

# Double-blind, multicenter trial comparing acetyl L-carnitine with placebo in the treatment of fibromyalgia patients

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## Abstract Objective

*Fibromyalgia (FMS) is a chronic syndrome characterized by widespread pain, troubled sleep, disturbed mood, and fatigue. Several analgesic strategies have been evaluated but the results are moderate and inconsistent. Antidepressant agents are now considered the treatment of choice in most patients. It has been recently suggested that FMS may be associated with metabolic alterations including a deficit of carnitine. In this multicenter randomized clinical trial we evaluated the efficacy of acetyl L-carnitine (LAC) in patients with overt FMS.*

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## Methods

*One hundred and two patients meeting the American College of Rheumatology criteria for FMS were randomized into the study. The treatment consisted of 2 capsules/day of 500 mg LAC or placebo plus one intramuscular (i.m.) injection of either 500 mg LAC or placebo for 2 weeks. During the following 8 weeks the patients took 3 capsules daily containing either 500 mg LAC or placebo. The patients were seen during treatment after 2 (visit 3), 6 (visit 4) and 10 weeks (visit 5). The patients were also visited 4 weeks after treatment discontinuation (follow-up visit). Outcome measures included the number of positive tender points, the sum of pain threshold (kg/cm<sup>2</sup> or "total myalgic score"), the Short Form 36 (SF36), a 100 mm visual analog scale (VAS) for self-perceived stiffness, fatigue, tiredness on awakening, sleep, work status, depression, and muscular-skeletal pain, and the Hamilton depression scale.*

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## Results

*The "total myalgic score" and the number of positive tender points declined significantly and equally in both groups until the 6<sup>th</sup> week of treatment. At the 10<sup>th</sup> week both parameters remained unchanged in the placebo group but they continued to improve in the LAC group with a statistically significant between-group difference. Most VAS scores significantly improved in both groups. A statistically significant between-group difference was observed for depression and musculo-skeletal pain. Significantly larger improvements in SF36 questionnaire were observed in LAC than in placebo group for most parameters. Treatment was well-tolerated.*

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## Conclusion

*Although this experience deserves further studies, these results indicate that LAC may be of benefit in patients with FMS, providing improvement in pain as well as the general and mental health of these patients.*

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## Key words

Fibromyalgia, L-carnitine, pain.

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## Introduction

Fibromyalgia (FMS) is a chronic syndrome characterized by widespread pain, troubled sleep, disturbed mood, and fatigue (1). It is estimated to be the second most common rheumatologic disorder (2).

The cause of fibromyalgia has not been clearly defined, but several mechanisms may be involved. Abnormalities in muscle structure, and a variety of neurotransmitter and neuroendocrine changes may contribute to the development of fibromyalgia (3-5).

A range of treatments are employed to treat the various symptom facets of FMS. These include neuromodulatory medications such as antidepressants, opioids, nonsteroidal antiinflammatory drugs, sedatives, muscle relaxants, and anti-epileptics, or nonpharmaceutical treatment modalities, including education, exercise, physical therapy, massage, and cognitive behavioral therapy (5-9). These therapies, both pharmacologic and nonpharmacologic, show only limited success, although drugs that affect serotonin or nor-epinephrine at the receptor site (such as antidepressants) seem to generate the most consistent results.

In recent studies it has been suggested that FMS may be associated with metabolic alterations contributing to the development of the syndrome (10). For example a deficit of carnitine has been suspected in fibromyalgic patients. Carnitine plays an important role in energy supply by controlling the influx of long-chain fatty acids into mitochondria. Disorders associated with carnitine deficiency may impair the function of liver, heart and skeletal muscle; clinically muscle carnitine deficiency is characterized by weakness, fatigue, and exercise intolerance that are important symptoms in FMS patients. In muscle biopsies from FM patients ragged red fibers have been found and a metabolic disturbance with low levels of high energy phosphates has also been demonstrated, but the content of carnitine was normal (11-13). Recently, however, a carnitine deficiency has been described in the skeletal muscle tissues of a subgroup of patients with FMS (14). There was also increased pyruvicemia and

acylcarnitine/free carnitine ratio, indicating a deficit of carnitine (15). L-carnitine may have a role in reducing the hypoxic stress of tissues: ischemia in endothelial cells can result in carnitine release, increased oxidative stress, and compromised blood flow; these responses can be ameliorated by carnitine administration (16).

