

Palmitoylethanolamide and acetyl-L-carnitine act synergistically with duloxetine and pregabalin in fibromyalgia: results of a randomised controlled study

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Abstract

Objective

Fibromyalgia (FM) is characterised by a form of debilitating pain that is unresponsive to standard analgesics. The aim of this study was to evaluate the efficacy of supplementing ongoing pregabalin (PGB) and duloxetine (DLX) treatment with palmitoylethanolamide (PEA) and acetyl-L-carnitine (ALC) for 24 weeks in FM patients.

Methods

After undergoing three months of stable treatment with DLX+PGB, FM patients were randomised to continue the same treatment (Group 1) or to add PEA 600 mg b.i.d + ALC 500 mg b.i.d. (Group 2) for a further 12 weeks. Every two weeks throughout the study, cumulative disease severity was estimated using the Widespread Pain Index (WPI) as the primary outcome measure; the secondary outcomes were the fortnightly scores of the patient-completed revised Fibromyalgia Impact Questionnaire (FIQR) and the modified Fibromyalgia Assessment Status (FASmod) questionnaire. All three measures were expressed as time-integrated area under the curve (AUC) values.

Results

One hundred and thirty (91.5%) of the initial 142 FM patients completed the study: 68 patients in Group 1 and 62 in Group 2. Twenty-four weeks after randomisation, the Group 2 patients showed additional significant improvements in all three outcome measures. Although there was some fluctuation in both groups during the study period, the AUC values of the WPI scores steadily decreased in Group 2 ($p=0.048$), which also showed better outcomes in terms of the AUC values of the FIQR ($p=0.033$) and FASmod scores ($p=0.017$).

Conclusion

This is the first randomised controlled study demonstrating the effectiveness of the adding on therapy of PEA+ALC to DLX+PGB in FM patients.

Key words

fibromyalgia, duloxetine, pregabalin, acetyl-L-carnitine, palmitoylethanolamide

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Introduction

Chronic widespread pain (CWP) is a defining feature of fibromyalgia (FM), which affects at least 2% of the world's population (1, 2), but FM patients also frequently experience other symptoms (mainly fatigue, and sleep and cognitive disturbances) that have a detrimental impact on their personal relationships, jobs, and everyday activities (3, 4).

FM is the prototype of the so-called central sensitisation syndrome (5-7), and has no gold standard treatment (8): patients rarely experience full symptom remission, and only 25% achieve long-term improvement (9). The persistent lack of proven effective treatments is at least partially due to the absence of any pathophysiological certainties (10). The recent redefinition of fibromyalgic pain as nociplastic pain underlies the absence of stimuli capable of causing nociceptor activation (thus preventing its definition as nociceptive pain), and the absence of lesions to the somatosensory system prevents its definition as neuropathic pain (11). It seems that nociplastic changes in the nervous system account for the patients' amplified perception of pain but, despite this new definition of FM pain, there is still no unequivocal pathophysiological theory underlying it. Other than central amplification mechanisms, what has emerged concerning its pathogenesis is the presence of neuro-inflammation in both the peripheral and central nervous systems, and the possibility that glial cell activation plays a central role. Neuro-inflammation plays a significant role in the induction and maintenance of CWP (12, 13), and it has been suggested that inflammation may be a mitochondrial dysfunction-dependent event that is involved in the pathophysiology of FM, thus making the mitochondria a potential therapeutic target (14).

Gabapentinoids influence enhanced functional connectivity between brain regions and glutamatergic activity in patients with chronic pain. Pregabalin (PGB), which blocks calcium channels and lowers the release of pre-synaptic neurotransmitters and post-synaptic excitability (15), has been approved for the treatment of FM despite the fact that it is primarily an anticonvulsant

and has effects on central pain regulation (16). Its efficacy and safety in FM patients have been examined in randomised controlled trials alone and in combination with duloxetine (DLX), a serotonin and norepinephrine reuptake inhibitor (SNRI) (17-19). PGB significantly reduces pain intensity over 12-26 weeks, but has more side effects than placebo in approximately 10% of patients.

