and surgical interventions, requires a multimodal and multidisciplinary approach[1,5,7].

The economic burden of chronic LBP, in general, is relevant, spine diseases being fifth in terms of hospitalization/inpatients costs and first as a cause of absenteeism and burden of disability[8].

The optimal management of chronic LBP with sciatica is still a matter of debate. A large panel of therapeutic options is available[5,9-12].

Surgery doesn't seem to be a first choice treatment for radicular neuropathy, except the cases in which it can't be avoided. A systematic review with meta-analysis of cohort studies revealed that patients with sciatica still experience pain and disability 5 years after surgery[7].

Non-pharmacologic therapies for chronic LBP with sciatic neuropathy include acupuncture, exercise therapy, massage therapy, yoga, cognitive behavioral therapy or progressive relaxation, spinal manipulation, and intensive interdisciplinary rehabilitation. Although the level of supporting evidence for the different therapies varies from fair to good, at the moment there is no consensus about a first choice treatment[9-11].

Notably, recent evidence suggests that a multimodal and multidisciplinary approach involving orthopedics, physiatrists, rheumatologists, and neurologists may be the most appropriate for sciatic neuropathy. That approach also implies a detailed knowledge of pathophysiological and clinical data in order to obtain a 360-degree framework of the condition and to address the priority needs in its management.

This study focused on patients with chronic LBP with sciatica, is part of a wider project aimed at proposing an appropriate and shared management at a national level of all patients with peripheral compression neuropathy (e.g. carpal tunnel syndrome and sciatic neuropathy)[12]. Thus, the Management of Peripheral Neuropathies Study Group, composed of Specialists in Physical and Rehabilitation Medicine, Orthopaedics, Neurology, Neurosurgery, Rheumatology, Anesthesiology and Pain Medicine, has designed (March-May 2012) and conducted for the following 14 months (May 2012-June 2013) this observational study aimed at providing an updated picture of chronic LBP with sciatica, including the clinical characteristics of the patients (etiology, location, severity, duration) and the management of the disease. Participating centers were outpatients care services in hospitals or in centers for outpatients care, both public or private, spread throughout Italy.

To develop a shared management of LPB with sciatica, a dedicated clinical record was proposed to collect data about diagnosis, treatment, and outcomes.

The main objectives were to determine the clinical and demographic characteristics of patients, the concomitant diseases and the response to the multimodal treatment proposed.

As regards diagnosis, we included in the clinical report the etiology, location, clinical characteristics of the disease, a complete physical examination including Lasegue's and Wassermann's maneuvers and osteotendinous reflexes, in order to propose a single shared protocol for the diagnosis of the compression neuropathy.

Previous diagnostic procedures, previous and ongoing treatments (physical therapy, pharmacological therapy or neurotrophic agents) were also included in the clinical report.

The Study Group decided to recommend the use of neurotrophic agents, and in particular of alpha-lipoic acid (ALA), because of the increasing evidence of effectiveness in neuropathic pain and considering the good tolerability of the treatment[12-25].

ALA is an antioxidant that has been recently identified as a first-choice treatment for chronic neuropathic pain[13], because of the proven effectiveness compared to placebo in the treatment of neuropathic pain[13-22].

ALA exerts a protective effect on the nerve fibers, acting on the nerve inflammation and the progression of nerve damage. Furthermore, it does not interfere with other pharmacological treatments and is generally well tolerated[21], so we decided to recommend its use as an adjuvant for the treatment of neuropathy in the patients enrolled in the study.

The study group recommended a multimodal treatment, including physical, pharmacological and neurotrophic therapies, but decided not to give a precise indication about which treatment to select within the various options. This decision was taken in order to observe the current man-

agement of sciatic pain in a real world setting.