This provides a reasonable rationale for evaluating the effect of L-acetylcarnitine (LAC) therapy which is also known to exert a positive effect in the elderly with mood disturbances and depression (17-22). In this multicenter randomized clinical trial we evaluated the efficacy of LAC in patients with overt FMS.

## Methods

### Patients

Subjects were recruited from 7 rheumatology outpatient clinics in Italy. Enrolment began in January 2002 and the study was completed in June 2004. The patients were eligible for inclusion in the study if they were at least 18 years of age and met the American College of Rheumatology 1990 criteria for FMS (1). Patients were excluded if they had evidence of: any inflammatory disease involving bone, joints, entheses or skin, symptomatic osteoarthritis; recent trauma; infectious or endocrine diseases; clinically unstable medical illness; a history of seizure, head trauma, or stroke; history of severe psychiatric conditions (hypomania, mania, psychosis, dementia); lifetime history of alcohol or drug dependence; use of antidepressants within 6 months before randomization or recent (< 1 year) initiation of hormone replacement therapy; received non-steroidal anti-inflammatory drugs or analgesic compounds within 3 and 7 days, respectively, before randomization; pregnant or fertile women not on contraception.

### Outcome measurements

Subjects were examined for the number of positive tender points by a "Pressure Threshold Meter", with a rubber disc of 1 cm<sup>2</sup> applied at a 90° vertical angle to the 18 tender point sites (23). Pressure was progressively increased until subjects indicated verbally when they first felt discomfort. The pressure was

then stopped and the weight read on the digitalized manometer. The individual scores were summed to give the “total myalgic score”.

A 100 mm visual analog scale (VAS) was used to evaluate self-perceived stiffness, fatigue, tiredness on awakening, sleep, work status, depression, and muscular-skeletal pain. The general health profile of the patients was assessed by the Short Form 36 (SF36) questionnaire and the typical 9 domain calculated separately (24). The 17-item Hamilton scale was used for assessing depression (25). The screening protocol included an interview for demographic information; medical, psychiatric, and family history.

#### Study treatment

The eligibility of the patients for the study was evaluated at the screening visit. The main inclusion criteria was the presence of at least 11 positive trigger points with pain defined as unbearable at a pressure  $< 4 \text{ kg/cm}^2$ .

After the screening visit, the patients were invited to discontinue any chronic treatment with non-steroidal anti-inflammatory or analgesic drugs and invited to attend the randomization visit 7 days later (visit 2). The randomization code was obtained by phone according to a randomization list for either L-acetylcarnitine (LAC) or placebo in a 1:1 ratio. Treatment was double blind and double dummy throughout. The treatment was 2 capsules/day of 500 mg LAC or placebo plus one intramuscular (i.m.) injection of either 500 mg LAC or placebo for 2 weeks. During the following 8 weeks the patients took 3 capsules daily containing either 500 mg LAC or placebo. All formulations for both active and placebo were prepared and provided by Sigma Tau (Pomezia, Rome, Italy).

The patients were seen during treatment after 2 (visit 3), 6 (visit 4) and 10 weeks (visit 5). The patients were also visited 4 weeks after treatment discontinuation (follow-up visit).

The “total myalgic score” that was obtained at all visits, was the primary end point of the study. The Hamilton test was performed at visit 2, 3 and 5, while all VAS scores and the SF 36

questionnaire were assessed only at the screening visit and at visit 5 (end of treatment); all these outcomes were secondary end points of the study.

The study protocol was approved by the local Ethics Committee and all subjects provided written informed consent.