These outcomes are comparable with those of other FM treatments such as DLX (18), which has been approved by the American Food and Drug Administration (FDA) for the treatment of major depressive disorder, generalised anxiety disorder, FM, chronic musculo-skeletal pain, and diabetic peripheral neuropathy. DLX increases the activity of noradrenergic and serotonergic neurons in the descending spinal dorsal horn pathway, and is used to treat various neuropathic and chronic pain syndromes (20). The descending pathway inhibits the activity of dorsal horn neurons, thus preventing the brain from receiving excessive inputs that are thought to be interpreted as pain (21, 22).

As the insufficient efficacy and/or unacceptable side effects of PGB and DLX at therapeutic doses means that most patients only partially benefit from them (23, 24), they are frequently used in combination in clinical practice. Guidelines issued by the American Pain Society, the European League Against Rheumatism, and the Association of Scientific Medical Societies in Germany made no specific recommendations for or against combined pharmacotherapy (25), but the joint guidelines of the Canadian Pain Society and Canadian Rheumatology Association stated that "an ideal pharmacological choice may address multiple symptoms simultaneously and may require a combination of medications, in which case attention must be paid to drug interactions (level 5, grade D)" (26), and an expert panel of the Italian Society for Rheumatology has confirmed this multi-modal approach (27).

Combined therapeutic strategies also benefit from integrating drugs and nutraceuticals. It has been found that the fatty acid amide palmitoylethanol-

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olamide (PEA) and acetyl-L-carnitine (ALC) both have an effect on CWP (28,29), and one study has investigated the analgesic and anti-inflammatory effects of PEA in FM patients (30). PEA is an endogenous chemical that is thought to regulate inflammatory analgesic events and tissue reactivity (31) by activating the cell surface cannabinoid (CB) 2-like receptor, the orphan G protein-coupled receptor (GPR)-55, and the nuclear receptor of the peroxisome proliferator-activated receptor (PPAR) family, and down-regulating mast cell degranulation autacoid local inflammation antagonism (ALIA) mechanisms (32).

ALC provides another approach to nociceptive pain therapy (33) as it increases the effects of nerve growth factor (NGF) while acting as an acetyl-group donor, and contributes to mitochondrial energy homeostasis and detoxification (34). Its anti-nociceptive action has been demonstrated in a number of experimental models of neuropathic pain (35), and is due to various mechanisms. It is the only drug whose analgesic effect is epigenetically based on the acetylation of p65/RelA, a transcription factor in the NFkB family. It also has an effect at the level of dorsal root ganglia and the dorsal horns of the spinal cord p65/RelA acetylation increases the expression of metabotropic glutamate receptor type 2 (mGlu2), which inhibits glutamate release from primary afferent sensory fibres (36). Given its structural affinity to acetylcholine, it may also increase the absorption of acetyl-CoA by mitochondria and have cholinomimetic effects (37).

On the basis of the above considerations, the aim of this study was to evaluate the potential benefits of adding PEA and ALC to the combined DLX+PGB treatment of FM patients.

Materials and methods

Patients and study design

In order to be consistent with most current studies of FM, the 2011 American College of Rheumatology (ACR) diagnostic criteria (38) were used during this two-period randomised clinical-study (Fig. 1), which was approved by the Ethics Committee of the Università

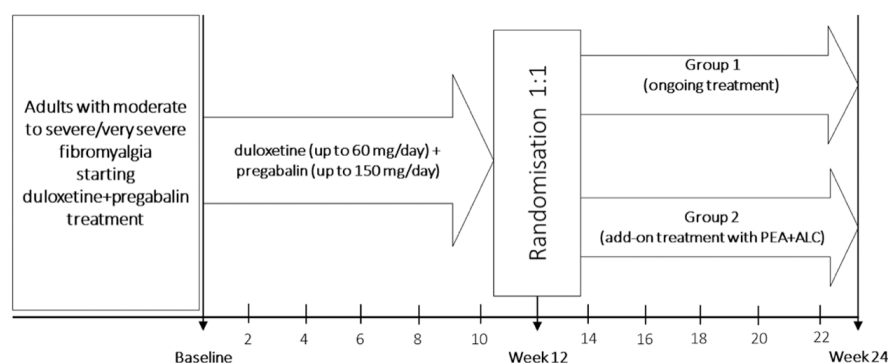


Fig. 1. Description of the study design.