At the same time, the study was designed to provide a feedback on the efficacy of current clinical practice and of the multimodal approach proposed, through the registration of clinical data at baseline and at the end of the follow-up. The Study Group selected the parameters to be evaluated and the questionnaires to be administered on the basis of the international literature. Among the questionnaires, the Numeric Rating Scale (NRS)[26,27] was adopted by Pain in Europe (http://www.paineurope.com), the European survey about chronic pain; the Roland and Morris Disability Questionnaire (RMDQ)[28,29] is aimed at evaluating disability; the Brief Pain Inventory-short form (BPI)[30,31] is focused on measuring pain and its interference on activities of daily living; the Short Form-12 Health Survey (SF-12)[32-34] is used to evaluate the quality of life.

Patients and Methods

Study Design

The observational study was carried out between May 2012 and June 2013, enrolling 394 consecutive patients with chronic LBP with sciatica followed in 44 specialized Italian centers participating in the Management of Peripheral Neuropathies Study Group (see the list of participating centers).

The main objectives were to determine (i) the pattern of this condition; (ii) the concomitant diseases and the characteristics of patients; (iii) the response to treatments.

Patients of both genders older than 18 years with chronic (>12-week duration) LBP with sciatica were included.

A model of dedicated clinical record was developed to homogeneously collect the most relevant data about diagnosis, monitoring, and outcomes.

The study was conducted in accordance with the current guidelines of good clinical practice (GCP) regulations relating to clinical trials and the Declaration of Helsinki and was approved by the local Ethics Committee.

Informed consent was obtained from all the patients after explaining the aim of the work and the relevance of the questionnaires.

Data Collection

At baseline, the following information was collected: demographic data (age, gender, anthropometric data); lifestyle and work activity and their relation to the condition; referral from general practitioners (GP) or specialists; comorbidities; aetiology, location, and clinical characteristics of the compression neuropathy; complete physical examination including Lasegue's and Wassermann's maneuvers and osteotendinous reflexes; previous diagnostic procedures, previous and ongoing treatments (physical therapy, pharmacological therapy, or neurotrophic agents used for at least 10 days consecutively).

Patients were asked to state if they considered the previous treatments effective or not.

Pain Assessment

The pain was assessed by means of standardized questionnaires whose Italian translations have been previously validated: the NRS, the RMDQ, the Italian version of the BPI, and the SF-12 questionnaire.

The NRS[26,27] is a segmented numeric horizontal bar on which patients select a whole number (from 0 "no pain" to 10 "worst possible pain") that best reflects the intensity of their pain at rest and on movement. It has become a widely used instrument for pain screening and is ubiquitous as a screener in many health care environments.

The RMDQ[28,29] is a patient-reported measure of back pain which explore the patients' ability to perform 24 activities of daily living. Items are scored to yield a total score from 0 "no disability" to 24 "maximum disability". It is used to assess the patients' subjective rating of perceived disability and helps the clinician to address the functional limitations of the patients. Scores were categorized as follows:

- **From 0 to 9:** sub-acute or chronic LBP with mild disability (may be managed by the general practitioner);
- **From 10 to 13:** sub-acute or chronic LBP with a moderate disability;
- **> 14:** sub-acute or chronic LBP with severe disability (a multimodal and multidisciplinary management is needed).

The BPI[30] is a self-administered assessment tool which measures pain interference. It consists of 9 items measuring interference, experience of pain on the current day, and localization of pain occurrence. Scores are assigned on a scale from 0 "does not interfere" to 10 "completely interferes". Its short form[31] is used for clinical trials and translated in foreign languages, as in the case of the short Italian version named BQVD, Breve Questionario per la Valutazione del Dolore).

Scores were categorized as follows:
• Factor 1 – Pain intensity (range 0-50);
• Factor 2 – Affective interference (range 0-30);
• Factor 3 – Activity interference (range 0-30).

The SF-12[32-34] is a generic health status measure including 12 items which yield a profile of functional health and well-being. It is recommended for self-administration, brevity, simplicity, validity and reliability.