#### Statistical analysis

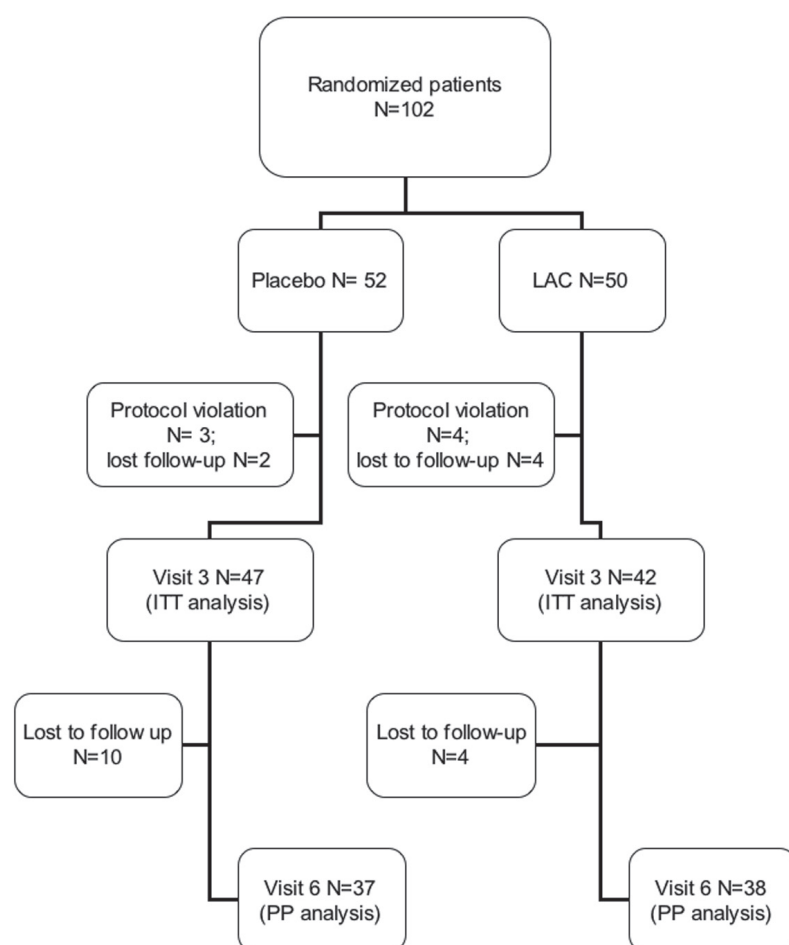
The study was designed to enrol 100 patients in order to detect a treatment group difference of  $0.3 \text{ kg/cm}^2$  in the “total myalgic score” with a 90% power. The difference was based on the wish to power this study to demonstrate a clinically meaningful effect.

The statistical significance of changes from baseline was determined using the paired *t*-test. Differences in outcome parameters response were calculated using analysis of covariance (ANCOVA) with Bonferroni test for adjusting significance to multiple com-

parisons and with pretreatment drug as the factor and the corresponding baseline parameter values as the covariate. The primary analysis was by intention-to-treat, without regard to adherence, applied to patients in whom at least one post-treatment evaluation was obtained. We computed outcomes for patients with missing measurements by carrying forward the most recent post-enrolment measurement (last observation carried forward).

#### Results

One hundred and two patients were enrolled and randomized to receive study treatment by an automatic procedure. Three of these patients were male. During a post-enrollment evaluation of the Clinical Research Forms by the Contract Research Organization (CRO), 7 patients were excluded either for violation of inclusion-exclusion criteria or



**Fig 1.** Diagram of patient flow. The diagram represents the outcome of all patients who entered the study. ITT = intent-to-treat; PP = per-protocol.

because after enrolment they continued non allowed therapies. Six patients did not attend the first post-treatment visit, thus leaving the number of patients available for the ITT analysis at 42 and 47 for LAC and placebo respectively (Fig. 1). Fourteen patients were then lost to follow-up and the final number of patients left for a per protocol analysis (PP) were 38 and 37 for LAC and placebo, respectively. Seven additional patients did not attend the post-treatment follow-up visit.

The main baseline characteristics of the study population are listed in Table I. The two groups were comparable for all characteristics by considering both the ITT (Table I) and the PP population (data not shown).