PEA: palmitoylethanolamide; ALC: acetyl-L-carnitine.

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After giving their written informed consent to taking part in the study, all participants received DLX 30 mg/day plus PGB 75 mg/day for the first week, followed by DLX 60 mg/day plus PGB 150 mg/day for a total of 24 weeks. After 12 weeks of treatment (period 1), the patients were randomly divided 1:1 into two groups using a computer-generated blocked random allocation sequence: Group 1 continued the period 1 treatment unchanged (controls), and Group 2 continued the period 1 treatment with the addition of PEA 600 mg b.i.d. and ALC 500 mg b.i.d. Randomisation was carried out on patients able to tolerate combination treatment with DLX and PGB. No other treatment was allowed throughout the 24 weeks of the study. The patients were evaluated at the beginning of the study (baseline), and then every two weeks until week 24 by the same investigator (SF) with experience in collecting patient-reported measures, and the accuracy of the collected information was verified by a second investigator (MDC).

Outcome measures

The primary outcome measure was the Widespread Pain Index (WPI) (38); the secondary outcome measures were the revised Fibromyalgia Impact Questionnaire (FIQR) and the modified Fibromyalgia Assessment Status (FASmod) (39, 40). Every two weeks, all of the patients were asked to complete these patient-reported questionnaires electronically using the Italian Fibromyalgia Registry platform, which allows

data to be collected anonymously (41). At the end of the study, the data were extracted and analysed.

The WPI requires patients to indicate the presence/absence of pain in 19 body areas (right and left jaw, right and left scapular girdle, right and left upper arm, right and left lower arm, right and left hip/gluteus, right and left upper leg, right and left lower leg, upper and lower back, neck, chest, and abdomen) during the previous week. One point is allocated to each area in which pain is present, and so the total score ranges from 0 to 19 (38).

The FIQR consists of 21 items investigating the three primary health domains of function, overall impact, and symptoms (40), including new questions concerning memory, tenderness, balance, and environmental awareness that were intended to enhance the original version (42). The final score (range 0–100, with higher values indicating greater disease severity) is the sum of the scores of the three health domains: the algebraic sum of the 9-item function domain (range 0–90) is divided by three, the algebraic sum of the 2-item overall impact domain (range 0–20) remains as it is, and the algebraic sum of the 10-item symptom domain (range 0–100) is divided by two. The FIQR cut-off values for disease severity are 0–23 = remission, 24–40 = mild disease, 41–63 = moderate disease, 64–82 = severe disease, and 83–100 = very severe disease (43).

The FASmod is an updated version of the FAS that combines the patient's assessment of fatigue and sleep disturbances (each of which is scored using an 0–10 numerical rating scale) with a

Table I. Demographic and clinical characteristics of the two treatment groups at the time of randomisation.

	Treatment groups							
	Group 1 (68 patients)				Group 2 (62 patients)			
	Mean	Median	SD	25-75 percentile	Mean	Median	SD	25-75 percentile
Age, years	53.43	54.00	13.16	45.00 - 63.00	52.9	53.00	12.11	44.00 - 61.00
Disease duration, years	6.172	5.50	6.11	2.00 - 8.00	5.09	5.00	5.23	1.33 - 6.46
BMI, kg/m ²	26.23	26.50	2.97	25.00 - 27.00	25.9	25.00	2.79	24.00 - 27.00
Married, no. (%)			45 (66.2%)				40 (64.5%)	
Education								
Primary school, no. (%)			23 (33.9%)			23 (37.1%)		
Secondary school, no. (%)			31 (45.5%)			26 (41.9%)		
High school/university, no. (%)			14 (20.6%)			13 (21.0%)		
WPI (0-19)	10.23	10.84	3.53	7.68 - 12.92	9.35	10.00	4.39	5.84 - 12.60
FIQR (0-100)	49.26	50.00	16.84	37.00 - 62.00	47.86	44.00	20.06	29.00 - 60.00
FASmod (0-39)	22.15	23.34	5.74	19.26 - 26.42	20.96	22.08	7.40	15.66 - 25.84