Statistical Analysis

Quantitative variables were reported as mean ± standard deviation (SD) and range, qualitative variables as absolute and relative frequencies. Data were summarized in tables and figures as appropriate.

The data collected were analyzed by standard descriptive statistics.

The intragroup differences in NRS, RMDQ, BPI (baseline *vs.* end of follow-up) were assessed by means of paired *t*-test. Differences have been considered significant where $p < 0.05$.

As regards the SF-12, we only reported the variation of the answers to each item, so as to point out which ones were more influenced by the treatments.

No direct comparison of the treatments was performed.

No missing data have been replaced and no replacement policy has been implemented; as a matter of fact, the analysis fully reflects the observed values.

The statistical analysis has been performed using the software SPSS Statistical Package, version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients

Baseline characteristics of the 394 patients (age, mean ± SD 55.7 ± 14.1 years, 57.1% females) with chronic LBP with sciatica enrolled in the study are reported in Table I. Among all patients, 12.4% were menopausal and 2% pregnant women.

For the majority of patients (63.5%) time since the initial diagnosis ranged from 3 to 12 months, while for the others initial diagnosis was made more than one year before enrolment. The most common comorbidities were osteoarthritis (28.2%), diabetes (19.3%), osteoporosis (17%), thyroid disorders (10.9%) and rheumatoid arthritis (3.6%).

Physical Examination

Following physical examination, patients were classified as having: sciatica (82.7%, n = 326), low back pain (9.4%, n = 37), cruralgia (3.6%, n = 14). The diagnosis after the physical examination was missing in 17 (4.3%) patients.

As regards semiotic maneuvers a positivity in Lasègue's test was observed in 68.8% of patients, and a positivity in Wassermann's test in 30.2% of patients. Osteotendinous reflexes were normal in 47.2%, reduced in 36.3%, absent in 3.5% of patients. Muscle wasting was observed in 26.7% of patients.

49.7% of patients reported diurnal paresthesia and 45.9% reported nocturnal paresthesia.

Instrumental Diagnostic Procedures

Considering diagnostic imaging, 52.3% (n = 206) of patients underwent conventional X-ray,

Table I. Demographic and clinical characteristics of patients at baseline.

	All patients (N = 394)
Gender	no. (%)
- Female	225 (57.1%)
- Male	169 (42.9%)
Age (years)	55.7 ± 14.1
mean ± SD (range)	(25-87)
Body weight (kg)	73.4 ± 12.9
mean ± SD (range)	(47-120)
Height (cm)	168.7 ± 8.5
mean ± SD (range)	(140-197)
BMI (kg/m^2)	26.1 ± 4.2
mean ± SD (range)	(17.9-43.8)
BMI categories (reference values)	no. (%)
- Underweight (< 18.5 kg/m^2)	2 (0.5%)
- Normal weight (18.5-24.9 kg/m^2)	165 (41.9%)
- Overweight (25-29.9 kg/m^2)	143 (36.3%)
- Obesity (≥ 30 kg/m^2)	62 (15.7%)
- ND	22 (5.6%)
Smoking habit	no. (%)
1. No	226 (57.3%)
2. Yes	122 (31.0%)
- ND	46 (11.7%)
Work activity no. (%)	no. (%)
1. Blue collar	59 (15.0%)
2. White collar	103 (26.1%)
3. Homeworker	82 (20.8%)
4. Retiree	79 (20.1%)
5. Others	63 (16.0%)
- ND	8 (2.0%)
Work-related chronic back pain	no. (%)
1. No	169 (42.9%)
2. Yes	80 (20.3%)
3. Uncertain	106 (26.9%)
- ND	39 (9.9%)

ND: Not determined.

Table II. Baseline treatments before enrolment.