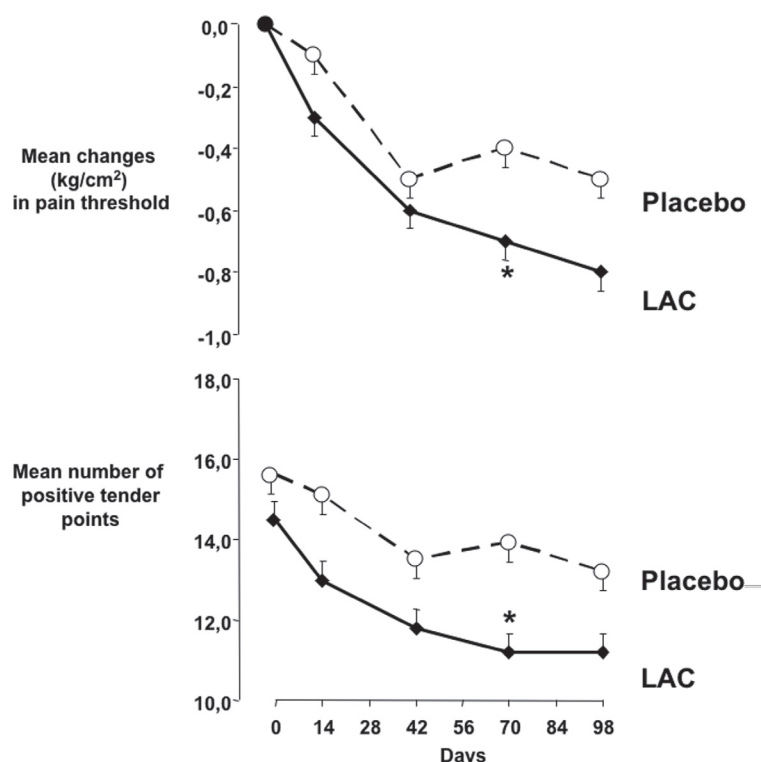
The changes in the primary end point of the study, the total myalgic score over time are illustrated in Figure 2. The score declined significantly and equally in both groups until the 6<sup>th</sup> week of treatment. At the 10<sup>th</sup> week the score remained unchanged in the placebo group but it continued to improve in the LAC group with a statistically significant between-group difference. A similar pattern of changes was observed in the mean number of positive (< 4 kg pain threshold) tender points, with a significant between-treatment difference at week 10 both for the absolute number (Fig. 2, lower panel) and with regards to its change ( $p < 0.02$ ; data not shown). By analyzing the PP study population most of the significance either did not change or improved.

The changes in VAS score for subjective symptoms from baseline to the end of the treatment are illustrated in Figure 3. With the exception of depression in the placebo group, all other items significantly improved in both groups. A statistically significant between-group difference was observed for depression and musculo-skeletal pain.

The changes in the main domains of the SF36 questionnaire are shown in Figure 4. A significant improvement was observed in 7 out of 10 parameters and in 3 out of 10 in the LAC and placebo group respectively. A significant between-group difference was observed for bodily pain, mental health, general

**Table I.** Mean baseline clinical characteristics (standard deviation) of the patients who had at least one post-treatment evaluation (ITT group).

	Placebo (N = 47)	LAC (N = 42)
Age (years)	46.3 (10.4)	47.3 (11.7)
Height (cm)	160.4 (6.5)	158.6 (5.7)
Weight (kg)	66.7 (13.1)	62.9 (11.7)
BMI (kg/m <sup>2</sup> )	25.7 (4.3)	24.9 (4.3)
Mean tender point (kg) threshold	2.75 (0.24)	2.85 (0.32)
Mean number positive (< 4 kg) tender points	15.6 (2.9)	14.5 (3.8)
SF-36, range 1-100		
Physical functioning	50.9 (25.8)	56.6 (25.8)
Social functioning	52.7 (20.7)	55.4 (20.1)
Role limitation – physical	27.1 (30.3)	33.1 (38.2)
Bodily pain	33.8 (16.7)	38.7 (21.9)
Mental health	55.8 (20.6)	49.0 (18.1)
Role limitation- emotional	40.4 (39.3)	38.7 (37.3)
Vitality	33.5 (19.1)	37.0 (17.1)
General Health perception	39.0 (21.1)	43.0 (20.1)
Visual Analog Scale (1-100)		
Stiffness	65.3 (24.7)	66.6 (26.4)
Fatigue	75.5 (22.4)	73.5 (20.0)
Tiredness on awakening	75.9 (22.6)	76.9 (21.6)
Sleep disturbances	60.1 (29.4)	59.9 (29.1)
Pain and daily activities	68.0 (25.3)	69.1 (26.5)
Depression	50.0 (31.1)	61.3 (27.5)
Musculo-skeletal pain	72.5 (22.2)	74.8 (20.9)
Hamilton Rating Scale (0-22)	11.5 (6.1)	12.2 (4.3)



**Fig. 2.** Mean changes in pain threshold (pressure threshold meter, kg) and number of positive tender points over time. \*  $p < 0.05$

health perception and both mental and physical total scores. The longitudinal changes in the Ham-

ilton score are shown Figure 5. The mean score was approximately 12 in both groups, far below the 15-20,

which represents the minimum score for a longitudinal evaluation (26). The mean score significantly improved in the LAC group at week 10 but the between-group difference was not statistically significant.

Treatment was well tolerated and the number (42% in the placebo group and 36% in the LAC group) and severity of adverse events were similar in the two groups of patients. They were associated to treatment discontinuation for 3 and 5 subjects of the placebo and LAC group, respectively.