BMI: Body Mass Index; SD: standard deviation; WPI: Widespread Pain Index; FIQR: revised Fibromyalgia Impact Questionnaire; FASmod: modified Fibromyalgia Assessment Status.

pain assessment based on a Regional Pain Scale (RPS) applied to 19 non-articular sites indicated on an outline drawing of a person (41). The final score ranges from 0 to 39. The FASmod cut-off values for disease severity are 0–12 = remission, 13–20 = mild disease, 21–28 = moderate disease, 29–33 = severe disease, and >33 = extremely severe disease (43).

Sample size

The sample size calculation for estimating the impact of treatment on WPI scores is expressed as the percentage last-first difference determined for each patient during the course of the 24-week study. Patients with a clinically relevant decrease from baseline of at least 30% (as recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials, IMMPACT) are considered treatment responders (45): 29.4% of the patients in Group 1 (controls) and 54.8% of the patients in Group 2 (the patients also receiving PEA+ALC) experienced reductions of $\geq 30\%$ (see the data given in the appendix).

On the basis of a power analysis (a type I error rate of 5% and a power of 0.8), it was estimated that 59 patients in each group were required to detect a 30% decrease in the WPI. Consequently, assuming a 20% allowance for dropouts and patients lost to follow-up, a total of 142 patients had to be recruited for the study.

Statistical analysis

The Shapiro-Wilk test was used to determine whether the variables were normally distributed. The continuous variables are expressed as median values with their inter-quartile range (IQR) and mean values \pm standard deviation (SD). On the basis of the normality test findings, the Mann-Whitney U test was used to compare the two groups. The correlations between the continuous variables were analysed by means of correlation analysis, and Spearman correlation coefficients were calculated. Cumulative disease severity in both groups was estimated on the basis of each patient's fortnightly WPI, total FIQR and FASmod scores during the 24-week study, and is expressed in time-integrated area under the curve (AUC) values that can be considered a good representation of global outcomes in this type of study. The percentage change in FIQR was calculated as $(\text{follow-up score} - \text{baseline score}) / \text{baseline score} \times 100$ for further descriptive analysis. The data were processed using MedCalc Statistical Software for Windows XP, v. 20.07 (Ostend, Belgium). *P* values of <0.05 were considered statistically significant.

Results

Patient characteristics

The study initially involved 142 patients but 12 were lost to follow-up after randomisation and so the final number available for the per proto-

col analysis was 130: 68 in Group 1 (DLX+PGB) and 62 in Group 2 (DLX+PGB+PEA+ALC) (Fig. 1). Table I shows the characteristics of the study population at the time of randomisation. The patients were all female, and there were no statistically significant between-group differences in their age, schooling, marital status, or disease severity, with mean FIQR scores of 49.26 ± 16.84 in Group 1 and 47.86 ± 20.06 in Group 2 ($p=0.092$).

Efficacy of duloxetine+pregabalin treatment

After 12 weeks of DLX+PGB treatment, all of the 130 analysed patients showed a significant reduction in the major indices of disease severity: the mean FIQR score decreased from 60.9 ± 16.6 to 47.2 ± 18.1 ($p=0.041$), the mean FASmod score decreased from 27.7 ± 6.2 to 23.3 ± 5.6 ($p=0.066$), and the mean WPI score decreased from 12.6 ± 4.1 to 10.8 ± 3.7 ($p=0.065$).

Efficacy of add-on therapy with palmitoylethanolamide and acetyl-L-carnitine

Up to the 12th week of treatment, the mean WPI score decreased equally in both groups but, between week 12 (randomisation) and the end of follow-up, Group 2 showed a further improvement in WPI (Fig. 2), FASmod (Fig. 3), and FIQR (Fig. 4). The total WPI, FASmod, and FIQR scores of each patient, expressed as AUC values and as the

