A randomised controlled trial comparing duloxetine and acetyl L-carnitine in fibromyalgic patients: preliminary data

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ABSTRACT

Objective. *Fibromyalgia syndrome (FMS) is a chronic disorder characterised by widespread musculoskeletal pain, troubled sleep, disturbed mood, and fatigue. Recently published reviews have demonstrated that it is influenced by various psychological aspects, and antidepressants are now considered the treatment of choice for most patients.*
The aim of this randomised controlled trial was to compare the effects of duloxetine and acetyl L-carnitine on pain, depression, anxiety and well-being in FMS patients.

Methods. *Sixty-five female outpatients with FMS diagnosed by a rheumatologist were recruited between January 2011 and May 2012, and randomised to receive duloxetine 60 mg/day or acetyl L-carnitine 1500 mg/day (500 mg t.i.d.). Drug efficacy and side effects were assessed by the same psychiatrist at baseline, and four and 12 weeks later.*

Results. *Both drugs led to a general clinical improvement, with positive effects on pain and depressive symptoms; but neither induced a significant improvement in anxiety. Both drugs had a positive effect on the physical component of the quality of life, but only duloxetine improved the psychological component.*

Conclusion. *Although they need to be confirmed by further studies, these preliminary findings confirm the efficacy of duloxetine, and suggest that acetyl L-carnitine is also efficacious in improving depressive symptoms, pain, and the quality of life of FMS patients.*

Introduction

Fibromyalgia syndrome (FMS) is a chronic pain syndrome characterised by diffuse pain for more than three months and tenderness in at least 11 of 18 tender points (1), although the diagnostic criteria have recently been revised to give more weight to the complexity of the symptoms associated with generalised pain (including non-restorative sleep, fatigue and cognitive dysfunction) and less to the number of painful tender points (2).

Its aetiology is still unknown, but the most widely supported hypothesis is that the persistent muscle pain is caused by an enhanced mechanism of central sensitisation (3). However, as in the case of all forms of chronic pain, psychological factors such as depression, anxiety, stress and life events play an important role in FMS (4-11), and so its treatment requires a multimodal approach that not only takes into account its somatic aspects, but also emotional, cognitive and environmental factors (12-15). The most widely prescribed drugs are antidepressants (16-20), especially serotonin and norepinephrine reuptake inhibitors (SNRIs) such as duloxetine (DLX) and milnacipran, which have been approved to treat FMS in the USA (21).

Acetyl L-carnitine (ALC) has been tested in only one study of FMS (22), but its usefulness in relieving neuropathic pain (23) and improving depressive symptoms (24, 25) offers a rationale for its use.

The aim of this study was to further explore the efficacy of DLX and ALC in the treatment of FMS by considering, as primary outcome measures, pain, mood and clinical general improvement, and as secondary outcomes anxiety and well-being.

Methods

Study design and sample

This prospective, randomised and controlled study involved 65 of the 80 patients attending the Fibromyalgia Integrated Outpatient Unit (FIOU), a multidisciplinary unit of rheumatologists, psychologists and psychiatrists at the

AO Città della Salute e della Scienza Hospital, Turin, Italy, between January 2011 and May 2012. The inclusion criteria were: 1) female patients aged 18–65 years; 2) a diagnosis of FMS made by an expert rheumatologist on the basis of the criteria of the American College of Rheumatology; and 3) a pain intensity visual analogue scale (VAS) score of >3 (the patients were receiving non-steroidal anti-inflammatory drugs). The exclusion criteria were: 1) a concomitant DSM-IV TR axis I psychiatric syndrome, including mood and anxiety disorders; 2) pain due to trauma; 3) rheumatic disease; 4) autoimmune disease; 5) contraindications to the use of DLX or ALC; 6) current antidepressant treatment.

The patients were randomised to receive DLX 30–60 mg/day or ALC 500mg three times a day.