	Patients treated (no.)	Clinical response		
		No	Yes	ND
Physical therapy no. (%)				
Corset	89	25 (28.1%)	51 (57.3%)	13 (14.6%)
Laser/Carbon dioxide laser	66	34 (51.5%)	19 (28.8%)	13 (19.7%)
Electroanalgesia	36	21 (58.3%)	6 (16.7%)	9 (25.0%)
Ultrasound	51	27 (52.9%)	14 (27.5%)	10 (19.6%)
TENS	85	44 (51.8%)	27 (31.8%)	14 (16.5%)
Diadynamic	42	23 (54.8%)	7 (16.7%)	12 (28.6%)
Others	24	13 (54.2%)	8 (33.3%)	3 (12.5%)
Pharmacological therapy no. (%)				
NSAIDs	226	86 (38.1%)	97 (42.9%)	43 (19.0%)
Corticosteroids (oral)	88	19 (21.6%)	52 (59.1%)	17 (19.3%)
Corticosteroids (infiltration)	43	7 (16.3%)	19 (44.2%)	17 (39.5%)
Paracetamol	94	49 (52.1%)	37 (39.4%)	8 (8.5%)
Opioids	42	6 (14.3%)	25 (59.5%)	11 (26.2%)
Others	29	14 (48.3%)	11 (37.9%)	4 (13.8%)
Neurotrophic therapy no. (%)				
ALA	37	6 (16.2%)	24 (64.9%)	7 (18.9%)
Carnitine	46	16 (34.8%)	9 (19.6%)	21 (45.7%)
B complex vitamins	61	21 (34.4%)	9 (14.8%)	31 (50.8%)
Others	9	4 (44.4%)	4 (44.4%)	1 (11.1%)

57.4% (n = 226) nuclear magnetic resonance (NMR), and 17.5% (n = 69) computed tomography (CT). Electromyography was performed in 10.7% (n = 42) of patients.

Final Diagnosis

All in all, the most prevalent conditions were herniated disc in 53.8% (n = 212) of patients and disc space narrowing in 11.9% (n = 47).

Baseline Treatments Before Enrolment

Previous treatments before enrolment had been prescribed by the GPs in 62.9% of patients, by a specialist in 32.5%. The response to previous treatments, classified in three main categories (physical therapy, pharmacological therapy, and neurotrophic therapy), is reported in Table II. Physical therapy interventions were associated to low response rates (in general less than a third of patients) with the exclusion of corset (57.3% of responders), TENS (31.8%), laser/carbon dioxide laser (28.8%), and ultrasound (27.5%). Response rates to pharmacological therapy ranged between 39.4% and 59.5% with the different options. Among neurotrophic medications, only ALA obtained satisfactory response rates (64.9%).

Prescribed Treatments

The prescribed treatments at baseline, classified in the same three main categories, are reported in Table III.

A wide variability in the interventions was apparent. The most prescribed physical treatments were TENS (28.9%) and corsets (26.1%).

Table III. Prescribed treatments.

	All patients No. (%)
Physical therapy	
Corset	103 (26.1%)
Laser/Carbon dioxide laser	60 (15.2%)
Electroanalgesia	34 (8.6%)
Ultrasound	47 (11.9%)
TENS	114 (28.9%)
Diadynamic	28 (7.1%)
Others	104 (26.4%)
Pharmacological therapy	
NSAIDs	135 (34.3%)
Corticosteroids (oral)	59 (15.0%)
Corticosteroids (infiltration)	33 (8.4%)
Paracetamol	101 (25.6%)
Opioids	75 (19.0%)
Others	40 (10.2%)
Neurotrophic agents	
ALAnerv ON	226 (57.4%)
ALA600 SOD	86 (21.8%)
Carnitine	27 (6.9%)
B complex vitamins	14 (3.6%)
Others	10 (2.5%)

As regards pharmacological therapy, NSAIDs and paracetamol (34.3% and 25.6%, respectively) were more frequently used than corticosteroids (oral 15% and infiltration 8.4%). A considerable amount of cases (19%) required opioids.