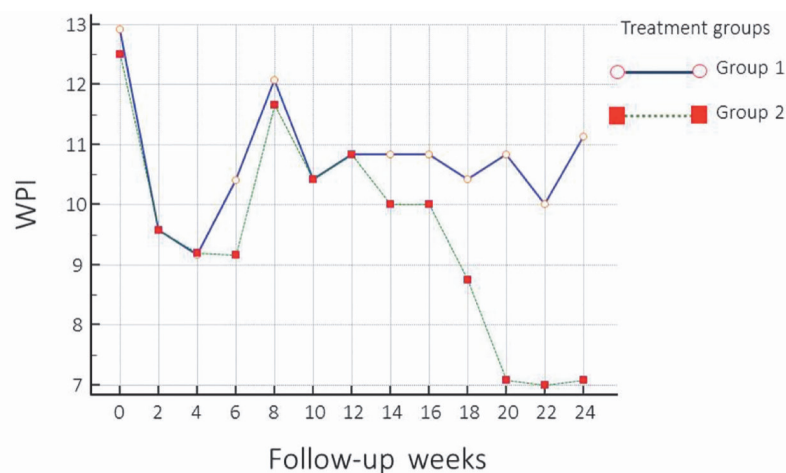


Fig. 2. Comparison of the trend of mean Widespread Pain Index (WPI) scores in the two groups.

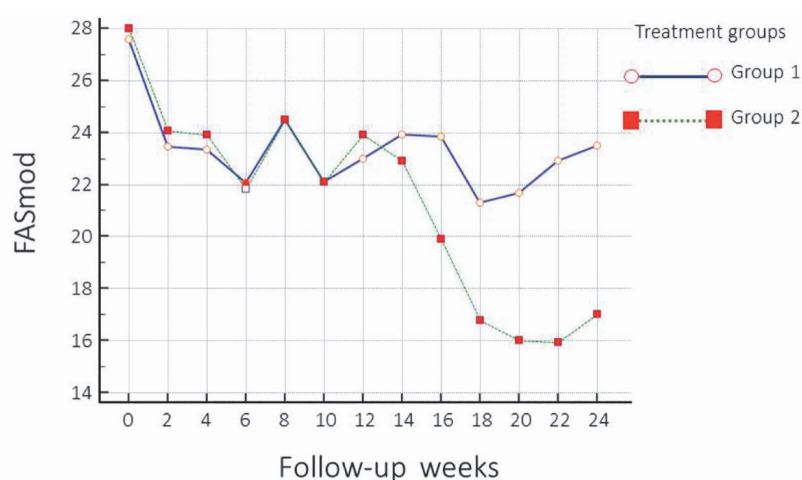


Fig. 3. Comparison of the trend of mean modified Fibromyalgia Assessment Status (FASmod) scores in the two groups.

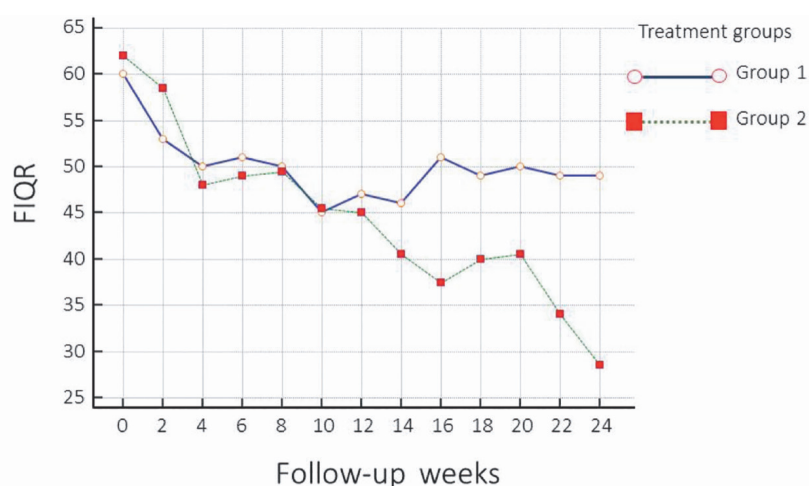


Fig. 4. Comparison of the trend of mean revised Fibromyalgia Impact Questionnaire (FIQR) scores in the two groups.

last-first percentage change, revealed a considerably greater advantage in Group 2. At the end of the study, 29.4% of the patients in Group 1 and 54.8%

of those in Group 2 showed a reduction of at least 30% in their WPI scores. Although there was some fluctuation in both groups during the course of the

study, there was a gradual improvement in both the AUC values ($p=0.0487$) and percentage changes in WPI scores ($p=0.0477$) (Table II); similarly, there were also substantial gains between week 12 and week 24 in the FASmod ($p=0.0173$ and $p=0.0001$) (Table III) and FIQR scores ($p=0.0333$ and $p=0.0033$) (Table IV).