Drug efficacy and side effects were assessed by the same psychiatrist at baseline (T0), and after four (T1) and 12 weeks (T2). At T0, the patients' sociodemographic, clinical and psychological data were recorded, and they were administered the Montgomery Asberg Depression Rating Scale (MADRS), the Hospital Anxiety and Depression Scale (HADS), the pain VAS, the Distress Thermometer (DT), the 36-item Short-Form Health Survey (SF36), and Clinical Global Impression – Improvement (CGI-I); at T1 they were administered the same questionnaires except the SF36; and at T2, the same questionnaires plus SF36.

The study was approved by the hospital's ethics committee, and all of the patients gave their written informed consent before enrolment.

Assessment instruments

The MADRS is clinician administered questionnaire, designed to assess the severity of depression. Scores range from 0 to 60, and higher scores reflect more severe symptoms.

The self-administered HADS is divided into depression and anxiety subscales, each of which ranges from 0 to 21; a score of ≥8 suggests a clinically relevant level of depression/anxiety symptoms.

Current pain (CP) intensity was measured using a VAS whose scores ranged from 0 (no pain) to 10 (extreme pain).

The SF-36 includes eight health status domains whose scores range from 1 to 100, with higher scores indicating better health. The results are divided into two component scores measuring overall mental health (the mental component) and physical health (the physical component).

The CGI-I is a well-known, clinician-administered instrument used to evaluate illness severity, the degree of improvement, and the balance between treatment effectiveness and the burden of side effects.

Statistical analysis

The sample distribution was tested using the Shapiro-Wilk normality test. Descriptive statistics were used to summarise the data and detect outliers, whereas the changes in the patients' treatment responses from one time point to another were evaluated analysis of variance (ANOVA) for repeated measures. Mauchly's test of sphericity was used to assess variances in the differences between all of the group combinations. Bonferroni's correction was used to compare the main effects. The data were analysed using SPSS® software, version 20.0 for Windows.

Table I. Demographic and clinical data of the patients included in the study.

Mean age, years (SD)	51.88 ± 10.17
Mean duration of education, years, (SD)	9.73 ± 3.42
Working position, %	occupied 60% retired 16% housewife 20% unemployed 4 %
Marital status, %	married 71% divorced 18% single 4% vidow 7%
FIQ total score, mean (SD)	58.36 ± 19.38
VAS pain, mean (SD)	5.69 ± 2.81
Duration of FM, years (SD)	7.56 ± 6.79
CGI-S score, mean (SD)	4.44 ± 0.54

SD: standard deviation; FIQ: Fibromyagia Impact Questionnaire; VAS: Intensity of pain as measured by the Visual Analogue Scale; CGI-S: Clinical Global Impression- Severity of Illness scale.

Results

General description

• *Sample*

Fifty-one of the 65 enrolled patients (78.5%) completed the study; there were no demographic or clinical differences between the completers and non-completers (Table I).

The mean age and standard deviation (SD) of the completers was 51.78±10.17 years (SD), and their mean duration of education was 10.07±3.25 years). Twenty-nine patients were randomised to receive DLX and 22 to receive ALC; there were no demographic or clinical differences between the two groups at baseline.

• *Side effects*

Eight patients in the DLX group experienced mild-severe side effects during the two weeks of treatment (nausea, anxiety, insomnia, and diarrhoea). No side effects emerged in the ALC-group.

• *Dropouts*

The 14 dropouts excluded from the analysis included 10 from the DLX group (eight due to side effects and two who were lost to follow-up), and four from the ALC group (all of whom dropped out because of difficulties in drug self-provision).

Outcome measures

• *Primary outcome measures*

There was a significant improvement in the pain intensity VAS score between T0 and T1 only in the DLX group (Table II).

Both drugs significantly improved MADRS scores between T0 and T2, whereas only the DLX group showed a significant improvement in the HADS depression subscale score between T1 and T2 (Table II).

Table II. Comparison among primary outcomes (pain, depression, clinical improvement) and secondary outcomes (anxiety and well being).