Among neurotrophic agents, the most prescribed were ALAnerv ON® (ALA 300 mg, gamma-linolenic acid, GLA, 180 mg, honokiol 27 mg, selenium 25 µg, vitamin B1 1.05 mg, vitamin B2 1.2 mg, vitamin B5 4.5 mg, vitamin B6 1.4 mg, vitamin E 7.5 mg, and selenium 25 µg; Alfa Wassermann, Bologna, Italy) and ALA600 SOD® (ALA 600 mg, superoxide dismutase, SOD, 140 IU/day, vitamin E 7.5 mg, and selenium 25 µg; Alfa Wassermann, Bologna, Italy). The associations have been prescribed to 57.4% and 21.8% of patients, respectively. The use of carnitine or B complex vitamins was relatively limited, accounting for approximately 10%.

At the final evaluation after a two-month follow-up, the compliance to treatments and the need for dose changing were recorded.

Physical therapy was completed as planned in 65.2% of patients.

Considering pharmacological therapy, daily administration schedule was unchanged in 72.1% of patients and withdrawn in 1.5%; while a dose increase was needed in 9.4% of patients, and a dose reduction in 4.1%.

Considering neurotrophic therapy, daily administration schedule was unchanged in 78.7% of patients and withdrawn in 2.5%; while a dose increase was needed in 4.1% of patients, and a dose reduction in 3.8%.

An analysis of patients' characteristics according to the prescribed treatments is reported in Table IV. The analysis focuses on the association of physical, pharmacological and neurotrophic therapies and their prescription according to age, gender and intensity of pain (mild, moderate, severe according to the NRS scale). We observed a good adherence to the recommendation of the Study Group to adopt a multimodal strategy, with a greater prescription of all the three categories of treatments (neurotrophic, pharmacological and physical) in the patients with the higher levels of pain.

Pain and Disability Scores

At the end of the study, a general improvement in both perceived pain and functional disabilities was observed.

Specifically, the NRS (cases assessed, baseline *vs.* end of follow-up 360 *vs.* 341) significantly improved in both pain at rest (baseline *vs.* end of follow-up, mean ± SD 6.6 ± 2.2 *vs.* 2.1 ± 1.8, $p < 0.001$) and pain on movement (7.6 ± 1.9 *vs.* 2.6 ± 1.8, $p < 0.001$).

Table IV. Prescribed treatments according to patients' characteristics and pain intensity.

		Prescribed therapy				
	NO NT (Phys T or Phar T or both)	NT	NT + Phys T	NT + Phar T	NT + Phys T + Phar T	Total
Patients No.	**33**	**25**	**44**	**87**	**205**	**394**
Age						
< 65 years	24 (75.0%)	15 (60.0%)	29 (67.4%)	63 (73.3%)	149 (73.0%)	280 (71.8%)
≥ 65 years	8 (25.0%)	10 (40.0%)	14 (32.6%)	23 (26.7%)	55 (27.0%)	110 (28.2%)
Gender						
- Female	17 (53.1%)	18 (72%)	23 (54.8%)	45 (51.7%)	119 (58.6%)	222 (57.1%)
- Male	15 (46.9%)	7 (28.0%)	19 (45.2%)	42 (48.3%)	84 (41.4%)	167 (42.9%)
NRS at rest						
Mild (1-3)	2 (7.7%)	4 (16.6%)	5 (12.2%)	8 (10.1%)	7 (3.7%)	26 (7.3%)
Moderate (4-6)	9 (34.6%)	10 (41.7%)	17 (41.5%)	18 (22.8%)	67 (35.7%)	121 (33.8%)
Severe (7-10)	15 (57.7%)	10 (41.7%)	19 (46.3%)	53 (67.1%)	114 (60.6%)	211 (58.9%)
NRS on movement						
Mild (1-3)	0 (0%)	1 (4.2%)	1 (2.4%)	1 (1.2%)	7 (3.7%)	10 (2.8%)
Moderate (4-6)	1 (4.0%)	10 (41.6%)	16 (39.1%)	16 (19.8%)	35 (18.5%)	78 (21.6%)
Severe (7-10)	24 (96%)	13 (54.2%)	24 (58.5%)	64 (79.0%)	147 (77.8%)	272 (75.6%)

NT: Neurotrophic Therapy; Phys T: Physical Therapy; Phar T: Pharmacological Therapy.