The addition of PEA and ALC to PGB+DLX treatment was generally well tolerated. The most frequently reported adverse effects were dizziness, headache, nausea, blurred vision, sleepiness, and dry mouth; there were no serious adverse events. None of the patients discontinued treatment prematurely.

Discussion

To the best of our knowledge, this is the first randomised controlled trial comparing the effectiveness of PGB+DLX with and without the addition of PEA+ALC in FM patients, and its findings show that the addition of PEA+ALC to ongoing DLX+PGB treatment leads to a significant additional benefit in terms of the reduction in pain as assessed by the WPI. By week 24, 54.8% of the patients treated with the addition of PEA+ALC showed at least a 30% reduction in their WPI scores, as against only 29.4% of the patients treated with DLX+PGB alone. A 30% reduction in symptoms is accepted as being clinically significant in the context of chronic pain studies (45).

The management of FM is challenging (46), but both PGB and DLX have received FDA approval. PGB reportedly improves pain, sleeping problems, and fatigue in FM patients (47), and DLX has been approved for a variety of indications including the treatment of neuropathic pain, generalised anxiety disorder, osteoarthritis, and stress incontinence (48). PGB inhibits calcium channels and thus reduces pre-synaptic neurotransmitter release and post-synaptic excitability (15). Clair and Emir collected data from five double-blind RCTs of PGB in FM patients (49), and demonstrated that it was superior to placebo in improving pain and sleep scores. It has also been demonstrated that DLX is superior to placebo in reducing pain starting from the first week of treatment,

Table II. WPI scores expressed as the time-integrated values (AUC) and percentage last-first difference calculated for each patient during the 24 weeks of the study.

Summary measure of interest		AUC: WPI				
Group	n	Mean	95% CI	SD	Median	95% CI
Group 1	68	240.33	227.75 - 252.92	51.99	248.11	234.03 - 263.63
Group 2	62	224.57	209.91 - 239.24	57.75	229.99	209.62 - 244.60
Average rank of Group 1	71.24					
Average rank of Group 2	59.20					
Mann-Whitney U-test	1717.50					
Test statistic Z (corrected for ties)	2.62					
Two-tailed probability	<i>p</i> =0.0487					
Summary measure of interest		% last-first difference: WPI				
Group	n	Mean	95% CI	SD	Median	95% CI
Group 1	68	16.930	-12.30 - 46.16	120.77	-6.64	-18.24 - 0.00
Group 2	62	-0.19	-32.31 - 30.92	122.52	-27.39	-50.72 - 0.48
Average rank of Group 1	70.57					
Average rank of Group 2	69.93					
Mann-Whitney U-test	1763.00					
Test statistic Z (corrected for ties)	2.70					
Two-tailed probability	<i>p</i> =0.0477					

WPI: Widespread Pain Index; CI: confidence interval; SD: standard deviation.

Table III. FASmod scores expressed as the time-integrated values (AUC) and percentage last-first difference calculated for each patient during the 24 weeks of the study.

Summary measure of interest		AUC: FASmod				
Group	n	Mean	95% CI	SD	Median	95% CI
Group 1	68	537.25	512.53 - 561.97	102.12	548.90	529.80 - 561.10
Group 2	62	501.22	476.48 - 525.96	97.42	511.77	487.68 - 531.32
Average rank of Group 1	73.00					
Average rank of Group 2	57.26					
Mann-Whitney U-test	1597.50					
Test statistic Z (corrected for ties)	2.38					
Two-tailed probability	<i>p</i> =0.0173					
Summary measure of interest		% last-first difference: FASmod				
Group	n	Mean	95% CI	SD	Median	95% CI
Group 1	68	-3.13	-15.49 - 9.22	51.04	-8.31	-21.38 - 1.58
Group 2	62	-28.09	-41.92 - -14.26	54.47	-34.65	-53.91 - -27.59
Average rank of Group 1	78.44					
Average rank of Group 2	51.30					
Mann-Whitney U-test	1228.00					
Test statistic Z (corrected for ties)	4.10					
Two-tailed probability	<i>p</i> <0.0001					