		T0 (SD)	T2 (SD)	*p*-value
VAS				
	Dulo-group	5.70 ± 2.98	3.86 ± 2.68	0.033*
	ALC-group	5.69 ± 2.70	4.51 ± 2.61	0.148
MADRS				
	Dulo-group	19.43 ± 6,27	9.56 ± 4.28	<0.001*
	ALC-group	16.31 ± 6.36)	9.81 ± 3.81	<0.001*
HADS-D				
	Dulo-group	9.17 ± 3.78	7.00 ± 4.03	0.066
	ALC-group	7.45 ± 4.25	8.50 ± 5.00	0.457
CGI-S				
	Dulo-group	4.34 ± 0.57	2.38 ± 1.46	<0.001*
	ALC-group	4.54 ± 0.50	2.36 ± 1.21	<0.001*
HADS-A				
	Dulo-group	9.43 ± 3.97	7.47 ± 4.28	0.115
	ALC-group	7.50 ± 4.27	7.95 ± 5.18	0.755
SF 36 score				
SF 36 Ment	Dulo-group	157.22 ± 81.33	217.48 ± 85.41	0.002*
	ALC-group	201.18 ± 90.41	199.83 ± 108.65	0.939
SF 36 Phys	Dulo-group	129.37 ± 57.02	200.44 ± 80.46	<0.001*
	ALC-group	152.81 ± 88.33	177.10 ± 91.21	0.017*

SD: standard deviation: VAS: Intensity of pain measured by the Visual Analogue Scale; MADRS: Level of Depression measured by Montgomery Asberg Depression Rating Scale; HADS-D: Level of Depression measured by the Depression subscale of the Hospital Anxiety and Depression Scale; CGI-S: Clinical Global Impression- Severity of Illness scale; HADS-A: Level of Anxiety measured by the Anxiety subscale of the Hospital Anxiety and Depression Scale; SF-36 Ment: the mental component summary of the SF-36; SF 36 Physical: the physical component summary of the SF-36. *:$p<0.005$.

The CGI-I scores showed that both groups experienced a significant general clinical improvement between T0 and T2 (Table II).

• *Secondary outcome measures*

There was no significant improvement in the HADS anxiety subscale in either group.

By the end of the study, there was a significant improvement in the physical component of the SF-36 in both groups, but only the DLX group showed a significant improvement in the mental component.

Discussion

The results of this randomised and controlled trial seem to confirm previous findings concerning the efficacy of DLX treating FMS, but also suggest a possible role for ALC.

The improvement in pain in the DLX group corroborates previous findings concerning the efficacy of SNRIs (17). However, unlike Rossini *et al*. (22), we did not observe any significant improvement in VAS-measured pain in the ALC group, although the patients did report a significant improvement in the physical component of the SF-36. Both drugs led to significant improvements in mood (MADRS), thus confirming previous findings (17, 22), but DLX seems to have a greater effect on depression as suggested by the improvement in the HADS depression score and the SF-36 psychological component.

Finally, both drugs seemed to contribute to a significant general clinical improvement, as shown by the CGI-I scores at T2.

Neither drug seemed to improve anxiety, but both led to an improvement in well-being (ALC only in relation to the physical component of the SF-36, DLX in relation to both the physical and the mental component).

Finally, also on the basis of the number of dropouts, ALC seemed to have less severe side effects.

The main limitations of this study are the lack of a placebo control group and the small size of both treatment groups, which may partially affect the generalisability of the results. Nevertheless, to the best of our knowledge, this is the first study comparing the use of DLX and ALC in patients with FMS and this contributes to compensating for the relative paucity of data concerning these drugs.

The results seem to confirm the efficacy of DLX in treating pain and depressive symptoms of FMS patients, and also the possible therapeutic role for ALC which, besides being easy to manage, had a positive effect on depressive symptoms and was partially effective in relieving pain.

Further studies should be carried out to confirm these results in larger samples and to assess the psychological aspects of pain perception in more detail in order to clarify the conflicting results emerging in this field (26).

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