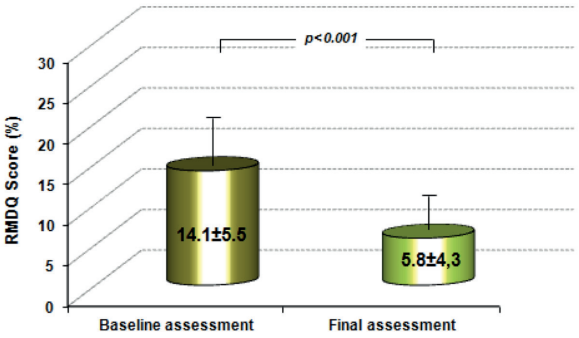

Figure 1. Roland and Morris Disability Questionnaire (RMDQ) at baseline and at the end of treatment.

The RMDQ mean proportion of positive responses (cases assessed 203 *vs.* 192) passed from 14.1 ± 5.5% to 5.8 ± 4.3% ($p < 0.001$) (Figure 1). For all the items a trend towards a reduction (ranging from –3% to –59%) was observed.

An improvement in all three factors of BPI short Italian version was recorded (factor 1, pain intensity 284 ± 93 *vs.* 111 ± 84; factor 2, affective interference 150 ± 76 *vs.* 47 ± 57; factor 3, activity interference 186 ± 65 *vs.* 74 ± 59, $p < 0.001$ for all). Pain relief from any treatment in the last 24 hours was reported more frequently at the end of the study (39.6 ± 20.6% *vs.* 60.4 ± 29.2%, $p < 0.001$).

An improvement in all the SF-12 items was observed (Table V).

Discussion

This observational study with descriptive purposes provides a "real life" representation of chronic LBP with sciatica in Italy, in terms of patients' characteristics and therapeutic interventions.

The group of patients selected is likely representative of the whole population suffering from this condition: young-elderly, the onset of signs and symptoms generally occurring in the last 12 months, a broad range of causes, clinical presentation and radiologic features.

However, the presence of pain and disability is a quite common aspect, confirming the high burden on health and on quality of life of chronic LBP with sciatica.

Similarly, a wide variability in the management of the disease is apparent. This is consistent with the fact that guidelines do not express homogenous and straightforward recommendations[9-11].

Notably, according to the Italian Diagnostic, Clinical and Therapeutic pathway for patients with LBP[35], the first level approach should include, in both acute and chronic conditions, counseling, modification of daily life, and active lifestyle, followed by conventional palliative medical treatment and rehabilitation. This latter aimed at functional recovery by means of several different interventions (exercises, cognitive-behavioral therapy, back school and multidisciplinary treatments).

Unfortunately treatment guidelines usually refer to LBP with or without sciatica as a unique pathology. So, as the targets are both LBP and neuropathic sciatic pain, a multimodal strategy targeting both kinds of pain should be followed.

At the moment considering the individual patient's characteristics, including not only the symptoms but also the level of disability, is adviced. Therefore, there is consensus about a multimodal and multidisciplinary approach, focused on the pathophysiology of the disease, and more specifically acting on two main directories: pain and disability.

As far as the pharmacological treatments are concerned, when choosing the pharmacological therapy, typically anti-inflammatory and analgesic medications, the average age of patients with chronic LBP and the even increasing prevalence in the older population have to be taken into account to prevent a higher occurrence of side effects and reach an acceptable harm to benefit ratio. To this aim, pathogenetic therapies represent a promising option and, accordingly, their prescription is recommended in neuropathic pain[13,14].