FASmod: modified Fibromyalgia Assessment Status; CI: confidence interval; SD: standard deviation.

and this continued each subsequent week for 12 weeks (50, 51). DLX increases the activity of noradrenergic and serotonergic neurons in the descending spinal pathway on the dorsal horn (20), thus inhibiting the activity of dorsal horn neurons. It is hypothesised that a

deficiency in this inhibition leads to the brain being overwhelmed by signals that FM patients perceive as pain (21, 22). In addition to pharmacological treatments, the use of molecules with better tolerability and safety profiles is of increasing interest. One of these

molecules is PEA, a fatty acid amide belonging to the family of N-acylethanolamines that is thought to be an endogenous regulator of tissue reactivity (31). It has been extensively studied in FM because of its analgesic and anti-inflammatory properties (30). It suc-

Table IV. Total FIQR scores expressed as the time-integrated values (AUC) and percentage last-first difference calculated for each patient during the 24 weeks of the study.

Summary measure of interest		AUC: FIQR				
Group	n	Mean	95% CI	SD	Median	95% CI
Group 1	68	1158.41	1091.23 - 1225.60	277.57	1183.50	1124.56 - 1243.21
Group 2	62	1072.00	994.41 - 1149.59	305.52	1072.25	1033.02 - 1126.40
Average rank of Group 1	72.21					
Average rank of Group 2	58.13					
Mann-Whitney U-test	1651.50					
Test statistic Z (corrected for ties)	2.12					
Two-tailed probability	p=0.0333					
Summary measure of interest		% last-first difference: FIQR				
Group	n	Mean	95% CI	SD	Median	95% CI
Group 1	68	-17.30	-27.52 - -9.07	38.10	-21.11	-32.62 - -9.25
Group 2	62	-37.42	-45.45 - -27.38	35.58	-46.71	-58.29 - -34.14
Average rank of Group 1	74.77					
Average rank of Group 2	55.33					
Mann-Whitney U-test	1477.50					
Test statistic Z (corrected for ties)	2.93					
Two-tailed probability	p=0.0033					

FIQR: revised Fibromyalgia Impact Questionnaire; CI: confidence interval; SD: standard deviation.

cessfully inhibits the over-activation of astrocytes and glial cells (52), and controls the neuropathic pain caused by lesions of the peripheral and central nervous systems (53).

In the treatment of nociplastic pain, PEA integrates well with ALC, which is crucial for maintaining mitochondrial energy balance and detoxification, enhancing NGF activity, and promoting the regeneration of peripheral nerves (54). Its analgesic effects have led to it being increasingly studied as a potential treatment for many types of chronic pain, and as a means of preventing pain (35, 55). These studies suggest that ALC may help FM patients by reducing their pain and improving their physical and mental health. In models of chronic inflammatory and neuropathic pain, the analgesic effect of ALC lasts for several days or weeks after the conclusion of treatment, thus supporting the use of epigenetic mechanisms in the treatment of chronic pain and reinforcing the use of ALC as an analgesic (56). Multiple animal studies have shown that nicotinic and muscarinic antagonists can influence its effect on pain, which suggests the importance of the cholinergic pathway in its anti-nociceptive activity (57).

The findings of our clinical study provide evidence supporting the efficacy of DLX+PGB and demonstrating the added value of PEA+ALC in the treatment of FM patients. To the best of our knowledge, this is the first study of this form of combination therapy.

The limitations of this study include the absence of male participants and the lack of blinding procedures. There is a paucity of robust evidence supporting the practice of combining different treatments; consequently, additional high-quality randomised controlled trials involving larger populations and possibly longer follow-up periods are required to identify specific combinations that provide additional benefits as well as those that are actually harmful or cost-ineffective.

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