### Discussion

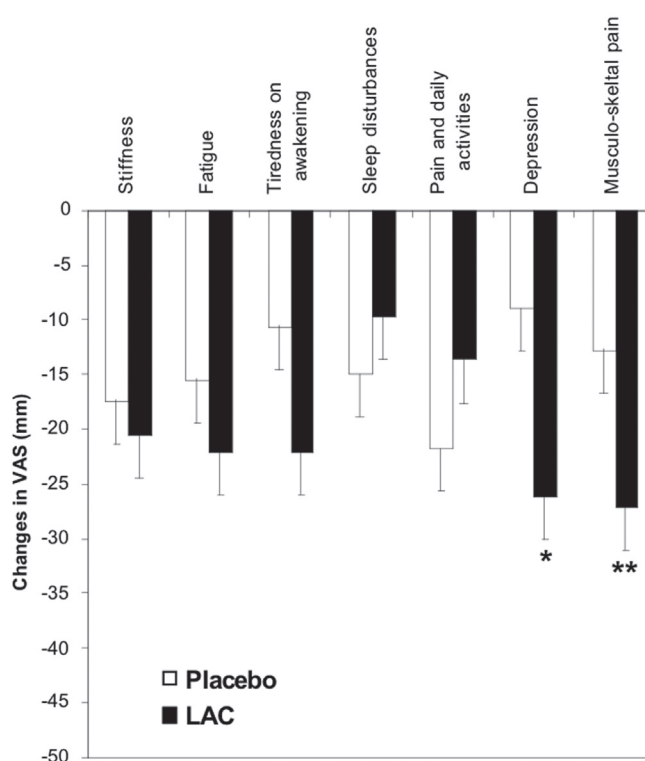
In this randomized, double blind, 10 week trial in subjects with ACR-defined primary FMS, LAC treatment had significantly greater efficacy than placebo on the primary end-point of the study (total myalgic score) but also on several other outcome measures. The baseline assessment demonstrated that this study population was similar to those in other studies of patients with FMS (6). The efficacy of LAC on pain was consistent for all adopted assessment tools: total myalgic score, number of positive tender points, VAS for musculo-skeletal pain, SF-36 domain for bodily pain. Improvements in general health status and mental health were also observed. These improvements were likely linked to improvement in pain, since there appears to be a significant correlation between changes in pain and in general health perception in the two groups individually and in the study population as a whole (data not shown).

Self-evaluated depression also improved, and this finding is in line with some preliminary reports on the efficacy of LAC on primary depression (17-22). However, it should be pointed out that depression in our cohort was moderate and therefore the Hamilton score could not be properly used for assessing improvements. It remains to be established whether these minor improvements in depression were the cause or the consequence of the pain benefits. All anti-depressant agents, including to a certain extent also LAC, seem to provide symptomatic relief in patients with FMS, before or inde-