A recent Post-hoc analysis of the NATHAN I trial, in which patients with diabetic neuropathy were treated with ALA 600 mg/day by oral route for 4 years, highlighted the significant effectiveness of ALA in particular in older people (>65 years), with a significant reduction in the Neuropathy Impairment Score (NIS) *vs.* placebo[21].

Among neuropathic mechanisms of sciatica pain, oxidative stress which develops after the peripheral neuropathic lesion is acknowledged as a relevant factor responsible for neuropathic pain, leading to the activation of an inflammatory pathway involving the whole peripheral nerve up to the spinal dorsal horn, and, subsequently, of microglia[36-39]. This process may result in spine sensitization and in chronic neuropathic pain[14,38].

Recently, ALA and superoxide dismutase (SOD), another antioxidant agent endowed with

Table V. SF-12 Health Survey Questionnaire at baseline and at the end of treatment.

	Baseline	Final
1. In general, would you say your health is		
Excellent	0.6%	1.3%
Very good	7%	**23.9%**
Good	**43.6%**	**50.3%**
Fair	**31.4%**	**21.4%**
Poor	**17.4%**	3.1%
Does your health now limit you in these activities? If so, how much?		
2. Moderate activities		
Yes, limited a lot	**61.6%**	9.9%
Yes, limited a little	34.3%	**62.3%**
No, not limited at all	4.1%	27.8%
3. Climbing several flights of stairs		
Yes, limited a lot	48.3%	5.6%
Yes, limited a little	42.4%	54.9%
No, not limited at all	9.3%	39.5%
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?		
4. Accomplished less than you would like		
Yes	**84.8%**	38.3%
No	15.2%	**61.7%**
5. Were limited in the kind of work or other activities		
Yes	**91.2%**	**58%**
No	8.8%	42%
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?		
6. Accomplished less than you would like		
Yes	**78.4%**	29.4%
No	21.6%	**70.6%**
7. Did work or activities less carefully than usual		
Yes	**57.3%**	13.9%
No	42.7%	**86.1%**
8. During the past 4 weeks, how much did pain interfere with your normal work (including both housework and work outside the home)?		
Not at all	1.2%	4.4%
A little bit	2.3%	38.1%
Moderately	26.9%	**45%**
Quite a bit	**48.5%**	10%
Extremely	21.1%	2.5%
How much of the time during the past 4 weeks		
9. Have you felt calm and peaceful?		
All of the time	1.2%	12.7%
Most of the time	15.3%	**36.1%**
A good bit of the time	7.1%	20.8%
Some of the time	**45.3%**	22.2%
A little of the time	22.9%	6.3%
None of the time	8.2%	1.9%
10. Did you have a lot of energy?		
All of the time	1.8%	7.1%
Most of the time	5.9%	22.4%
A good bit of the time	5.9%	23.1%
Some of the time	29.3%	35.2%
A little of the time	40%	9.6%
None of the time	17.1%	2.6%

Table continued

Table V *(Continued)*. SF-12 Health Survey Questionnaire at baseline and at the end of treatment.

	Baseline	Final
11. Have you felt downhearted and depressed?		
All of the time	9.3%	2.5%
Most of the time	14%	3.8%
A good bit of the time	20.5%	5.7%
Some of the time	**32.2%**	28.9%
A little of the time	19.3%	**44.7%**
None of the time	4.7%	14.4%
12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?		
All of the time	7.6%	2.5%
Most of the time	19.9%	2.5%
Some of the time	33.3%	7.5%
A little of the time	31%	44.4%
None of the time	8.2%	43.1%

anti-inflammatory properties[40,41], have been proven effective in the management of diabetic neuropathy[42], low back pain[43], and chronic neck pain[44].

Therefore, antioxidant agents like ALA and SOD may be a useful choice in the multimodal treatment strategy for chronic LBP patients, since they can contribute to pain control due to their prevalently anti-inflammatory action[42-44].

The benefit of ALA in association with neurotrophic agents has been demonstrated in patients with chronic conditions characterized by an impairment in the nerve fiber function. Clinical trials on patients with radiculopathies and carpal tunnel syndrome show that the combination of ALA and GLA, a polyunsaturated n-3 (omega-3) fatty acid, exerts a synergistic positive effect on symptoms and peripheral nerve fiber conduction[19,20,24]. Neurotrophic agents such as GLA, honokiol and vitamin B complex have been used in association with ALA to improve sensory-motor function[12,23-25].

Antioxidant and neurotrophic agents may contribute to pain control, thus allowing to reduce analgesic medications and, as a consequence, to improve the safety profile of the therapeutic strategy adopted.

On the other hand, the effectiveness of physical therapies is controversial because of the lack of high quality clinical trials[9-12,45,46]. Transcutaneous electrical nerve stimulation (TENS) is based on the delivering of electrical stimulation to the underlying nerves via electrodes placed over the intact skin surface near the source of maximal pain.

Four high-quality randomised controlled trials (585 patients) comparing TENS with placebo for chronic low-back pain have been published. Due to conflicting evidence, it is unclear if TENS is beneficial in reducing back pain intensity[45].

It has to be highlighted that any intervention has to be considered in the framework of a multidisciplinary approach in order to address the various pathogenetic mechanisms with an appropriate multimodal treatment.

On the base of these considerations, our Study Group decided to recommend a multimodal approach including pharmacological, physical and neurotrophic treatments, with particular consideration to ALA, that has the higher degree of evidence among neurotrophic agents in neuropathic pain. We decided not to recommend a particular kind of pharmacological or physical treatment. The reason for this is that patients enrolled suffered from different levels of pain (mild, moderate or severe) and could be suffering from various comorbidities, thus a unique drug could not be recommended for all the patients. Furthermore, as regards physical therapies there is not a clear indication from literature and the participating centers could not have all the instruments for the various physical therapies available, so we decided to let the centers have freedom of choice in the pharmacological and physical treatments on the basis of patients' characteristics.

In this investigation, we observed a clinically significant improvement in symptoms, disability and quality of life.

Key results of the study are in our opinion the general and considerable improvement in both perceived pain (NRS and BPI) and functional disability (RMDQ), that can be considered a remarkable result, considering that the most effective drugs used alone for neuropathic pain have a NRS pain reduction *vs.* placebo ranging

from -1.30 for gabapentin to -1.06 for duloxetine[17]. Furthermore, we observed a good adherence to the recommendation of the Study Group to adopt a multimodal strategy, with a greater prescription of all the three categories of treatments (neurotrophic, pharmacological and physical) in the patients with the higher levels of pain.

This report has several limitations, as it is an observational study which comprises a wide variety of treatments and can't demonstrate the effectiveness of a particular treatment or of an association of treatments. It can only suggest that the association of ALA with pharmacological and physical therapies produce a clinically significant improvement in pain, functional disability and quality of life in patients suffering from LBP with sciatica.

Another limitation is that, although the Study group recommended to include in the study only patients suffering from LBP with sciatica, a little percentage of the patients enrolled didn't have a clear diagnosis of sciatic neuropathy. Despite this data, we considered all the patients included by the centers for the analysis, in the certainty that they all were endowed with a neuropathic component in LBP.

Conclusions

This study describes a likely representative population of patients suffering from chronic LBP with sciatica whose conditions were carefully assessed by means of standardized and validated questionnaires and followed prospectively for 2 months. Since a multimodal and multidisciplinary approach was adopted, a broad range of therapeutic options were used, which resulted in a general improvement in both perceived pain and functional disabilities. These results suggest that a multimodal approach can be beneficial in the treatment of LBP with sciatica.

Notes

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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