**Fig. 3.** Changes in VAS score for subjective symptoms from baseline to the end of the treatment.

\*  $p < 0.05$

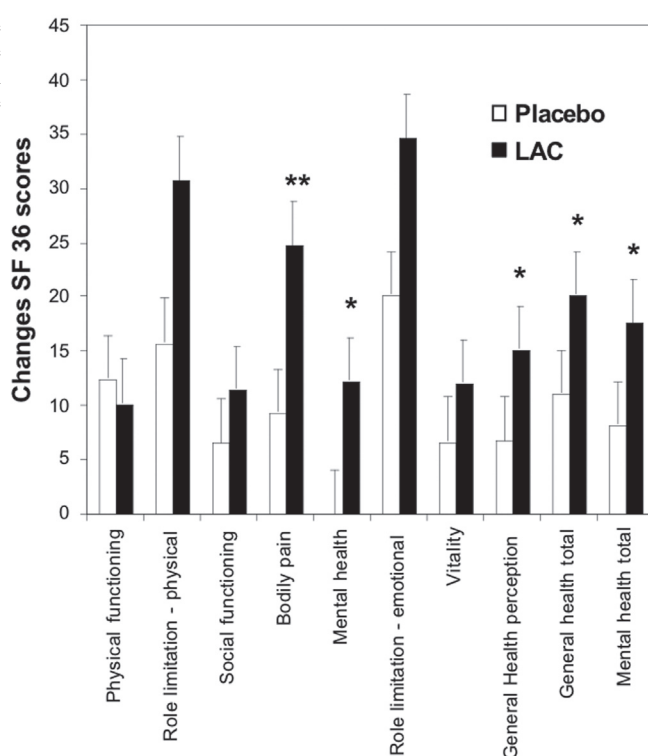
\*\*  $p < 0.001$



**Fig. 4.** Changes in the main domains of the SF36 questionnaire from baseline to the end of the treatment.

\*  $p < 0.05$

\*\*  $p < 0.001$

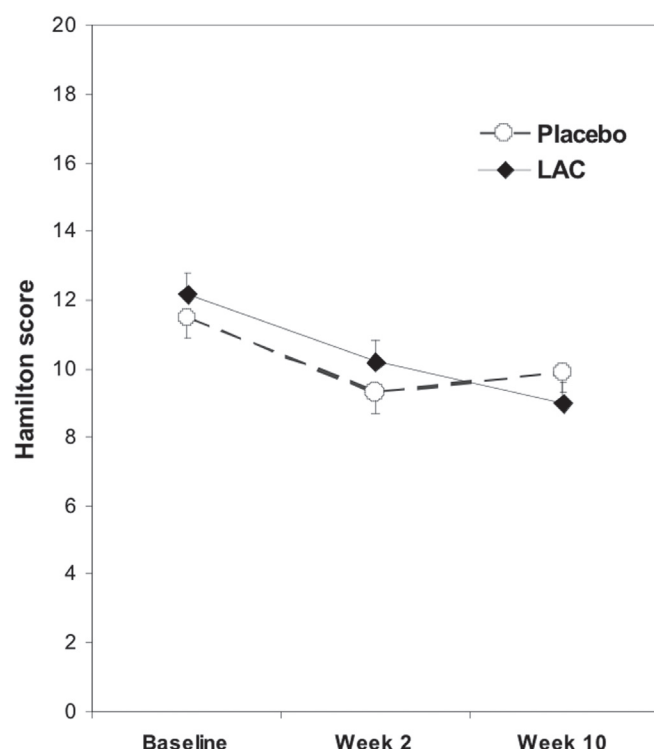


pendent of their effect on depression. This might suggest a pain-modulating effect of these compounds on peripheral or central nervous system, not dependent on the modulation of mood (27-29).

The changes in pain and general health

we observed are comparable to those recently reported in two randomized clinical trials of duloxetine and pregabalin, even though the placebo effect in our cohort was somewhat greater, with significant improvements for most efficacy assessment items (28, 30). This





**Fig. 5.** Longitudinal changes in the Hamilton score during the treatment.

might be attributed to the complexity of the dosing regimen that included an intra-muscular injection, perceived in the Italian population as a “strong” treatment approach. Anyhow, our results emphasize the need for accurate double blind randomized clinical trials when evaluating any pharmacologic treatment of FMS. The placebo effect may possibly explain the delay in the longitudinal pain response to LAC. The difference between the two groups becomes statistically significant only when, as expected, the placebo effect waned after the first 4-6 weeks of observation.

The delayed response may also be related to the mechanism of action of LAC. LAC is a physiological compound synthesized in the mitochondria. When given at an apparent cholinergic effect associated with an inhibitory competitive effect on the GABA-receptor complex, thereby explaining the anti-depressant activity of LAC (17-22). In addition LAC facilitates mitochondrial beta-oxidation of fatty acids, through the Krebs’ cycle with a potential beneficial effect on both sensitive and motor peripheral nerves (31-33). These latter metabolic effects are likely to be fully expressed only with

an extended time lag. LAC may also have a role in reducing the disturbances of muscle blood flow described in FM patients, the hypoxic stress of tissues, especially at the onset of exercise, and the oxidative disorder recently reported in primary FMS (34-38).

The analysis of our results as well as those recently reported with duloxetine and pregabalin, may provide some insights on the pathophysiology of FMS (28, 30). In these trials the beneficial effect on pain was not associated with improvement in fatigue or anxiety indicating that some of the underlining psychological and/or metabolic abnormalities remain unsolved.

Recent studies demonstrate that LAC treatment improves fatigue in patients with chronic fatigue syndrome and in multiple sclerosis, and is efficacious in alleviating symptoms, particularly pain, and improves nerve fiber regeneration and vibration perception in patients with established diabetic neuropathy (39-41).

Although this experience deserves further studies, these results indicate that LAC may be of benefit in patients with FMS, providing improvement in pain as well as the general and mental health of these patients.

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